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	2008-000144-14
Trial protocol	BE CZ DE SE
Global end of trial date	15 February 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	N01276

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00698581
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB, Inc.
Sponsor organisation address	1950 Lake Park Drive, Smyrna, United States, 30080
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	05 October 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 February 2010
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of N01276 was to evaluate the efficacy of Brivaracetam (BRV) in the conversion to monotherapy at the doses of 50 and 100 mg/day (administered in 2 equal doses per day) in subjects with Partial Onset Seizures (POS) when compared to a historical pseudo-Placebo control group. This objective was based on the White Paper on Alternative Monotherapy Design in the Treatment of Epilepsy (French et al, 2005).

Protection of trial subjects:

Standard measures to minimize pain and stress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	25 August 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United States: 34
Worldwide total number of subjects	88
EEA total number of subjects	33

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)	1
Adults (18-64 years)	84
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll patients in August 2008 and concluded in February 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	Carer, Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Brivaracetam 50 mg/day

Arm description:

Brivaracetam: 25 mg tablet - 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	ucb 34714
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg and 25 mg oral tablets of Brivaracetam.

Arm title	Brivaracetam 100 mg/day

Arm description:

Brivaracetam: 25 mg tablet - 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	ucb 34714
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg and 25 mg oral tablets of Brivaracetam.

Number of subjects in period 1	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Started	68	20
Completed	23	8
Not completed	45	12
Consent withdrawn by subject	6	-
AE, non-serious non-fatal	4	-
AE of unknown type	1	-
Other reason	9	1
SAE, non-fatal	1	-
Lack of efficacy	23	11
SAE, non-fatal + AE, non-serious non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Brivaracetam 50 mg/day
Reporting group description:	
Brivaracetam: 25 mg tablet - 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 100 mg/day
Reporting group description:	
Brivaracetam: 25 mg tablet - 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 50 mg/day	Brivaracetam 100 mg/day	Total
Number of subjects	68	20	88
Age categorical Units: Subjects			
< 65	66	19	85
>= 65	2	1	3
Age continuous Units: years			
arithmetic mean	37.7	43.6	
standard deviation	± 11.7	± 13.2	-
Gender Categorical Units: Subjects			
Female	33	8	41
Male	35	12	47

End points

End points reporting groups

Reporting group title	Brivaracetam 50 mg/day

Reporting group description:

Brivaracetam: 25 mg tablet - 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 100 mg/day

Reporting group description:

Brivaracetam: 25 mg tablet - 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 Analysis Set (BRV 50 mg/day treated subjects)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Efficacy Analysis Set (EFF) consists of all randomized subjects with at least one intake of study medication who also entered into the Baseline antiepileptic drug (AED) Tapering Period and started 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 Week 1 up to Week 17

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, 0.626, was lower than the historical control exit rate of 0.772. Therefore the BRV 50 mg/day arm was considered statistically superior to historical control.

End point values	Efficacy Analysis Set (BRV 50 mg/day treated subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: percentage of subjects				
number (confidence interval 95%)				
number (95% confidence interval)	0.487 (0.347 to 0.626)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of patients reporting at least one Treatment-Emergent Adverse Event (TEAE) during the course of the study

End point title	The Number of patients reporting at least one Treatment-Emergent Adverse Event (TEAE) during the course of the study

End point description:

End point type	Secondary

End point timeframe:

Baseline through Re-conversion (approximately 31 weeks)

End point values	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	20		
Units: Participants				
number of participants	53	11		

Statistical analyses

No statistical analyses for this end point

Secondary: The number of patient withdrawal due to Adverse Events (AEs) during the course of the study

End point title	The number of patient withdrawal due to Adverse Events (AEs) during the course of the study

End point description:

End point type	Secondary

End point timeframe:

Baseline through Re-conversion (approximately 31 weeks)

End point values	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	20		
Units: Participants				
number of participants	9	2		

Statistical analyses

No statistical analyses for this end point

Secondary: The number of patients reporting at least one Serious Adverse Event (SAE) during the course of the study

End point title	The number of patients reporting at least one Serious Adverse Event (SAE) during the course of the study

End point description:

End point type	Secondary

End point timeframe:

Baseline through Re-conversion (approximately 31 weeks)

End point values	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	20		
Units: Participants				
number of participants	5	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from Visit 1 (Week -8) over the BRV Add-On Period and Evaluation Period up to the end of the Re-conversion Follow-up Period (Week 23).

Adverse event reporting additional description:

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

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Brivaracetam 50 mg/day

Reporting group description:

Brivaracetam: 25 mg tablet - 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 100 mg/day

Reporting group description:

Brivaracetam: 25 mg tablet - 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 50 mg/day	Brivaracetam 100 mg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 68 (7.35%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	2 / 68 (2.94%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 68 (1.47%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 68 (1.47%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paraesthesia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 68 (1.47%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 68 (1.47%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 68 (48.53%)	10 / 20 (50.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 68 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 68 (13.24%)	0 / 20 (0.00%)	
occurrences (all)	10	0	
Convulsion			
subjects affected / exposed	3 / 68 (4.41%)	4 / 20 (20.00%)	
occurrences (all)	3	5	
Somnolence			

subjects affected / exposed	4 / 68 (5.88%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Dizziness			
subjects affected / exposed	0 / 68 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 68 (7.35%)	2 / 20 (10.00%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 68 (4.41%)	2 / 20 (10.00%)	
occurrences (all)	3	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 68 (8.82%)	1 / 20 (5.00%)	
occurrences (all)	6	1	
Depression			
subjects affected / exposed	7 / 68 (10.29%)	0 / 20 (0.00%)	
occurrences (all)	7	0	
Insomnia			
subjects affected / exposed	5 / 68 (7.35%)	0 / 20 (0.00%)	
occurrences (all)	6	0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 68 (2.94%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 68 (5.88%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Urinary tract infection			
subjects affected / exposed	1 / 68 (1.47%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 7	1 / 20 (5.00%) 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. • 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 Criterion 1 or 2.
04 April 2008	Protocol Amendment 1 was finalized on 04 Apr 2008, before any subjects were enrolled, and resulted in the following: • 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. • 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.” • Correction of typographical errors.

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