Clinical trial results:
Open-label, single-arm, multicenter, pharmacokinetic, safety, and efficacy study of adjunctive administration of brivaracetam in subjects from 1 month to <16 years old with epilepsy

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2006-006536-22
Trial protocol	BE CZ ES PL Outside EU/EEA
Global end of trial date	13 March 2013

Results information

Result version number	v2 (current)
This version publication date	09 November 2017
First version publication date	30 July 2015
Version creation reason	• Correction of full data set Correction of full data set: outcome measure titles correction.

Trial information

Trial identification

Sponsor protocol code	N01263

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00422422
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	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000332-PIP01-08
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	08 May 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from ≥1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations.

Protection of trial subjects:

Informed consent was obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information was given in a language and at a level of complexity understandable in both oral and written form by the Investigator (or designee). Parent(s), legal representative(s), and subject if applicable had the opportunity to discuss the study and its alternatives with the Investigator.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	05 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Mexico: 19
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	100
EEA total number of subjects	52

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)	30
Children (2-11 years)	52
Adolescents (12-17 years)	18
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The N01263 study began recruitment in July 2011, with subjects enrolled in the European Union, Mexico, and the United States. The study concluded in March 2013.

Pre-assignment

Screening details:

Participant Flow data is taken from the Enrolled Set, which is all subjects enrolled into the study.

Period 1

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

Arms

Arm title	Brivaracetam (ES)

Arm description:

Enrolled Subjects, which is all subjects enrolled into the study.

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

Dosage and administration details:

For subjects ≥8 years:
• 0.4 mg/kg bid for Week 1
• 0.8 mg/kg bid for Week 2
• 1.6 mg/kg bid for Week 3
For subjects <8 years:
• 0.5 mg/kg bid for Week 1
• 1.0 mg/kg bid for Week 2
• 2.0 mg/kg bid for Week 3
Down-titration period (up to 2 weeks):
For subjects ≥8 years:
• 0.8 mg/kg bid for Week 4
• 0.4 mg/kg bid for Week 5
For subjects <8 years:
• 1.0 mg/kg bid for Week 4
• 0.5 mg/kg bid for Week 5

Number of subjects in period 1	Brivaracetam (ES)
Started	100
Completed	90
Not completed	10
Consent withdrawn by subject	2
AE, non-serious non-fatal	5
SAE, non-fatal	1

Lack of efficacy	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Brivaracetam (ES)
Reporting group description:	
Enrolled Subjects, which is all subjects enrolled into the study.	

Reporting group values	Brivaracetam (ES)	Total	
Number of subjects	100	100	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	6.3		
standard deviation	± 4.8	-	
Gender Categorical Units: Subjects			
Male	49	49	
Female	51	51	
Racial Group Units: Subjects			
Black or African American	4	4	
White	80	80	
Other	16	16	
Weight Units: kilograms			
arithmetic mean	24.2		
standard deviation	± 16.2	-	
Height Units: centimeters			
arithmetic mean	111.8		
standard deviation	± 32.9	-	
BMI Units: kg/m^2			
median	17.1		
standard deviation	± 3.4	-	

End points

End points reporting groups

Reporting group title	Brivaracetam (ES)
Reporting group description:	
Enrolled Subjects, which is all subjects enrolled into the study.	
Subject analysis set title	Brivaracetam (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set, which is all subjects in the Safety Set, who have at least 1 completed post-Baseline Daily Record Card (DRC) or electroencephalogram (EEG).	
Subject analysis set title	Brivaracetam (SS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Set, which is all enrolled subjects who took at least 1 dose of study medication. All safety analyses will be performed on the Safety Set.	
Subject analysis set title	Brivaracetam (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
Pharmacokinetic Per Protocol Set consists of all subjects who provided at least 1 measurable plasma sample on at least 1 visit with documented drug intake times.	

Primary: Mean Trough Plasma Concentration at 3rd Level for age range greater or equals to 1 month to less than 2 years

End point title	Mean Trough Plasma Concentration at 3rd Level for age range greater or equals to 1 month to less than 2 years[1]
End point description:	
End point type	Primary
End point timeframe:	
Day 21	

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: The primary objectives of study N01263 were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from ≥1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations. Descriptive statistics were used for the description of the PK profile of BRV across several variables. Therefore, no statistical analysis is entered.

End point values	Brivaracetam (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: ug/mL				
arithmetic mean (standard deviation)				
mean (standard deviation)	0.825 (± 0.826)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Trough Plasma Concentration at 3rd Level for age range greater or equals to 2 to less than 12 years

End point title	Mean Trough Plasma Concentration at 3rd Level for age range greater or equals to 2 to less than 12 years[2]

End point description:

End point type	Primary

End point timeframe:

Day 21

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: The primary objectives of study N01263 were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from ≥1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations. Descriptive statistics were used for the description of the PK profile of BRV across several variables. Therefore, no statistical analysis is entered.

End point values	Brivaracetam (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: ug/mL				
arithmetic mean (standard deviation)				
mean (standard deviation)	0.967 (± 0.536)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Trough Plasma Concentration at 3rd Level for age range greater or equals to 12 to less than 16 years

End point title	Mean Trough Plasma Concentration at 3rd Level for age range greater or equals to 12 to less than 16 years[3]

End point description:

End point type	Primary

End point timeframe:

Day 21

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: The primary objectives of study N01263 were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from ≥1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations. Descriptive statistics were used for the description of the PK profile of BRV across several variables. Therefore, no statistical analysis is entered.

End point values	Brivaracetam (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: ug/mL				
arithmetic mean (standard deviation)				
mean (standard deviation)	1.117 (± 0.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Max Plasma Concentration for age range greater or equals to 1 month to less than 2 years

End point title	Mean Max Plasma Concentration for age range greater or equals to 1 month to less than 2 years[4]

End point description:

End point type	Primary

End point timeframe:

Day 7 - 21

Notes:

[4] - 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: The primary objectives of study N01263 were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from ≥1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations. Descriptive statistics were used for the description of the PK profile of BRV across several variables. Therefore, no statistical analysis is entered.

End point values	Brivaracetam (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: ug/mL				
arithmetic mean (full range (min-max))				
mean (full range)	2.071 (0.32 to 4.305)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Max Plasma Concentration for age range greater or equals to 2 to less than 12 years

End point title	Mean Max Plasma Concentration for age range greater or equals to 2 to less than 12 years[5]

End point description:

End point type	Primary

End point timeframe:

Day 7 - 21

Notes:

[5] - 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: The primary objectives of study N01263 were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from ≥1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations. Descriptive statistics were used for the description of the PK profile of BRV across several variables. Therefore, no statistical analysis is entered.

End point values	Brivaracetam (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: ug/mL				
arithmetic mean (full range (min-max))				
mean (full range)	2.673 (0.561 to 5.418)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean Max Plasma Concentration for age range greater or equals to 12 to less than 16 years

End point title	Mean Max Plasma Concentration for age range greater or equals to 12 to less than 16 years[6]

End point description:

End point type	Primary

End point timeframe:

Day 7 - 21

Notes:

[6] - 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: The primary objectives of study N01263 were to characterize the steady-state pharmacokinetics (PK) of brivaracetam (BRV) and its metabolites in subjects from ≥1 month to <16 years of age, evaluate their relationship with physiological developmental variables, and develop dosing adaptations. Descriptive statistics were used for the description of the PK profile of BRV across several variables. Therefore, no statistical analysis is entered.

End point values	Brivaracetam (PPS)			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: ug/mL				
arithmetic mean (full range (min-max))				
mean (full range)	2.861 (2.627 to 3.371)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one treatment-emergent adverse event reported during the 3-week evaluation period

End point title	Number of subjects with at least one treatment-emergent adverse event reported during the 3-week evaluation period

End point description:

End point type	Secondary

End point timeframe:

Baseline to end of the 3-week evaluation period

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	99			
Units: participants				
number	66			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent compliance with brivaracetam oral solution during the 3-week evaluation period

End point title	Percent compliance with brivaracetam oral solution during the 3-week evaluation period

End point description:

End point type	Secondary

End point timeframe:

Baseline to the end of the 3-week evaluation period

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	97			
Units: participants				
number (not applicable)				
<80 % 80 % to 120 % >120 %	5 90 2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with a 50 % reduction in seizures based on seizure diary data from baseline to end of the 3-week evaluation period

End point title	Number of subjects with a 50 % reduction in seizures based on seizure diary data from baseline to end of the 3-week evaluation period

End point description:

End point type	Secondary

End point timeframe:

Baseline to end of the 3-week evaluation period

End point values	Brivaracetam (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	80			
Units: participants				
number	17			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent Adverse Events (TEAEs) were collected during the course of the study, which started July 2011 and concluded March 2013. The Safety Set will be utilized for TEAE reporting.

Adverse event reporting additional description:

The Safety Set is all enrolled subjects who took at least 1 dose of study drug.

Subjects had the ability to report more than one event. The Serious Adverse Events and Non-serious Adverse Events sections are reported in this manner.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Brivaracetam (SS)

Reporting group description:

Safety Set, which is all enrolled subjects who took at least 1 dose of study medication. All safety analyses will be performed on the SS.

Serious adverse events	Brivaracetam (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 99 (8.08%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Cytomegalovirus test positive			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	4 / 99 (4.04%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxoplasmosis			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 99 (2.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brivaracetam (SS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 99 (33.33%)		
Nervous system disorders			
Somnolence			
subjects affected / exposed	8 / 99 (8.08%)		
occurrences (all)	9		
Convulsion			

subjects affected / exposed occurrences (all)	6 / 99 (6.06%) 7		
General disorders and administration site conditions Irritability subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	 8 / 99 (8.08%) 9 7 / 99 (7.07%) 8 5 / 99 (5.05%) 5		
Infections and infestations Pharyngotonsillitis subjects affected / exposed occurrences (all)	 5 / 99 (5.05%) 5		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 7 / 99 (7.07%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2011	Protocol Amendment 1 (dated 24 Feb 2011) was implemented prior to the date of first patient first visit (FPFV on 05 Jul 2011). The rationale for this amendment was to update the Sponsor's name and to add the Investigational New Drug number. Also, the Food and Drug Administration (FDA) recommendation that a PK blood sample should be taken whenever the subject reports a Serious Adverse Event (SAE) was added.
26 August 2011	Protocol Amendment 2 (dated 26 Aug 2011) was implemented after the date of FPFV. The rationale for this amendment was to include the Bayley Scales of Infant Development™, Second Edition (BSID-II™) in order to assess the cognitive development of pediatric subjects <18 months at Baseline in response to the European Medicines Agency's (EMA) Paediatric Committee's (PDCO) request. Exclusion and withdrawal criteria were extended to include the consequences of any findings related to the results of the liver function tests (LFTs). Procedures for reporting SAEs were updated to implement the FDA Final Rule requirements (Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans, 21 Code of Federal Regulations [CFR] Parts 312 and 320, 2010). The Columbia-Suicide Severity Rating Scale (C-SSRS) was added to address the request of the FDA that prospective assessments for suicidality should be included in clinical studies involving all drugs for neurological indications. Some operational updates (eg, the replacement of the paper-based Case Report form [CRF] with an eCRF) were also considered.
15 December 2011	Protocol Amendment 3 (dated 15 Dec 2011) was implemented after the date of FPFV. The rationale for this amendment was to replace the pediatric subjects' version of the C-SSRS with the version validated in multiple languages for subjects 6 years of age and older. The BSID-II score was replaced by the Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®) scales in order to apply the most recent version of the cognition scale; no data were collected using the BSID-II before this change was implemented. In addition, it was clarified that the cognition scale would be used only in English-speaking countries, since it was validated only in English. The requirements for blood sampling (volumes and frequencies of the blood samples) were updated based on the subject's body weight and all sections referring to biochemistry assessments were amended in order to clarify that tests for hepatic monitoring were to be included in all safety laboratory assessments. Furthermore, an error in the mathematical symbols used for the presentation of the age limits of the EEG assessments was corrected, and the SAE reporting details were updated. Administrative changes included the update of the Clinical Project Manager contact details and typographical corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported