



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 | v1 |
| This version publication date | 31 December 2022 |
| First version publication date | 31 December 2022 |

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 | 21.9 | 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 | 21.6 | | |

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 | 3.1 | 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 | 1.4 | | |

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: seizure frequency 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 | = 0.0004 ^[5] |
| Method | ANCOVA |
| Parameter estimate | Percent reduction over Placebo |
| Point estimate | 24.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.8 |
| upper limit | 35.6 |

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 | 33.3 |
| 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: 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: 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- |
|-----------------|--|

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: 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: seizure frequency 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 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

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 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.

| Serious adverse events | Placebo | BRV 50 mg/day | BRV 200 mg/day |
|--|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 149 (0.67%) | 2 / 151 (1.32%) | 4 / 148 (2.70%) |
| 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 / 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 |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |
| Cervicogenic headache | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |
| General disorders and administration site conditions | | | |
| Drowning | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 1 / 151 (0.66%) | 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 / 1 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |
| Social circumstances | | | |
| Miscarriage of partner | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 / 149 (0.00%) | 0 / 151 (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 | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |
| Psychiatric disorders | | | |
| Postictal psychosis | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 1 / 151 (0.66%) | 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 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |
| Infections and infestations | | | |
| Corona virus infection | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 149 (0.67%) | 0 / 151 (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 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 149 (0.00%) | 0 / 151 (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 |

| Serious adverse events | Placebo to OLTP BRV | BRV 50 mg/day to OLTP BRV | BRV 200 mg/day to OLTP BRV |
|--|---------------------|---------------------------|----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 68 (0.00%) | 1 / 74 (1.35%) |
| 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 / 68 (0.00%) | 0 / 74 (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 |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 2 / 64 (3.13%) | 0 / 68 (0.00%) | 0 / 74 (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 |
| Cervicogenic headache | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Drowning | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (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 / 68 (0.00%) | 0 / 74 (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 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (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 | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 68 (0.00%) | 0 / 74 (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 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 64 (1.56%) | 0 / 68 (0.00%) | 0 / 74 (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 |
| Psychiatric disorders | | | |
| Postictal psychosis | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (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 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (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 / 68 (0.00%) | 0 / 74 (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%) | 0 / 68 (0.00%) | 1 / 74 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| 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 200 mg/day |
|--|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 149 (26.17%) | 42 / 151 (27.81%) | 54 / 148 (36.49%) |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 12 / 149 (8.05%) | 15 / 151 (9.93%) | 28 / 148 (18.92%) |
| occurrences (all) | 14 | 15 | 29 |
| Dizziness | | | |
| subjects affected / exposed | 6 / 149 (4.03%) | 17 / 151 (11.26%) | 21 / 148 (14.19%) |
| occurrences (all) | 6 | 19 | 24 |
| Headache | | | |
| subjects affected / exposed | 11 / 149 (7.38%) | 11 / 151 (7.28%) | 7 / 148 (4.73%) |
| occurrences (all) | 15 | 16 | 8 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 149 (4.70%) | 10 / 151 (6.62%) | 8 / 148 (5.41%) |
| occurrences (all) | 8 | 14 | 9 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 10 / 149 (6.71%) | 7 / 151 (4.64%) | 10 / 148 (6.76%) |
| occurrences (all) | 11 | 10 | 10 |

| Non-serious adverse events | Placebo to OLTP BRV | BRV 50 mg/day to OLTP BRV | BRV 200 mg/day to OLTP BRV |
|--|---------------------|---------------------------|----------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 3 / 64 (4.69%) | 4 / 68 (5.88%) | 4 / 74 (5.41%) |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 64 (0.00%) | 0 / 68 (0.00%) | 0 / 74 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 64 (4.69%) | 4 / 68 (5.88%) | 4 / 74 (5.41%) |
| occurrences (all) | 3 | 5 | 4 |

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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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