# Clinical trial results:
# A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of Brivaracetam in subjects (16 to 80 years old) with partial onset seizures

## Summary

| | |
|---|---|
| EudraCT number | 2010-019361-28 |
| Trial protocol | BE DE CZ ES IT GB SE FR FI AT NL EE LT LV HU BG RO |
| Global end of trial date | 22 May 2014 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 28 June 2016 |
| First version publication date | 30 July 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | N01358 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01261325 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | UCB BIOSCIENCES Inc. |
| Sponsor organisation address | 8010 Arco Corporate Drive, Raleigh, United States, 27617 |
| Public contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

**Results analysis stage**

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 30 June 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 May 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of brivaracetam (BRV) at doses of 100 and 200mg/day compared with placebo (PBO) as adjunctive treatment in adult focal epilepsy subjects with partial-onset seizures (POS) not fully controlled despite current treatment with 1 or 2 concomitant antiepileptic drugs (AEDs).

Protection of trial subjects:

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Background therapy:

N/A

Evidence for comparator:

N/A

| | |
|---|---|
| Actual start date of recruitment | 10 December 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 49 |
| Country: Number of subjects enrolled | Sweden: 15 |
| Country: Number of subjects enrolled | Taiwan: 18 |
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Country: Number of subjects enrolled | United States: 165 |
| Country: Number of subjects enrolled | Austria: 7 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Brazil: 20 |
| Country: Number of subjects enrolled | Bulgaria: 8 |
| Country: Number of subjects enrolled | Canada: 22 |
| Country: Number of subjects enrolled | Czech Republic: 36 |
| Country: Number of subjects enrolled | Estonia: 23 |
| Country: Number of subjects enrolled | Finland: 7 |
| Country: Number of subjects enrolled | France: 13 |

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Hong Kong: 4 |
| Country: Number of subjects enrolled | Hungary: 20 |
| Country: Number of subjects enrolled | India: 36 |
| Country: Number of subjects enrolled | Italy: 52 |
| Country: Number of subjects enrolled | Japan: 7 |
| Country: Number of subjects enrolled | Korea, Republic of: 26 |
| Country: Number of subjects enrolled | Latvia: 9 |
| Country: Number of subjects enrolled | Lithuania: 11 |
| Country: Number of subjects enrolled | Mexico: 66 |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Poland: 65 |
| Country: Number of subjects enrolled | Puerto Rico: 1 |
| Country: Number of subjects enrolled | Russian Federation: 28 |
| Worldwide total number of subjects | 768 |
| EEA total number of subjects | 375 |

Notes:

| **Subjects enrolled per age group** | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 20 |
| Adults (18-64 years) | 725 |
| From 65 to 84 years | 23 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment for the N01358 study began in December 2010. The study concluded in May 2014.

### Pre-assignment

Screening details:

The Participant Flow and Baseline Demographics data is taken from the Randomized Set (RS). The RS consists of all subjects who were randomized.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall 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:

Matching placebo tablets administered twice daily

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PBO |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral film-coated tablets taken twice a day.

| | |
|---|---|
| **Arm title** | Brivaracetam 100 mg/day |

Arm description:

Brivaracetam 50 mg administered twice daily.

| | |
|---|---|
| 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:

Oral film-coated tablets of BRV 10mg, BRV 25mg, or BRV 50mg taken orally twice a day.

| | |
|---|---|
| **Arm title** | Brivaracetam 200 mg/day |

Arm description:

Brivaracetam 100 mg administered twice daily

| | |
|---|---|
| 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:
Oral film-coated tablets of BRV 10mg, BRV 25mg, or BRV 50mg taken orally twice a day.

| **Number of subjects in period 1** | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day |
|---|---|---|---|
| Started | 263 | 254 | 251 |
| Completed | 246 | 225 | 225 |
| Not completed | 17 | 29 | 26 |
| Protocol deviation | - | 3 | 1 |
| Randomized by mistake | - | 1 | - |
| Lack of efficacy | 1 | 1 | - |
| SAE, non-fatal | 1 | 5 | 1 |
| AE, serious fatal | - | - | 2 |
| Consent withdrawn by subject | 2 | 2 | 4 |
| Randomized in error | - | - | 1 |
| Erroneously Randomized | 1 | - | - |
| SAE, non-fatal + AE, non-serious non-fatal | - | 1 | 1 |
| Non Compliance | 2 | - | - |
| Screen Failure | 1 | - | - |
| AE, non-serious non-fatal | 9 | 15 | 13 |
| Lost to follow-up | - | 1 | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo tablets administered twice daily | |
| Reporting group title | Brivaracetam 100 mg/day |
| Reporting group description: | |
| Brivaracetam 50 mg administered twice daily. | |
| Reporting group title | Brivaracetam 200 mg/day |
| Reporting group description: | |
| Brivaracetam 100 mg administered twice daily | |

| Reporting group values | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day |
|---|---|---|---|
| Number of subjects | 263 | 254 | 251 |
| Age Categorical | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: Subjects | | | |
| 12-<18 | 7 | 6 | 7 |
| 18-<65 | 250 | 237 | 238 |
| 65-<85 | 6 | 11 | 6 |
| Age Continuous | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: years | | | |
| arithmetic mean | 39.8 | 39 | 39.7 |
| standard deviation | ± 12.8 | ± 13.4 | ± 12.8 |
| Gender Categorical | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: Subjects | | | |
| Male | 135 | 102 | 134 |
| Female | 128 | 152 | 117 |
| Racial Group | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 10 | 8 | 11 |
| Asian | 32 | 32 | 29 |
| Black or African American | 11 | 8 | 7 |
| White | 190 | 183 | 183 |
| Other | 17 | 21 | 18 |
| Missing | 3 | 2 | 3 |
| Weight | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: kilograms | | | |
| median | 76.1 | 74.1 | 75.5 |
| standard deviation | ± 19.9 | ± 16.8 | ± 19 |

| | | | |
|---|---|---|---|
| Height | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: centimeters | | | |
| arithmetic mean | 168.4 | 166.6 | 168.7 |
| standard deviation | ± 10 | ± 9.8 | ± 9.9 |
| BMI | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: kg/m^2 | | | |
| arithmetic mean | 26.6 | 26.7 | 26.4 |
| standard deviation | ± 5.7 | ± 5.6 | ± 6 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 768 | | |
| Age Categorical | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: Subjects | | | |
| 12-<18 | 20 | | |
| 18-<65 | 725 | | |
| 65-<85 | 23 | | |
| Age Continuous | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender Categorical | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: Subjects | | | |
| Male | 371 | | |
| Female | 397 | | |
| Racial Group | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 29 | | |
| Asian | 93 | | |
| Black or African American | 26 | | |
| White | 556 | | |
| Other | 56 | | |
| Missing | 8 | | |
| Weight | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: kilograms | | | |
| median | | | |
| standard deviation | - | | |
| Height | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: centimeters | | | |

| | | | |
|---|---|---|---|
| arithmetic mean<br>standard deviation | -<br> | | |
| BMI | | | |
| This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study. | | | |
| Units: kg/m^2<br>arithmetic mean<br>standard deviation | -<br> | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: Matching placebo tablets administered twice daily | |
| Reporting group title | Brivaracetam 100 mg/day |
| Reporting group description: Brivaracetam 50 mg administered twice daily. | |
| Reporting group title | Brivaracetam 200 mg/day |
| Reporting group description: Brivaracetam 100 mg administered twice daily | |

### Primary: Percent reduction over placebo for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration

| | |
|---|---|
| End point title | Percent reduction over placebo for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration |
| End point description: Primary endpoint: United States of America (FDA) | |
| End point type | Primary |
| End point timeframe: 12 week Treatment Period | |

| End point values | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[1] | 252[2] | 249[3] | |
| Units: Percentage of reduction | | | | |
| number (not applicable) | | | | |
| percentage | 0 | 22.8 | 23.2 | |

Notes:

[1] - Intent-to-Treat (ITT) Population

[2] - Intent-to-Treat (ITT) Population

[3] - Intent-to-Treat (ITT) Population

### Statistical analyses

| Statistical analysis title | Statistical Analysis - BRV 100 mg/ day v Placebo |
|---|---|
| Statistical analysis description: Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure. | |
| Comparison groups | Brivaracetam 100 mg/day v Placebo |
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | other[4] |
| P-value | < 0.001 [5] |

| | |
|---|---|
| Method | ANCOVA |
| Parameter estimate | Percent reduction over PBO |
| Point estimate | 22.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.3 |
| upper limit | 31.2 |

Notes:

[4] - ANCOVA (analysis of covariance), with Log-transformed Treatment Period 28-day adjusted POS frequency as the outcome, and effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[5] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

| **Statistical analysis title** | Statistical Analysis - BRV 200 mg/ day v Placebo |
|---|---|

Statistical analysis description:

Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.

| | |
|---|---|
| Comparison groups | Placebo v Brivaracetam 200 mg/day |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| P-value | < 0.001 [7] |
| Method | ANCOVA |
| Parameter estimate | Percent reduction over PBO |
| Point estimate | 23.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.8 |
| upper limit | 31.6 |

Notes:

[6] - ANCOVA (analysis of covariance), with Log-transformed Treatment Period 28-day adjusted POS frequency as the outcome, and effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[7] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

## Primary: 50% responder rate for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration

| | |
|---|---|
| End point title | 50% responder rate for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration |

End point description:

Primary Endpoint: European Regulatory Authorities

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Baseline to 12 week Treatment Period

| End point values | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[8] | 252[9] | 249[10] | |
| Units: Percentage of responders | | | | |
| number (not applicable) | | | | |
| Responders | 21.6 | 38.9 | 37.8 | |
| Non-Responders | 78.4 | 61.1 | 62.2 | |

Notes:

[8] - Intent-to-Treat (ITT) Population

[9] - Intent-to-Treat (ITT) Population

[10] - Intent-to-Treat (ITT) Population

## Statistical analyses

| Statistical analysis title | Statistical Analysis - BRV 100 mg/ day v Placebo |
|---|---|

Statistical analysis description:

Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.

| | |
|---|---|
| Comparison groups | Brivaracetam 100 mg/day v Placebo |
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | other[11] |
| P-value | < 0.001 [12] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (BRV versus PBO) |
| Point estimate | 2.39 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.6 |
| upper limit | 3.6 |

Notes:

[11] - Logistic regression model, with effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[12] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

| Statistical analysis title | Statistical Analysis - BRV 200 mg/ day v Placebo |
|---|---|

Statistical analysis description:

Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.

| | |
|---|---|
| Comparison groups | Brivaracetam 200 mg/day v Placebo |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | other[13] |
| P-value | < 0.001 [14] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (BRV versus PBO) |
| Point estimate | 2.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.5 |

| | |
|---|---|
| upper limit | 3.3 |

Notes:

[13] - Logistic regression model, with effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[14] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

## Secondary: Percent reduction in partial onset seizure (Type I) frequency from the Baseline to the Treatment Period

| | |
|---|---|
| End point title | Percent reduction in partial onset seizure (Type I) frequency from the Baseline to the Treatment Period |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline to 12 week Treatment Period

| **End point values** | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[15] | 252[16] | 249[17] | |
| Units: percentage of reduction | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| median (Q1 - Q3) | 17.6 (-8.3 to 46) | 37.2 (0.1 to 69.4) | 35.6 (4.8 to 66.2) | |

Notes:

[15] - Intent-to-Treat (ITT) Population

[16] - Intent-to-Treat (ITT) Population

[17] - Intent-to-Treat (ITT) Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis - BRV 100 mg/ day v Placebo |
|---|---|

Statistical analysis description:

Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test. Hodges-Lehmann non-parametric effect estimates and corresponding two-sided 95% confidence intervals are provided for the effect difference between each BRV treatment group and placebo.

| | |
|---|---|
| Comparison groups | Brivaracetam 100 mg/day v Placebo |
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | other[18] |
| P-value | < 0.001 [19] |
| Method | Hodges-Lehmann non-parametric analysis |
| Parameter estimate | Median difference vs placebo |
| Point estimate | 15.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.6 |
| upper limit | 24.2 |

Notes:

[18] - Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test.

[19] - p-values not adjusted for multiplicity.

| **Statistical analysis title** | Statistical Analysis - BRV 200 mg/ day v Placebo |
|---|---|

Statistical analysis description:

Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test. Hodges-Lehmann non-parametric effect estimates and corresponding two-sided 95% confidence intervals are provided for the effect difference between each BRV treatment group and placebo.

| | |
|---|---|
| Comparison groups | Placebo v Brivaracetam 200 mg/day |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | other[20] |
| P-value | < 0.001 [21] |
| Method | Hodges-Lehmann non-parametric analysis |
| Parameter estimate | Median difference vs placebo |
| Point estimate | 18.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 10.4 |
| upper limit | 26.4 |

Notes:

[20] - Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test.

[21] - p-values not adjusted for multiplicity.

## Secondary: Categorized percent reduction form Baseline in seizure frequency for partial onset seizure (Type I) over the Treatment Period

| | |
|---|---|
| End point title | Categorized percent reduction form Baseline in seizure frequency for partial onset seizure (Type I) over the Treatment Period |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline to 12 week Treatment Period

| **End point values** | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[22] | 252[23] | 249[24] | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| <-25 % | 16.6 | 14.3 | 10.8 | |
| -25 % to <25 % | 40.5 | 28.6 | 29.3 | |
| 25 % to <50 % | 21.2 | 18.3 | 22.1 | |
| 50 % to <75 % | 13.9 | 19 | 18.1 | |
| 75 % to <100 % | 6.9 | 13.9 | 13.7 | |
| 100 % | 0.8 | 6 | 6 | |

Notes:
[22] - Intent-to-Treat (ITT) Population
[23] - Intent-to-Treat (ITT) Population
[24] - Intent-to-Treat (ITT) Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Seizure freedom rate (all seizure types) during the 12-week Treatment Period

| End point title | Seizure freedom rate (all seizure types) during the 12-week Treatment Period |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
12 week Treatment Period

| End point values | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[25] | 252[26] | 249[27] | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Seizure free | 0.8 | 5.2 | 4 | |
| No seizures but discontinued | 0.4 | 1.2 | 1.2 | |
| Not seizure free | 98.8 | 93.7 | 94.8 | |

Notes:
[25] - Intent-to-Treat (ITT) Population
[26] - Intent-to-Treat (ITT) Population
[27] - Intent-to-Treat (ITT) Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: All seizure frequency (Type I + II + III) during the 12-week Treatment Period

| End point title | All seizure frequency (Type I + II + III) during the 12-week Treatment Period |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
12 week Treatment Period

| End point values | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[28] | 252[29] | 249[30] | |
| Units: seizure frequency | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| median (Q1 - Q3) | 8.7 (4.3 to 23.6) | 6.3 (2.7 to 17.8) | 5.8 (2.3 to 14.2) | |

Notes:

[28] - Intent-to-Treat Population

[29] - Intent-to-Treat Population

[30] - Intent-to-Treat Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to the first Type I seizure during the Treatment Period

| End point title | Time to the first Type I seizure during the Treatment Period |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

12 week Treatment Period

| End point values | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[31] | 252[32] | 249[33] | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| median days (CI) | 3 (2 to 3) | 5 (3 to 7) | 6 (4 to 7) | |

Notes:

[31] - Intent-to-Treat (ITT) Population

[32] - Intent-to-Treat (ITT) Population

[33] - Intent-to-Treat (ITT) Population

### Statistical analyses

| Statistical analysis title | Statistical Analysis - Brivaracetam 100 mg/ day |
|---|---|

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

| Comparison groups | Brivaracetam 100 mg/day v Placebo |
|---|---|
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | other[34] |
| P-value | < 0.001 |
| Method | Semi-parametric hazards regression model |

| | |
|---|---|
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.82 |

Notes:

[34] - N/A

| **Statistical analysis title** | Statistical Analysis - Brivaracetam 200 mg/ day |
|---|---|

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

| | |
|---|---|
| Comparison groups | Brivaracetam 200 mg/day v Placebo |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | other[35] |
| P-value | < 0.001 |
| Method | Semi-parametric hazards regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.79 |

Notes:

[35] - N/A

## Secondary: Time to the fifth Type I seizure during the Treatment Period

| | |
|---|---|
| End point title | Time to the fifth Type I seizure during the Treatment Period |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

12 week Treatment Period

| **End point values** | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[36] | 252[37] | 249[38] | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| median days (CI) | 16 (12 to 19) | 21 (17 to 25) | 23 (20 to 26) | |

Notes:

[36] - Intent-to-Treat (ITT) Population

[37] - Intent-to-Treat (ITT) Population

[38] - Intent-to-Treat (ITT) Population

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis - Brivaracetam 200 mg/ day |
|---|---|

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

| | |
|---|---|
| Comparison groups | Brivaracetam 200 mg/day v Placebo |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | other[39] |
| P-value | < 0.001 |
| Method | Semi-parametric hazards regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 0.71 |

Notes:

[39] - N/A

| **Statistical analysis title** | Statistical Analysis - Brivaracetam 100 mg/ day |
|---|---|

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

| | |
|---|---|
| Comparison groups | Brivaracetam 100 mg/day v Placebo |
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | other[40] |
| P-value | < 0.001 |
| Method | Semi-parametric hazards regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.53 |
| upper limit | 0.8 |

Notes:

[40] - N/A

## Secondary: Time to the tenth Type I seizure during the Treatment Period

| End point title | Time to the tenth Type I seizure during the Treatment Period |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

12 week Treatment Period

| End point values | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 259[41] | 252[42] | 249[43] | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| median days (CI) | 32 (24 to 36) | 37 (29 to 46) | 43 (36 to 49) | |

Notes:

[41] - Intent-to-Treat (ITT) Population

[42] - Intent-to-Treat (ITT) Population

[43] - Intent-to-Treat (ITT) Population

### Statistical analyses

| Statistical analysis title | Statistical Analysis - Brivaracetam 100 mg/ day |
|---|---|
| Comparison groups | Placebo v Brivaracetam 100 mg/day |
| Number of subjects included in analysis | 511 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.009 |
| Method | Semi-parametric hazards regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 0.93 |

| Statistical analysis title | Statistical Analysis - Brivaracetam 200 mg/ day |
|---|---|
| Comparison groups | Placebo v Brivaracetam 200 mg/day |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | Semi-parametric hazards regression model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.68 |
| Confidence interval | |

| | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 0.85 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent Adverse Events (TEAE) were collected during the study, which began in Dec 2010 and concluded in May 2014.

Adverse event reporting additional description:

TEAEs are comprised of the Safety Population, which consists of all randomized subjects who receive at least 1 dose of study medication.

The Non-serious Adverse Events section represents a >= 5% threshold of subjects experiencing Non-serious TEAEs in any treatment group and not the total population.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Matching placebo tablets administered twice daily

| | |
|---|---|
| Reporting group title | Brivaracetam 100 mg/day |

Reporting group description:

Brivaracetam 50 mg  administered twice daily.

| | |
|---|---|
| Reporting group title | Brivaracetam 200 mg/day |

Reporting group description:

Brivaracetam 100 mg  administered twice daily

| Serious adverse events | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 261 (3.45%) | 8 / 253 (3.16%) | 8 / 250 (3.20%) |
| number of deaths (all causes) | 0 | 0 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (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 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 2 / 250 (0.80%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Craniocerebral injury | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 0 / 253 (0.00%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 0 / 253 (0.00%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (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 |
| Traumatic renal injury | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (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 |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (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 |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (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 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Thymoma | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (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 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (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 |

| | | | |
|---|---|---|---|
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (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 | | | |
| Grand mal convulsion | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure cluster | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 0 / 253 (0.00%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (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 |
| Postictal state | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 0 / 253 (0.00%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Sudden unexplained death in epilepsy | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 0 / 253 (0.00%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|---|---|---|
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Psychiatric disorders | | | |
| Adjustment disorder | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agitation | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conversion disorder | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epileptic psychosis | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 1 / 253 (0.40%) | 0 / 250 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 261 (0.00%) | 0 / 253 (0.00%) | 1 / 250 (0.40%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis viral | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (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 | | | |
| subjects affected / exposed | 1 / 261 (0.38%) | 0 / 253 (0.00%) | 0 / 250 (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 |

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

| **Non-serious adverse events** | Placebo | Brivaracetam 100 mg/day | Brivaracetam 200 mg/day |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 61 / 261 (23.37%) | 96 / 253 (37.94%) | 97 / 250 (38.80%) |
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 20 / 261 (7.66%) | 49 / 253 (19.37%) | 42 / 250 (16.80%) |
| occurrences (all) | 20 | 53 | 43 |
| Dizziness | | | |
| subjects affected / exposed | 13 / 261 (4.98%) | 26 / 253 (10.28%) | 36 / 250 (14.40%) |
| occurrences (all) | 14 | 27 | 38 |
| Headache | | | |
| subjects affected / exposed | 22 / 261 (8.43%) | 17 / 253 (6.72%) | 20 / 250 (8.00%) |
| occurrences (all) | 30 | 18 | 21 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 10 / 261 (3.83%) | 19 / 253 (7.51%) | 29 / 250 (11.60%) |
| occurrences (all) | 10 | 19 | 32 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 8 / 261 (3.07%) | 13 / 253 (5.14%) | 2 / 250 (0.80%) |
| occurrences (all) | 8 | 13 | 2 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 15 September 2011 | The protocol was amended for the following reasons:<br><br>•Procedures for reporting SAEs were updated to implement the Food and Drug Administration (FDA) Final Rule requirements (Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans, 21 Code of Federal Regulations Parts 312 and 320, 2010).<br><br>•The Columbia-Suicide Severity Rating Scale (C-SSRS) was added to address the requirement of the FDA that prospective assessments for suicidality be included in clinical studies involving all drugs for neurological indications.<br><br>There were also a few minor changes made to the protocol to update the name of the company, name and address of Study Physician, and SAE reporting contact numbers, and to clarify some study conduct details. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported