Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group Study to Evaluate the Efficacy and Safety of Adjunctive Brivaracetam in Subjects (>=16 to 80 Years of Age) With Partial Seizures With or Without Secondary Generalization

Summary

EudraCT number	2019-001203-21
Trial protocol	Outside EU/EEA
Global end of trial date	30 June 2022

Results information

Result version number	v3 (current)
This version publication date	30 May 2024
First version publication date	31 December 2022
Version creation reason	• Correction of full data set Alignment with final posting on ClinicalTrials.gov after CSR amendment.

Trial information

Trial identification

Sponsor protocol code	EP0083

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03083665
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)	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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2022
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy of brivaracetam (BRV) compared to placebo (PBO) as adjunctive treatment in subjects (>=16 to 80 years of age) with partial seizures with or without secondary generalization despite current treatment with 1 or 2 concomitant antiepileptic drugs (AEDs)

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	22 August 2017
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	China: 86
Country: Number of subjects enrolled	Japan: 98
Country: Number of subjects enrolled	Malaysia: 47
Country: Number of subjects enrolled	Philippines: 62
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Thailand: 145
Worldwide total number of subjects	449
EEA total number of subjects	0

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	20
Adults (18-64 years)	421
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll participants in August 2017 and concluded in June 2022.

Pre-assignment

Screening details:

The Participant Flow refers to the Randomized Set. Double-Blind Period included Treatment Period and the Down-Titration Period plus Study Drug-Free Period or the Transition Period.

Period 1

Period 1 title	Double-Blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching Placebo as film-coated tablets, administered orally, twice daily (bid), during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered long-term follow-up (LTFU) study (EP0085 (NCT03250377)) or managed access program (MAP), the same matching Placebo dose was kept during 2 weeks of Transition Period and brivaracetam (BRV) 100 milligrams/day (mg/day) in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received the same Placebo dose for 4 weeks.

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

Dosage and administration details:

Participants received matching placebo at pre-defined timepoints.

Arm title	BRV 50 mg/day

Arm description:

Participants received BRV 50 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered the LTFU study or MAP received BRV 50 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 25 mg/day for 1 week followed by Placebo for 3 weeks.

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:

Participants received Brivaracetam 50 mg/day at pre-defined timepoints.

Arm title	BRV 200 mg/day

Arm description:

Participants received BRV 200 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered LTFU study or MAP received BRV 150 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 150 mg/day for 1 week followed by BRV 100 mg/day for 1 week, followed by BRV 50 mg/day for 1 week, followed by BRV 25 mg/day for 1 week.

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:

Participants received Brivaracetam 200 mg/day at pre-defined timepoints.

Number of subjects in period 1	Placebo	BRV 50 mg/day	BRV 200 mg/day
Started	149	152	148
Started Treatment Period (12 weeks)	149	152	148
Started Down-Titration Period (4 weeks)	7 [1]	9 [2]	7 [3]
Started Study Drug-Free Period (2 weeks)	7 [4]	9 [5]	7 [6]
Started Transition Period (2 weeks)	133 [7]	139 [8]	137 [9]
Completed	138	147	140
Not completed	11	5	8
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	3	-	-
Consent withdrawn by subject due to concern on AE	1	-	-
Subjects were able to never take a study drug	-	1	-
Adverse event, non-fatal	5	3	5
Lost to follow-up	1	-	1
Protocol deviation	1	-	1
Lack of efficacy	-	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.
[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The milestones were created based on the the fact if Participants were conveyed to LTFU and MAP or not and hence whether they took BRV through Transition or Down-Titration Periods.

Period 2

Period 2 title	Open-Label Temporary Period (OLTP)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo to OLTP BRV

Arm description:

Participants who received Placebo during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during OLTP. BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

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:

Participants received Brivaracetam at pre-defined timepoints.

Arm title	BRV 50 mg/day to OLTP BRV

Arm description:

Participants who received BRV 50 mg/day during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during Open-Label Temporary

Period (OLTP). BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

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:

Participants received Brivaracetam at pre-defined timepoints.

Arm title	BRV 200 mg/day to OLTP BRV

Arm description:

Participants who received BRV 200 mg/day during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during Open-Label Temporary Period (OLTP). BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

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:

Participants received Brivaracetam at pre-defined timepoints.

Number of subjects in period 2[10]	Placebo to OLTP BRV	BRV 50 mg/day to OLTP BRV	BRV 200 mg/day to OLTP BRV
Started	64	68	74
Completed	60	67	68
Not completed	4	1	6
Consent withdrawn by subject	1	1	1
Patient not keen to continue open label	1	-	-
Adverse event, non-fatal	2	-	-
Subject enrolled to compassionate use program	-	-	1
Patient non compliant to open label study drug	-	-	1
Withdrawal by parent/guardian	-	-	1
Lack of efficacy	-	-	2

Notes:

[10] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: These are the participants who were assigned to enter MAP but who could not directly convert to MAP; started after the end date of the Transition Period and continued until date when participant could convert to MAP, BRV was commercially available or until UCB decides to close the study.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching Placebo as film-coated tablets, administered orally, twice daily (bid), during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered long-term follow-up (LTFU) study (EP0085 (NCT03250377)) or managed access program (MAP), the same matching Placebo dose was kept during 2 weeks of Transition Period and brivaracetam (BRV) 100 milligrams/day (mg/day) in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received the same Placebo dose for 4 weeks.	
Reporting group title	BRV 50 mg/day
Reporting group description:	
Participants received BRV 50 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered the LTFU study or MAP received BRV 50 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 25 mg/day for 1 week followed by Placebo for 3 weeks.	
Reporting group title	BRV 200 mg/day
Reporting group description:	
Participants received BRV 200 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered LTFU study or MAP received BRV 150 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 150 mg/day for 1 week followed by BRV 100 mg/day for 1 week, followed by BRV 50 mg/day for 1 week, followed by BRV 25 mg/day for 1 week.	

Reporting group values	Placebo	BRV 50 mg/day	BRV 200 mg/day
Number of subjects	149	152	148
Age Categorical Units: participants			
<=18 years	9	14	8
Between 18 and 65 years	137	135	138
>=65 years	3	3	2
Age Continuous Units: years			
arithmetic mean	34.5	33.7	35.2
standard deviation	± 13.2	± 12.6	± 13.2
Sex: Female, Male Units: participants			
Female	82	77	83
Male	67	75	65

Reporting group values	Total		
Number of subjects	449		
Age Categorical Units: participants			
<=18 years	31		
Between 18 and 65 years	410		
>=65 years	8		

Age Continuous Units: years arithmetic mean standard deviation	- 		
Sex: Female, Male Units: participants			
Female	242		
Male	207		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching Placebo as film-coated tablets, administered orally, twice daily (bid), during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered long-term follow-up (LTFU) study (EP0085 (NCT03250377)) or managed access program (MAP), the same matching Placebo dose was kept during 2 weeks of Transition Period and brivaracetam (BRV) 100 milligrams/day (mg/day) in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received the same Placebo dose for 4 weeks.

Reporting group title	BRV 50 mg/day

Reporting group description:

Participants received BRV 50 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered the LTFU study or MAP received BRV 50 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 25 mg/day for 1 week followed by Placebo for 3 weeks.

Reporting group title	BRV 200 mg/day

Reporting group description:

Participants received BRV 200 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered LTFU study or MAP received BRV 150 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 150 mg/day for 1 week followed by BRV 100 mg/day for 1 week, followed by BRV 50 mg/day for 1 week, followed by BRV 25 mg/day for 1 week.

Reporting group title	Placebo to OLTP BRV

Reporting group description:

Participants who received Placebo during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during OLTP. BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

Reporting group title	BRV 50 mg/day to OLTP BRV

Reporting group description:

Participants who received BRV 50 mg/day during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during Open-Label Temporary Period (OLTP). BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

Reporting group title	BRV 200 mg/day to OLTP BRV

Reporting group description:

Participants who received BRV 200 mg/day during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during Open-Label Temporary Period (OLTP). BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

Subject analysis set title	BRV 150 mg/day
Subject analysis set type	Per protocol

Subject analysis set description:

At the end of the Treatment Period, participants of arm BRV 200 mg/day who entered LTFU study or MAP received BRV 150 mg/day during 2 weeks of Transition Period. The number of participants for BRV 150 mg/day group are those who had BRV 200 mg/day and valid PK data in Transition Period.

Primary: Percentage of participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of participants with Treatment-Emergent Adverse Events (TEAEs)[1]

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. Treatment-Emergent AEs were defined as AEs which had onset on or after the first dose of IMP. As per planned analysis, safety data for all study periods was combined excluding Open-Label Temporary period. The Safety Set (SS) included all randomized study participants who received at least 1 dose of IMP.

End point type	Primary

End point timeframe:

From start of the Treatment Period (Week 0) until Safety Visit (up to Week 18); only for OLTP- From last visit of Transition Period to beginning of MAP (up to 4 Years 10 Months)

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	Placebo	Placebo to OLTP BRV	BRV 50 mg/day	BRV 50 mg/day to OLTP BRV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	149	64	151	68
Units: percentage of participants				
number (not applicable)	58.4	26.6	57.0	19.1

End point values	BRV 200 mg/day	BRV 200 mg/day to OLTP BRV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	74		
Units: percentage of participants				
number (not applicable)	60.1	23.0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with Treatment-Emergent AEs (TEAEs) leading to study withdrawal

End point title	Percentage of participants with Treatment-Emergent AEs (TEAEs) leading to study withdrawal[2]

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. Treatment-Emergent AEs were defined as AEs which had onset on or after the first dose of IMP. As per planned analysis, safety data for all study periods was combined excluding Open-Label Temporary period. The SS included all randomized study participants who received at least 1 dose of IMP.

End point type	Primary

End point timeframe:

From start of the Treatment Period (Week 0) until Safety Visit (up to Week 18); only for OLTP- From last visit of Transition Period to beginning of MAP (up to 4 Years 10 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 in tables as descriptive statistics only.

End point values	Placebo	Placebo to OLTP BRV	BRV 50 mg/day	BRV 50 mg/day to OLTP BRV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	149	64	151	68
Units: percentage of participants				
number (not applicable)	4.7	0	2.6	0

End point values	BRV 200 mg/day	BRV 200 mg/day to OLTP BRV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	74		
Units: percentage of participants				
number (not applicable)	3.4	0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with Treatment-Emergent Serious Adverse Events (SAEs)

End point title	Percentage of participants with Treatment-Emergent Serious Adverse Events (SAEs)[3]

End point description:

Serious Adverse event (SAE) was defined as any events which: • results in death, • is life-threatening threatening (note that this did not include a reaction that might have caused death had it occurred in a more severe form.), •results in significant or persistent disability/incapacity, • results in a congenital anomaly/birth defect (including that occurring in a fetus), • results in Important medical event that, based upon appropriate medical judgment, may jeopardize the participant and might require medical or surgical intervention to prevent 1 of the other outcomes listed here, and • results in initial inpatient hospitalization or prolongation of hospitalization. As per planned analysis, safety data for all study periods was combined excluding Open-Label Temporary period. The SS included all randomized study participants who received at least 1 dose of IMP.

End point type	Primary

End point timeframe:

From start of the Treatment Period (Week 0) until Safety Visit (up to Week 18); only for OLTP- From last visit of Transition Period to beginning of MAP (up to 4 Years 10 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 in tables as descriptive statistics only.

End point values	Placebo	Placebo to OLTP BRV	BRV 50 mg/day	BRV 50 mg/day to OLTP BRV
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	149	64	151	68
Units: percentage of participants				
number (not applicable)	0.7	4.7	1.3	0

End point values	BRV 200 mg/day	BRV 200 mg/day to OLTP BRV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	74		
Units: percentage of participants				
number (not applicable)	2.7	2.7		

Statistical analyses

No statistical analyses for this end point

Primary: Partial seizure frequency per 28 days during the 12-week Treatment Period

End point title	Partial seizure frequency per 28 days during the 12-week Treatment Period

End point description:

According to International League Against Epilepsy (ILAE) classification (1981), seizures were classified as type IA (IA1, IA2, IA3, and IA4), IB, IC, II (IIA, IIB, IIC, IID, IIE, and IIF) or III. 28 day adjusted seizure frequency for partial seizures (seizure types IA+IB+IC) was calculated for treatment period by dividing the number of partial seizures by the number of days for which the DRC was completed for treatment period and multiplying the resulting value by 28. The Full Analysis Set (FAS) consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure daily record card (DRC) data during the Treatment Period.

End point type	Primary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: seizures per 28 days				
median (full range (min-max))	7.17 (1.0 to 317.0)	5.93 (0.0 to 123.7)	4.19 (0.0 to 269.4)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BRV 50 mg/day
Number of subjects included in analysis	298
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0005 [5]
Method	ANCOVA
Parameter estimate	Percent reduction over Placebo
Point estimate	24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.7
upper limit	35.5

Notes:

[4] - Based on ANCOVA with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency.
[5] - Statistical testing with control of Type I error rate were based on a Hochberg multiple comparison procedure.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v BRV 200 mg/day
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	Percent reduction over Placebo
Point estimate	33.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.9
upper limit	43.1

Notes:

[6] - Based on ANCOVA with log-transformed [log(x+1)] Treatment Period 28-day adjusted partial seizure frequency.
[7] - Statistical testing with control of Type I error rate were based on a Hochberg multiple comparison procedure.

Secondary: 50% responder rate based on percent change in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

End point title	50% responder rate based on percent change in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

End point description:

Responders were those participants with at least 50% reduction from Baseline to the 12-week Treatment Period in partial seizure frequency per 28 days. 50% Responder rate was calculated for treatment period by dividing the number of 50% responders by the number of participants in the analysis set and multiplying the resulting value by 100. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: percentage of responders				
number (confidence interval 95%)	19.0 (13.0 to 26.3)	41.1 (33.1 to 49.3)	49.3 (41.0 to 57.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with categorized percent change in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

End point title	Percentage of participants with categorized percent change in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

End point description:

The percentage of participants within each of the following categories of percent change in partial seizure frequency from Baseline to the Treatment Period were summarized for each treatment group: 100%, 75% to less than 100%, 50% to less than 75%, 25% to less than 50%, -25% to less than 25%, and less than -25%. Percent change from Baseline to the Treatment Period in partial seizure frequency was calculated by subtracting 28-day adjusted Treatment Period partial seizure frequency from 28-day adjusted Baseline Period partial seizure frequency and multiplying the resulting quantity by 100 and dividing by the Baseline Period 28-day adjusted partial seizure frequency. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: percentage of participants				
number (not applicable)				
100%	0	5.3	7.4	
75% to less than 100%	3.4	14.6	17.6	
50% to less than 75%	15.6	21.2	24.3	
25% to less than 50%	27.2	16.6	20.9	
-25% to less than 25%	42.9	31.1	18.2	
less than -25%	10.9	11.3	11.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

End point title	Percent change in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period

End point description:

Percent change from Baseline to the Treatment Period in partial seizure frequency was calculated by subtracting 28-day adjusted Treatment Period partial seizure frequency from 28-day adjusted Baseline Period partial seizure frequency, and multiplying the resulting quantity by 100 and dividing by the Baseline Period 28-day adjusted partial seizure frequency. A negative value in percent change from Baseline indicates a decrease in partial seizure frequency from Baseline to the Treatment Period. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: percent change				
median (full range (min-max))	21.3 (-123 to 87)	38.9 (-233 to 100)	46.7 (-1097 to 100)	

Statistical analyses

No statistical analyses for this end point

Secondary: All seizure frequency (partial, generalized, and unclassified epileptic seizures) per 28 days during the 12-week Treatment Period

End point title	All seizure frequency (partial, generalized, and unclassified epileptic seizures) per 28 days during the 12-week Treatment Period

End point description:

There were three types of epileptic seizures: Partial epileptic seizures (Type I), Generalized epileptic seizures (Type II) and unclassified epileptic seizures (Type III). 28 day adjusted seizure frequency for all seizure types was calculated for treatment period by dividing the number of targeted seizures by the number of days for which the DRC was completed for treatment period and multiplying the resulting value by 28. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment Period.

End point type	Secondary

End point timeframe:

During the 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: seizures per 28 days				
median (full range (min-max))	7.17 (1.0 to 317.0)	5.93 (0.0 to 123.7)	4.19 (0.0 to 269.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who are seizure free (partial, all epileptic seizures) during the 12-week Treatment Period

End point title	Percentage of participants who are seizure free (partial, all epileptic seizures) during the 12-week Treatment Period

End point description:

Participants were defined as seizure free, if they did not have missing diary days and no reported seizures during the Treatment Period. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment Period.

End point type	Secondary

End point timeframe:

During the 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: percentage of participants				
number (not applicable)				
All epileptic seizures	0	4.6	6.8	
Partial onset seizures	0	4.6	6.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 1st partial seizure during the 12-week Treatment Period

End point title	Time to 1st partial seizure during the 12-week Treatment Period

End point description:

The evaluation of time to 1st partial seizure was based on the relative day of occurrence of the 1st partial seizure during the Treatment Period. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment Period.

End point type	Secondary

End point timeframe:

During the 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: days				
median (confidence interval 95%)	3 (2 to 3)	5 (3 to 6)	6 (5 to 8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 5th partial seizure during the 12-week Treatment Period

End point title	Time to 5th partial seizure during the 12-week Treatment Period

End point description:

The evaluation of time to 5th partial seizure was based on the relative day of occurrence of the 5th partial seizure during the Treatment Period. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment Period.

End point type	Secondary

End point timeframe:

During the 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: days				
median (confidence interval 95%)	17 (15 to 21)	28 (23 to 36)	32 (29 to 38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 10th partial seizure during the 12-week Treatment Period

End point title	Time to 10th partial seizure during the 12-week Treatment Period

End point description:

The evaluation of time to 10th partial seizure was based on the relative day of occurrence of the 10th partial seizure during the Treatment Period. The FAS consisted of all randomized study participants who received at least 1 dose of IMP and had at least 1 post Baseline seizure DRC data during the Treatment

Period. Here, '99999' signifies that Upper limit of 95% Confidence interval (CI) was not calculated due to less number of participants with events.

End point type	Secondary

End point timeframe:

During the 12-week Treatment Period

End point values	Placebo	BRV 50 mg/day	BRV 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	147	151	148	
Units: days				
median (confidence interval 95%)	43 (32 to 52)	59 (48 to 76)	69 (59 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Brivaracetam plasma concentration

End point title	Brivaracetam plasma concentration[8]

End point description:

Blood samples were collected at indicated time points for the 50mg/day and 200mg/day groups to determine the brivaracetam plasma concentration. Participants of arm 'BRV 200 mg/day' received BRV 200 mg/day until Week 12 only and 150 mg/day during the Transition Period at Week 14. Therefore, the data is reported according to the dosage information at specified time point. As per planned analysis, one blood sample was collected for BRV plasma levels during each dosing interval between 0 to 4 hours, 4 to 8 hours, and 8 to 12 hours postdose. The Pharmacokinetic Per-Protocol Set (PK-PPS) consisted of all study participants who took at least 1 dose of BRV and for whom at least 1 valid BRV plasma concentration time and dosing information were available. Here, 'n' signifies participants who were evaluable at specified time points. Here, 99999 signifies that 0 participants were analyzed at specified time point.

End point type	Secondary

End point timeframe:

Plasma samples were collected at >0-4hours, >4-8hours, >8hours in weeks 2, 4, 8, 12, and 14

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to be reported for Brivaracetam arms only.

End point values	BRV 50 mg/day	BRV 200 mg/day	BRV 150 mg/day	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	150	146	128	
Units: microgram/ millilitre (ug/mL)				
geometric mean (geometric coefficient of variation)				
Week 2: > 0 - 4 hours (n= 120, 99, 0)	0.68556 (± 95.6)	3.4340 (± 42.5)	99999 (± 99999)	
Week 2: > 4 - 8 hours (n= 18, 27, 0)	0.66523 (± 38.6)	2.0615 (± 334.4)	99999 (± 99999)	
Week 2: > 8 hours (n= 8, 15, 0)	0.18427 (± 979.4)	1.2144 (± 100.1)	99999 (± 99999)	

Week 4: > 0 - 4 hours (n= 118,101, 0)	0.75902 (± 88.8)	3.0038 (± 120.2)	99999 (± 99999)	
Week 4: > 4 - 8 hours (n= 18, 31, 0)	0.64781 (± 39.2)	2.8516 (± 43.2)	99999 (± 99999)	
Week 4: > 8 hours (n= 7, 7, 0)	0.39652 (± 54.7)	1.1054 (± 74.4)	99999 (± 99999)	
Week 8: > 0 - 4 hours (n= 115, 102, 0)	0.76942 (± 87.3)	2.9983 (± 127.7)	99999 (± 99999)	
Week 8: > 4 - 8 hours (n= 19, 24, 0)	0.76172 (± 34.0)	2.7030 (± 54.9)	99999 (± 99999)	
Week 8: > 8 hours (n= 7, 9, 0)	0.27840 (± 10.9)	1.5590 (± 67.7)	99999 (± 99999)	
Week 12: > 0 - 4 hours (n= 98, 97, 0)	0.77400 (± 89.5)	3.2508 (± 121.1)	99999 (± 99999)	
Week 12: > 4 - 8 hours (n=28, 29, 0)	0.65274 (± 39.4)	1.6017 (± 838.9)	99999 (± 99999)	
Week 12: > 8 hours (n= 10, 9, 0)	0.18229 (± 579.5)	1.5001 (± 45.4)	99999 (± 99999)	
Week 14 (Transition):> 0 - 4 hours (n= 106, 0, 95)	0.75949 (± 85.3)	99999 (± 99999)	2.4989 (± 54.8)	
Week 14 (Transition):> 4 - 8 hours (n= 15, 0, 28)	0.75692 (± 34.6)	99999 (± 99999)	1.4383 (± 309.5)	
Week 14 (Transition):> 8 hours (n= 7, 0, 5)	0.41286 (± 66.4)	99999 (± 99999)	0.82681 (± 30.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From start of the Treatment Period (Week 0) until Safety Visit (up to Week 18); only for OLTP- From last visit of Transition Period to beginning of MAP (up to 4 Years 10 Months)

Adverse event reporting additional description:

TEAEs were defined as AEs which had onset on or after the first dose of investigational medicinal product (IMP). The Safety Set (SS) included all randomized participants who took at least 1 dose of study medication. As per planned analysis, safety data for all study periods was combined excluding Open-Label Temporary period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching Placebo as film-coated tablets, administered orally, twice daily (bid), during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered long-term follow-up (LTFU) study (EP0085 (NCT03250377)) or managed access program (MAP), the same matching Placebo dose was kept during 2 weeks of Transition Period and brivaracetam (BRV) 100 milligrams/day (mg/day) in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received the same Placebo dose for 4 weeks.

Reporting group title	BRV 50 mg/day

Reporting group description:

Participants received BRV 50 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered the LTFU study or MAP received BRV 50 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 25 mg/day for 1 week followed by Placebo for 3 weeks.

Reporting group title	BRV 50 mg/day to OLTP BRV

Reporting group description:

Participants who received BRV 50 mg/day during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during Open-Label Temporary Period (OLTP). BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

Reporting group title	Placebo to OLTP BRV

Reporting group description:

Participants who received Placebo during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during OLTP. BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

Reporting group title	BRV 200 mg/day to OLTP BRV

Reporting group description:

Participants who received BRV 200 mg/day during Treatment Period and were eligible to enter MAP received BRV 100 mg/day due to delayed importation of medication during Open-Label Temporary Period (OLTP). BRV dose might be adjusted for an individual participant (between 50 mg/day to 200 mg/day) during the OLTP. The period was defined from immediately after the last visit of the Transition Period (Week 14) and until a visit when the participant could convert to MAP.

Reporting group title	BRV 200 mg/day

Reporting group description:

Participants received BRV 200 mg/day as film-coated tablets, administered orally, bid, during 12 weeks of Treatment Period. At the end of the Treatment Period, participants who entered LTFU study or MAP

received BRV 150 mg/day during 2 weeks of Transition Period and BRV 100 mg/day in LTFU study or MAP. Participants who did not enter the LTFU study or MAP had 4 weeks Down-Titration Period followed by a Study Drug-Free Period (no drug for 2 weeks). During Down-Titration Period, participants received BRV 150 mg/day for 1 week followed by BRV 100 mg/day for 1 week, followed by BRV 50 mg/day for 1 week, followed by BRV 25 mg/day for 1 week.

Serious adverse events	Placebo	BRV 50 mg/day	BRV 50 mg/day to OLTP BRV
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 149 (0.67%)	2 / 151 (1.32%)	0 / 68 (0.00%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Near drowning			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicogenic headache			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drowning			
subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Postictal psychosis			

subjects affected / exposed	0 / 149 (0.00%)	1 / 151 (0.66%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Corona virus infection			
subjects affected / exposed	1 / 149 (0.67%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 149 (0.00%)	0 / 151 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo to OLTP BRV	BRV 200 mg/day to OLTP BRV	BRV 200 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 64 (4.69%)	2 / 74 (2.70%)	4 / 148 (2.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Near drowning			
subjects affected / exposed	1 / 64 (1.56%)	0 / 74 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 64 (1.56%)	1 / 74 (1.35%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 64 (0.00%)	1 / 74 (1.35%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervicogenic headache			

subjects affected / exposed	0 / 64 (0.00%)	1 / 74 (1.35%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 64 (3.13%)	0 / 74 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drowning			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 74 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	1 / 64 (1.56%)	0 / 74 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Postictal psychosis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Corona virus infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 74 (1.35%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	BRV 50 mg/day	BRV 50 mg/day to OLTP BRV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 149 (26.17%)	42 / 151 (27.81%)	4 / 68 (5.88%)
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 149 (7.38%)	11 / 151 (7.28%)	0 / 68 (0.00%)
occurrences (all)	15	16	0
Dizziness			

subjects affected / exposed	6 / 149 (4.03%)	17 / 151 (11.26%)	0 / 68 (0.00%)
occurrences (all)	6	19	0
Somnolence			
subjects affected / exposed	12 / 149 (8.05%)	15 / 151 (9.93%)	0 / 68 (0.00%)
occurrences (all)	14	15	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 149 (4.70%)	10 / 151 (6.62%)	0 / 68 (0.00%)
occurrences (all)	8	14	0
Nasopharyngitis			
subjects affected / exposed	10 / 149 (6.71%)	7 / 151 (4.64%)	4 / 68 (5.88%)
occurrences (all)	11	10	5

Non-serious adverse events	Placebo to OLTP BRV	BRV 200 mg/day to OLTP BRV	BRV 200 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 64 (4.69%)	4 / 74 (5.41%)	54 / 148 (36.49%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	7 / 148 (4.73%)
occurrences (all)	0	0	8
Dizziness			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	21 / 148 (14.19%)
occurrences (all)	0	0	24
Somnolence			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	28 / 148 (18.92%)
occurrences (all)	0	0	29
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 74 (0.00%)	8 / 148 (5.41%)
occurrences (all)	0	0	9
Nasopharyngitis			
subjects affected / exposed	3 / 64 (4.69%)	4 / 74 (5.41%)	10 / 148 (6.76%)
occurrences (all)	3	4	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2019	Protocol amendment 3 (dated 01 Feb 2019) was a substantial amendment. A total of 158 participants were enrolled at the time of this amendment. The following changes were made: • Included non-Asian study participants • Included EU countries • An increase of levetiracetam (LEV) limitation from 20% to 30%, and the establishment of consistency between the protocol and Case Report Form (CRF) Completion Guidelines. Global changes to the protocol during this amendment included the inclusion of non-Asian study participants and an increase of prior LEV limitation from 20% to 30%.
10 January 2020	Protocol amendment 4 (dated 10 Jan 2020) was a substantial amendment. A total of 272 participants were enrolled at the time of this amendment. The following changes were made: • Reduced the total sample size from 504 to 444 study participants • Reduced the minimum required number of Japanese study participants • Added China Mainland to the list of participating countries and regions • Updated exclusion criteria 20 and 27 • Provided clarifications around the LEV use and LEV cap • Updated the study contact information • Updated the company designation from SPRL to SRL Additionally, minor administrative edits including typographical changes for formatting and/or spelling errors have been made Global changes to the protocol during this amendment included a change of "exploratory safety variable" language to "other safety variable" throughout the protocol. The pharmacodynamic variables were also removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported