Clinical trial results:
An Open-label, Multicenter, Follow-up Study to Evaluate the Long-term Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Subjects Aged 16 Years or Older with Epilepsy

Summary

EudraCT number	2012-000827-42
Trial protocol	GB DE ES IT
Global end of trial date	09 August 2016

Results information

Result version number	v2 (current)
This version publication date	18 August 2017
First version publication date	26 July 2017
Version creation reason	• Correction of full data set For consistency between registries

Trial information

Trial identification

Sponsor protocol code	N01372

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01728077
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma SA
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, B-1070
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	18 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

During the course of the study all subjects were closely monitored.
The following safety parameters were assessed at 6 month intervals:

- Vital signs
- Physical Exam
- Neurological Exam
- Psychiatric and mental status
- Electrocardiogram (ECG)
- Seizure assessment
- Laboratory assessment
- Pregnancy
- Review of Adverse Events(AEs)/Medical Procedures
- Suicidality Assessment
- Quality of Life (QOL) Assessment

There are withdrawal criteria specified within the protocol:

- Worsening of seizures
- Lack/Loss of efficacy
- Non-compliance
- Prohibited Concomitant Medication
- Pregnancy
- Significant Liver Function Test (LFT) results
- Illness (interfering with continued study participation)
- Suicidal ideation
- Withdrawal of consent
- Lost to follow-up
- Sponsor/agency request

Background therapy:

Background antiepileptic drug (AED) therapy was permitted as described in the protocol.

Evidence for comparator:

Not applicable

Actual start date of recruitment	17 October 2012
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	France: 3
Country: Number of subjects enrolled	Spain: 2

Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	26
EEA total number of subjects	8

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)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in October 2012 and concluded in August 2016.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set (SS), 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

Are arms mutually exclusive?	Yes
Arm title	Brivaracetam Focal Epilepsy

Arm description:

This arm includes subjects with focal epilepsy, who received a flexible dose of Brivaracetam (BRV) tablets, administered twice a day, starting with an individual dose that they had reached at the completion of study N01395 (feeder study). The BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day.

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

Dosage and administration details:

10 mg, 25 mg and 50 mg BRV tablets were used in this study. Subjects started with an individual dose that they had reached at the completion of study N01395 (feeder study). During the study the BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day. The BRV 10mg dose (20mg/day) was used only for down-titration.

Arm title	Brivaracetam Generalized Epilepsy

Arm description:

This arm includes subjects with generalized epilepsy, who received a flexible dose of Brivaracetam (BRV) tablets, administered twice a day, starting with an individual dose that they had reached at the completion of study N01395 (feeder study). The BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day.

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

Dosage and administration details:

10 mg, 25 mg and 50 mg BRV tablets were used in this study. Subjects started with an individual dose that they had reached at the completion of study N01395 (feeder study). During the study the BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day. The BRV 10mg dose (20mg/day)

was used only for down-titration.

Number of subjects in period 1	Brivaracetam Focal Epilepsy	Brivaracetam Generalized Epilepsy
Started	19	7
Completed	11	2
Not completed	8	5
Adverse event, serious fatal	-	1
Patient moving	1	-
Non compliance	1	-
Lost to follow-up	1	-
Subject choice	2	3
Lack of efficacy	3	1

Baseline characteristics

Reporting groups

Reporting group title	Brivaracetam Focal Epilepsy

Reporting group description:

This arm includes subjects with focal epilepsy, who received a flexible dose of Brivaracetam (BRV) tablets, administered twice a day, starting with an individual dose that they had reached at the completion of study N01395 (feeder study). The BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day.

Reporting group title	Brivaracetam Generalized Epilepsy

Reporting group description:

This arm includes subjects with generalized epilepsy, who received a flexible dose of Brivaracetam (BRV) tablets, administered twice a day, starting with an individual dose that they had reached at the completion of study N01395 (feeder study). The BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day.

Reporting group values	Brivaracetam Focal Epilepsy	Brivaracetam Generalized Epilepsy	Total
Number of subjects	19	7	26
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	19	7	26
>=65 years	0	0	0
Age Continuous Units: years			
arithmetic mean	38.6	30.7	
standard deviation	± 10.9	± 13.2	-
Gender Categorical Units: Subjects			
Female	7	5	12
Male	12	2	14

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 Focal Epilepsy (SS)	Brivaracetam Generalized Epilepsy (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	7		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	78.9	71.4		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects withdrawn due to an Adverse Event (AE) during the Evaluation Period

End point title	Percentage of subjects withdrawn due to an Adverse Event (AE) during the Evaluation Period[2]

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment. Results are presented as the percentage of subjects withdrawn due to an AE.

End point type	Primary

End point timeframe:

From Entry Visit (Month 0) to the Last Evaluation Period Visit or Early Discontinuation Visit (up to 46 months)

Notes:

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

End point values	Brivaracetam Focal Epilepsy (SS)	Brivaracetam Generalized Epilepsy (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	7		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	0	14.3		

Statistical analyses

No statistical analyses for this end point

Primary: Occurrence of a Serious Adverse Event (SAE) during the Evaluation Period

End point title	Occurrence of a Serious Adverse Event (SAE) during the Evaluation Period[3]

End point description:

SAEs include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity or are a congenital anomaly/birth defects. Results are presented as the percentage of subjects with at least one SAE during this study.

End point type	Primary

End point timeframe:

From Entry Visit (Month 0) to the Last Evaluation Period Visit or Early Discontinuation Visit (up to 46 months)

Notes:

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

End point values	Brivaracetam Focal Epilepsy (SS)	Brivaracetam Generalized Epilepsy (SS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	7		
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	26.3	28.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Partial-Onset Seizure (POS) Type I per 28 days during the Evaluation Period for subjects with focal-onset Epilepsy

End point title	Frequency of Partial-Onset Seizure (POS) Type I per 28 days during the Evaluation Period for subjects with focal-onset Epilepsy

End point description:

The POS frequency is standardized to a 28-day duration. Results are presented as the median number of seizures per 28 days.

End point type	Secondary

End point timeframe:

From Entry Visit (Month 0) to the Last Evaluation Period Visit or Early Discontinuation Visit (up to 46 months)

End point values	Brivaracetam Focal Epilepsy (EAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Seizures per 28 days				
median (full range (min-max))				
median (min, max)	0.4 (0 to 124)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of change in Partial-Onset-Seizure (POS) Type I frequency per 28 days from Baseline of the previous study to the Evaluation Period for subjects with focal-onset Epilepsy entering N01372 from a study where Baseline seizure data was collected

End point title	Percentage of change in Partial-Onset-Seizure (POS) Type I frequency per 28 days from Baseline of the previous study to the Evaluation Period for subjects with focal-onset Epilepsy entering N01372 from a study where Baseline seizure data was collected

End point description:

The POS frequency is standardized to a 28-day duration. Results are presented as the median percentage of reduction per 28 days. Negative values indicate improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline of the previous study to the Last Evaluation Period Visit or Early Discontinuation Visit (up to 49 months)

End point values	Brivaracetam Focal Epilepsy (EAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: percentage of change				
median (full range (min-max))				
median (min, max)	-56.3 (-97 to 717)			

Statistical analyses

No statistical analyses for this end point

Secondary: 50 % responder rate in Partial-Onset-Seizure (POS) Type I frequency from Baseline of the previous study to the Evaluation Period for subjects with focal-onset Epilepsy entering N01372 from a study where Baseline seizure data was collected

End point title	50 % responder rate in Partial-Onset-Seizure (POS) Type I frequency from Baseline of the previous study to the Evaluation Period for subjects with focal-onset Epilepsy entering N01372 from a study where Baseline seizure data was collected

End point description:

The POS frequency is standardized to a 28-day duration. A responder is defined as a subject with a >=50% reduction in seizure frequency from the Baseline Period of the previous study. Results are presented as the percentage of subjects with 50 % responder rate in POS Type I frequency.

End point type	Secondary

End point timeframe:

From Baseline of the previous study to the Last Evaluation Period Visit or Early Discontinuation Visit (up to 49 months)

End point values	Brivaracetam Focal Epilepsy (EAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: percentage of subjects				
number (not applicable)				
percentage of subjects	54.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events collection started at Day 0 and continued up to 30 days after last intake of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Brivaracetam Generalized Epilepsy (SS)

Reporting group description:

This arm includes subjects with generalized epilepsy, who received a flexible dose of Brivaracetam (BRV) tablets, administered twice a day, starting with an individual dose that they had reached at the completion of study N01395 (feeder study). The BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day. This arm is part of the Safety Set (SS).

Reporting group title	Brivaracetam Focal Epilepsy (SS)

Reporting group description:

This arm includes subjects with focal epilepsy, who received a flexible dose of Brivaracetam (BRV) tablets, administered twice a day, starting with an individual dose that they had reached at the completion of study N01395 (feeder study). The BRV dose could have been increased or decreased in increments of 50mg/day based on the individual subject's seizure control and/or tolerability, but was to not exceed 200mg/day. This arm is part of the Safety Set (SS).

Serious adverse events	Brivaracetam Generalized Epilepsy (SS)	Brivaracetam Focal Epilepsy (SS)	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	5 / 19 (26.32%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			

subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Conversion disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
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 Generalized Epilepsy (SS)	Brivaracetam Focal Epilepsy (SS)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	13 / 19 (68.42%)	
Investigations			

Crystal urine present			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	3	
White blood cell count increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Protein urine present			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	3	
Urinary casts			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 7 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	1 / 7 (14.29%)	7 / 19 (36.84%)	
occurrences (all)	1	68	
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	29	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	3	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 19 (5.26%)	
occurrences (all)	1	20	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	3	
Depression			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	3 / 19 (15.79%)	
occurrences (all)	2	3	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 7 (28.57%)	2 / 19 (10.53%)	
occurrences (all)	3	3	
Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Upper respiratory tract			

subjects affected / exposed	2 / 7 (28.57%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	4	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2013	This Amendment was implemented after the date of first subject first visit (FSFV, 25 subjects had enrolled in the study as of the date of this amendment). The rationale for this amendment was to clarify that data for the following variables were to only be collected and analyzed for subjects with epilepsy that entered N01372 from a study in which a Baseline value for that variable was previously collected: - Percent reduction in Type I partial-onset seizures (POS) frequency per 28 days from Baseline of the previous study into the Evaluation Period - Responder rate in POS (Type I) frequency over the Evaluation Period - Percent reduction in generalized (Type II) seizure days per 28 days from Baseline of the previous study to the Evaluation Period - Responder rate for generalized (Type II) seizure days over the Evaluation Period - Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score - Hospital stays and healthcare provider consultations. Additionally, Inclusion Criterion 7 was added, which required subjects to be able to take the oral film-coated tablets of Brivaracetam (BRV). References to specific BRV studies were removed and a statement was added to clarify that the study was to enroll subjects who had completed the Treatment Period of an applicable BRV study. Administrative changes included an update to the Clinical Trial Biostatistician and Study Physician.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported