Clinical trial results:
A Multicenter, Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Brivaracetam in Neonates with Repeated Electroencephalographic Seizures

Summary

EudraCT number	2015-002756-27
Trial protocol	IE DE GB BE CZ HU NL FR IT
Global end of trial date	29 May 2021

Results information

Result version number	v1 (current)
This version publication date	08 July 2022
First version publication date	08 July 2022

Trial information

Trial identification

Sponsor protocol code	N01349

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03325439
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma SRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000332-PIP02-17
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	09 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2020
Global end of trial reached?	Yes
Global end of trial date	29 May 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective was to evaluate the pharmacokinetics (PK) of brivaracetam (BRV) in neonates who have seizures that are not adequately controlled with previous antiepileptic drug (AED) treatment and to identify the optimum BRV dose (Exploratory Cohort) for the treatment of participants enrolled into the Confirmatory Cohorts of this study.

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 May 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Ireland: 5
Worldwide total number of subjects	9
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	2
Newborns (0-27 days)	7
Infants and toddlers (28 days-23 months)	0

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

Subject disposition

Recruitment

Recruitment details:

The study started to enroll participants in May 2019 and concluded in May 2021.

Pre-assignment

Screening details:

No eligible study participants were enrolled in the Confirmatory Cohorts. The study stopped prematurely due to enrolment challenges, the termination was not linked to any safety issues. The Participant Flow refers to the All Subjects Screened.

Period 1

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

Arms

Arm title	Exploratory Cohort

Arm description:

Participants in this arm received brivaracetam (BRV) 0.5 milligram per kilogram (mg/kg) administered as an intravenous (iv) solution for injection twice daily (bid) during the 48-hour Evaluation Period. An additional 3 doses of BRV (0.5 mg/kg) could have been administered every 12 hours for 48 hours (at the discretion of the Investigator). Treatment with antiepileptic drugs (AEDs) per standard of care (SToC) (first-line, second-line, or subsequent treatment) were continued in parallel with BRV treatment.

Arm type	Experimental
Investigational medicinal product name	Brivaracetam
Investigational medicinal product code	
Other name	BRV
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Eligible participants in this arm received BRV 0.5 mg/kg administered as iv solution for injection twice daily (bid) during the 48-hour Evaluation Period.

Number of subjects in period 1	Exploratory Cohort
Started	9
Treated	6
Completed	6
Not completed	3
Ineligibility	3

Baseline characteristics

Reporting groups	
Reporting group title	Exploratory Cohort

Reporting group description:

Participants in this arm received brivaracetam (BRV) 0.5 milligram per kilogram (mg/kg) administered as an intravenous (iv) solution for injection twice daily (bid) during the 48-hour Evaluation Period. An additional 3 doses of BRV (0.5 mg/kg) could have been administered every 12 hours for 48 hours (at the discretion of the Investigator). Treatment with antiepileptic drugs (AEDs) per standard of care (SToC) (first-line, second-line, or subsequent treatment) were continued in parallel with BRV treatment.

Reporting group values	Exploratory Cohort	Total	
Number of subjects	9	9	
Age Categorical Units: participants			
Gestational Age <37 weeks	2	2	
Gestational Age >=37 weeks	7	7	
Age Continuous			
Corrected gestational age at time of enrollment is reported.			
Units: weeks arithmetic mean standard deviation	 39.2 ± 1.9	 -	
Sex: Female, Male Units: participants			
Female	6	6	
Male	3	3	

End points

End points reporting groups

Reporting group title	Exploratory Cohort

Reporting group description:

Participants in this arm received brivaracetam (BRV) 0.5 milligram per kilogram (mg/kg) administered as an intravenous (iv) solution for injection twice daily (bid) during the 48-hour Evaluation Period. An additional 3 doses of BRV (0.5 mg/kg) could have been administered every 12 hours for 48 hours (at the discretion of the Investigator). Treatment with antiepileptic drugs (AEDs) per standard of care (SToC) (first-line, second-line, or subsequent treatment) were continued in parallel with BRV treatment.

Primary: Plasma concentration of Brivaracetam (BRV) following first dose on Day 1

End point title	Plasma concentration of Brivaracetam (BRV) following first dose on Day 1[1]

End point description:

Pharmacokinetic blood samples were taken 0.5 to 1 hour, 2 to 4 hours, and 8 to 12 hours after the BRV infusion on Day 1 to determine the BRV plasma concentration. The Pharmacokinetic Per-Protocol Set (PK-PPS) consisted of all study participants who provided at least 1 measurable post-Baseline plasma sample (with recorded sampling time) on at least 1 post-Baseline Visit with documented study drug intake times. Each participant was assessed once within the specified time-range and the average of the participants included in the given time-range is presented here. Here, 'n' signifies participants who were evaluable at specified time points.

End point type	Primary

End point timeframe:

Pharmacokinetic blood samples were taken 0.5 to 1 hour, 2 to 4 hours, and 8 to 12 hours after the BRV infusion on Day 1

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	Exploratory Cohort			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: nanograms per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
0.5-1 hour (n=5)	534.2 (± 15.4)			
2-4 hours (n=6)	500.1 (± 28.2)			
8-12 hours (n=5)	342.7 (± 13.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Adverse Events (AEs) as reported by the Investigator

End point title	Percentage of participants with Adverse Events (AEs) as reported by the Investigator

End point description:

An adverse event (AE) was any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment. The All Study Participants Screened Set consisted of all study participants who had signed the Informed Consent form (ICF) and underwent the study inclusion and exclusion criteria of the current protocol.

End point type	Secondary

End point timeframe:

Adverse Events were collected from Screening Period until the Safety Follow-Up Visit (up to Day 75)

End point values	Exploratory Cohort			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of participants				
number (not applicable)	55.6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Screening Period until the Safety Follow-Up Visit (up to Day 75)

Adverse event reporting additional description:

Safety analysis was done on All Study Participants Screened Set. Only 6 of 9 participants were treated with BRV. No eligible study participants were enrolled in the Confirmatory Cohorts. The study stopped prematurely due to enrolment challenges, the termination was not linked to any safety issues.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Exploratory Cohort

Reporting group description:

Participants in this arm received brivaracetam (BRV) 0.5 milligram per kilogram (mg/kg) administered as an intravenous (iv) solution for injection twice daily (bid) during the 48-hour Evaluation Period. An additional 3 doses of BRV (0.5 mg/kg) could have been administered every 12 hours for 48 hours (at the discretion of the Investigator). Treatment with antiepileptic drugs (AEDs) per standard of care (SToC) (first-line, second-line, or subsequent treatment) were continued in parallel with BRV treatment.

Serious adverse events	Exploratory Cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Exploratory Cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)		
Investigations			
Ammonia increased			

subjects affected / exposed occurrences (all) Liver function test abnormal subjects affected / exposed occurrences (all) Oxygen saturation decreased subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2019	Global Protocol Amendment 5.0, dated 10 Oct 2019, was a substantial protocol amendment created after 1 eligible study participant had been enrolled in the study. Protocol Amendment 5.0 was implemented through Global Protocol Amendment 6.0. The primary purpose of this substantial protocol amendment was to implement the changes from the agreed Pediatric Investigation Plan for BRV in order to improve the enrollment rate. The primary change was to remove restrictions in terms of concomitant medication and to simplify electroencephalogram (EEG) requirements; as a result, the primary and secondary objectives were revised. In addition, the age range at enrollment was modified. A brief list of important modifications and changes to this protocol amendment included the following: • Phenobarbital was no longer required as first line treatment prior to BRV and replaced by treatment of electroencephalographic neonatal seizures (ENS) allowed per SToC for the Exploratory Cohort, and 1 or more of the following AEDs: phenobarbital (PB), midazolam (MDZ), phenytoin (PHT), levetiracetam (LEV) (≤60mg/kg/day), or lidocaine (LDC) for the Confirmatory Cohorts. • Two hour Baseline EEG and 48-hour VEEG were removed from the Exploratory Cohort; required ENS to be confirmed by the Investigator via local EEG. • Duration of the 2-hour Baseline Period was shortened to up to 1 hour for the Confirmatory Cohorts and was separated by seizure activity: "at least 1 hour" for study participants with intermittent ENS and "up to 30 minutes" for study participants in status epilepticus. • Treatment with "MDZ only" during the first 3 hours of the Evaluation Period was removed from the Confirmatory Cohort; duration of the Evaluation Period hence shortened from 51 hours to 48 hours. • The initiation of LEV treatment after the first time BRV was introduced was prohibited throughout the study for the Confirmatory Cohorts.
24 May 2021	Global Protocol Amendment 7.0, dated 24 May 2021, was a substantial protocol amendment implemented after 6 eligible study participants had been enrolled in the study. The primary purposes of this substantial protocol amendment were as follows: • Specified the BRV dose recommended by the Data Monitoring Committee (DMC) for the Confirmatory Cohorts. • Incorporated the measures described in UCB's coronavirus disease 2019 (COVID-19) Contingency Plan for N01349. • Prolonged the BRV Extension Period for up to 90 days postnatal age (PNA) for sites that may not have been ready to transition study participants to EP0156 at the time that N01266 was closed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 March 2020	The study was interrupted due to COVID-19.	15 July 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No eligible study participants were enrolled in the Confirmatory Cohorts. The study stopped prematurely due to enrolment challenges, the termination was not linked to any safety issues.

Notes: