



Clinical trial results:

An International, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexible Dose Study: Evaluation of the Safety and Efficacy of Brivaracetam in Subjects (16 to 70 Years Old) Suffering From Localization-related or Generalized Epilepsy

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2006-006346-34 |
| Trial protocol | BE CZ SE DE AT IT |
| Global end of trial date | 15 December 2008 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 22 October 2016 |
| First version publication date | 22 October 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | N01254 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00504881 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB Pharma S.A. |
| Sponsor organisation address | Allée de la Recherche 70, Brussels, Belgium, 1070 |
| Public contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 15, clinicaltrials@ucb.com |
| Scientific contact | Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 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 | 31 March 2009 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 December 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the safety and tolerability of brivaracetam (BRV) at the dose range from 20 to 150 mg/day in twice daily administration in subjects suffering from localization-related or generalized epilepsy not fully controlled despite optimal treatment with 1 to 3 concomitant antiepileptic drug(s) (AED[s]), compared to placebo (PBO).

Protection of trial subjects:

Standard measure to minimize pain and distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 15 October 2007 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 8 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Austria: 29 |
| Country: Number of subjects enrolled | Belgium: 21 |
| Country: Number of subjects enrolled | Czech Republic: 35 |
| Country: Number of subjects enrolled | Germany: 33 |
| Country: Number of subjects enrolled | Hong Kong: 11 |
| Country: Number of subjects enrolled | India: 65 |
| Country: Number of subjects enrolled | Italy: 23 |
| Country: Number of subjects enrolled | Korea, Republic of: 88 |
| Country: Number of subjects enrolled | Norway: 15 |
| Country: Number of subjects enrolled | Russian Federation: 51 |
| Country: Number of subjects enrolled | Singapore: 9 |
| Country: Number of subjects enrolled | South Africa: 2 |
| Country: Number of subjects enrolled | Sweden: 19 |
| Country: Number of subjects enrolled | Taiwan: 27 |
| Country: Number of subjects enrolled | Ukraine: 52 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 480 |
| EEA total number of subjects | 175 |

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) | 8 |
| Adults (18-64 years) | 468 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted in 15 countries. It started in October 2007 and concluded in December 2008.

Pre-assignment

Screening details:

The Participant Flow refers to the Randomized Set (RS).

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 | Investigator, Carer, Subject, Assessor |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Matching Placebo tablets administered twice a day

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

Dosage and administration details:

Matching Placebo to Brivaracetam tablets.

| | |
|------------------|--------------|
| Arm title | Brivaracetam |
|------------------|--------------|

Arm description:

A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day

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

Brivaracetam

- Pharmaceutical form: Film-coated tablet
- Route of Administration: Oral use
- Concentration: 10 mg and 25 mg tablets

| Number of subjects in period 1 | Placebo | Brivaracetam |
|--|---------|--------------|
| Started | 121 | 359 |
| Completed | 111 | 323 |
| Not completed | 10 | 36 |
| AE, serious fatal | - | 1 |
| Consent withdrawn by subject | 1 | 4 |
| Non-Compliance | 1 | - |
| No Birth Control | - | 1 |
| AE, non-serious non-fatal | 4 | 14 |
| AE of unknown type | 1 | - |
| Safety Visit not performed | - | 1 |
| Lost to follow-up | - | 2 |
| SAE, non-fatal | 2 | 6 |
| Lack of efficacy | 1 | 5 |
| SAE, non-fatal + AE, non-serious non-fatal | - | 2 |

Baseline characteristics

Reporting groups

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

Reporting group description:

Matching Placebo tablets administered twice a day

| | |
|-----------------------|--------------|
| Reporting group title | Brivaracetam |
|-----------------------|--------------|

Reporting group description:

A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day

| Reporting group values | Placebo | Brivaracetam | Total |
|------------------------|---------|--------------|-------|
| Number of subjects | 121 | 359 | 480 |
| Age categorical | | | |
| Units: Subjects | | | |
| < 18 years | 3 | 5 | 8 |
| 18 - < 65 years | 116 | 352 | 468 |
| 65 - < 85 years | 2 | 2 | 4 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 36.5 | 35.6 | - |
| standard deviation | ± 11.5 | ± 11.5 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 52 | 178 | 230 |
| Male | 69 | 181 | 250 |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Placebo |
| Reporting group description: Matching Placebo tablets administered twice a day | |
| Reporting group title | Brivaracetam |
| Reporting group description: A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day | |

Primary: Percentage of subjects with at least one Adverse Event during the 16-week Treatment Period

| | |
|-----------------|---|
| End point title | Percentage of subjects with at least one Adverse Event during the 16-week Treatment Period ^[1] |
|-----------------|---|

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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

End point timeframe:

Week 2 to the end of the Treatment Period (Week 16)

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 | Brivaracetam | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 121 | 359 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Percentage of participants | 66.1 | 66.6 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Partial Onset Seizure (Type I) frequency per week over the 16-week Treatment Period

| | |
|-----------------|---|
| End point title | Partial Onset Seizure (Type I) frequency per week over the 16-week Treatment Period |
|-----------------|---|

End point description:

Partial (Type I) seizures can be classified into one of the following three groups:

- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to generalized tonic-clonic convulsions.

Partial Onset Seizure (POS) frequency per week over the Treatment Period (TP) was calculated as:
 (Total Type I seizures over the TP)*7/(Total number of days with no missing seizure count in the TP)

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

End point timeframe:

Baseline (Week 0) to the end of the Treatment Period (Week 16)

| End point values | Placebo | Brivaracetam | | |
|---------------------------------------|------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: seizures per week | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Median (Q1 - Q3) | 1.86 (1 to 3.98) | 1.74 (0.86 to 4.04) | | |

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Statistical Analysis |
|----------------------------|----------------------|

Statistical analysis description:

ANCOVA on log-transformed partial seizure frequency per week over the treatment period, with log-transformed baseline seizure frequency per week as covariate, and including terms for treatment and stratification factors.

| | |
|---|--------------------------------|
| Comparison groups | Placebo v Brivaracetam |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.125 |
| Method | ANCOVA |
| Parameter estimate | Percent Reduction over Placebo |
| Point estimate | 7.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 15.9 |

Secondary: Responder rate for partial onset seizures (Type I) frequency per week over the 16-week Treatment Period

| | |
|-----------------|---|
| End point title | Responder rate for partial onset seizures (Type I) frequency per week over the 16-week Treatment Period |
|-----------------|---|

End point description:

The responder rate was presented as the percentage of responders and non-responders. A subject is a responder, if the subject has at least 50 % reduction in Partial Onset Seizure frequency per week from Baseline to Treatment Period. Subjects with zero seizure frequency per week at Baseline were considered as non-responders.

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

End point timeframe:

Baseline (Week 0) to the end of Treatment Period (Week 16)

| End point values | Placebo | Brivaracetam | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders | 16.7 | 30.3 | | |
| Non-Responders | 83.3 | 69.7 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure frequency (all seizure types) per week over the 16-week Treatment Period

| | |
|-----------------|--|
| End point title | Seizure frequency (all seizure types) per week over the 16-week Treatment Period |
|-----------------|--|

End point description:

There are three different types of seizures:

- Type I: Partial seizures
- Type II: Generalized seizures
- Type III: Unclassified epileptic seizures.

All seizure frequency per week over Treatment Period (TP) was calculated as: (Total number of seizures over the TP)*7/(Total number of days with no missing seizure count in the TP)

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

End point timeframe:

Baseline (Week 0) to the end of Treatment Period (Week 16)

| End point values | Placebo | Brivaracetam | | |
|---------------------------------------|------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: seizure frequency per week | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Median (Q1 - Q3) | 1.87 (1 to 4.59) | 1.74 (0.86 to 4.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline to the 16-week Treatment Period in Partial Onset Seizure (Type I) frequency per week

| | |
|-----------------|---|
| End point title | Percent change from Baseline to the 16-week Treatment Period in Partial Onset Seizure (Type I) frequency per week |
|-----------------|---|

End point description:

Percent change from Baseline was calculated as percent reduction by:
(weekly seizure frequency Baseline - weekly seizure frequency Treatment)*100/(weekly seizure frequency Baseline).

A negative value in percent Change from Baseline indicates an improvement from Baseline.

The higher the negative values for percent change in Partial Onset Seizure (POS) frequency, the higher the improvement from Baseline.

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

End point timeframe:

Baseline (Week 0) to end of Treatment Period (Week 16)

| End point values | Placebo | Brivaracetam | | |
|---------------------------------------|--------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: seizure frequency per week | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Median (Q1 - Q3) | -18.93 (-39.05 to -7.83) | -26.92 (-55.98 to 11.44) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Categorized response from Baseline in seizure frequency for Partial Onset Seizure (Type I) over the 16-week Treatment Period

| | |
|-----------------|--|
| End point title | Categorized response from Baseline in seizure frequency for Partial Onset Seizure (Type I) over the 16-week Treatment Period |
|-----------------|--|

End point description:

Subjects were classified in 1 of the following categories based on their percent reduction from Baseline to Treatment Period in Partial Onset Seizure (POS) frequency per week: <-25 %, -25 % to <25 %, 25 % to <50 %, 50 % to <75 %, 75 % to <100 %, and 100 %.

Subjects having zero for Baseline seizure frequency per week were classified in the <-25 % category.

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

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| <- 25 % | 14.8 | 18.3 | | |
| -25 % to < 25 % | 44.4 | 29.1 | | |
| 25 % to < 50 % | 24.1 | 22.3 | | |
| 50 % to < 75 % | 13.9 | 17 | | |
| 75 % to < 100 % | 2.8 | 11.8 | | |
| 100 % | 0 | 1.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure freedom rate (all seizure types) over the 16-week Treatment Period

| | |
|-----------------|--|
| End point title | Seizure freedom rate (all seizure types) over the 16-week Treatment Period |
|-----------------|--|

End point description:

Subjects were considered seizure free if their seizure counts for every day over the Treatment Period (TP) was zero and if they did not discontinue before the end of the TP. Seizure freedom rate was calculated as:

$(\text{total number of seizure-free subjects in treatment group during TP}) / (\text{total number of evaluable Intent-To-Treat (ITT) subjects in treatment group})$

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

End point timeframe:

Baseline (Week 0) to the end of Treatment Period (Week 16)

| End point values | Placebo | Brivaracetam | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Seizure-free | 0 | 1.5 | | |
| No Seizure but non-completer | 0 | 0 | | |
| Not Seizure free | 100 | 98.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of Type IC/Type I seizure frequency ratio from Baseline to the 16-week Treatment Period

| | |
|------------------------|---|
| End point title | Reduction of Type IC/Type I seizure frequency ratio from Baseline to the 16-week Treatment Period |
| End point description: | This variable was not analyzed and no results are available. |
| End point type | Secondary |
| End point timeframe: | Baseline to 16-week Treatment Period |

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Not applicable | () | () | | |

Notes:

[2] - This analysis was not performed as it was not needed for labeling purposes.

[3] - This analysis was not performed as it was not needed for labeling purposes.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first Type I seizure during the 16-week Treatment Period

| | |
|------------------------|--|
| End point title | Time to first Type I seizure during the 16-week Treatment Period |
| End point description: | Time to first Type I seizure during the 16-week Treatment Period was measured in days. |
| End point type | Secondary |
| End point timeframe: | Baseline to 16-week Treatment Period |

| End point values | Placebo | Brivaracetam | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Median (95 % CI) | 3 (2 to 4) | 4 (4 to 5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to fifth Type I seizure during the 16-week Treatment Period

| | |
|--|--|
| End point title | Time to fifth Type I seizure during the 16-week Treatment Period |
| End point description: Time to fifth Type I seizure during the 16-week Treatment Period was measured in days. | |
| End point type | Secondary |
| End point timeframe: Baseline to 16-week Treatment Period | |

| End point values | Placebo | Brivaracetam | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Median (95 % CI) | 14 (11 to 19) | 18 (16 to 21) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tenth Type I seizure during Treatment Period

| | |
|--|--|
| End point title | Time to tenth Type I seizure during Treatment Period |
| End point description: Time to tenth Type I seizure during the 16-week Treatment Period was measured in days. | |
| End point type | Secondary |
| End point timeframe: Baseline to 16-week Treatment Period | |

| End point values | Placebo | Brivaracetam | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 323 | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Median (95 % CI) | 36 (23 to 44) | 38 (31 to 43) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in Total |
|-----------------|---|

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

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

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 284 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 3.04 (± 12.58) | 4.22 (± 13.73) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Seizure Worry Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in Seizure Worry Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

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

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 99 | 291 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 4.66 (± 23.23) | 10.29 (± 21.99) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Daily Activities / Social Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in Daily Activities / Social Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

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

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 99 | 290 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 5.61 (± 21.87) | 2.66 (± 23.48) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Hospital Anxiety score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in |
|-----------------|---|

End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate Anxiety and Depression. The HADS was developed as a self-administered scale to assess the presence and severity of Anxiety and Depression. It consists of 14 items that are scored on a 4-point severity scale ranging from 0 to 3. A score per dimension was calculated with each score ranging from 0 to 21 (higher scores indicating greater problems). A negative value in change from Baseline indicates an improvement from Baseline.

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

End point timeframe:

| |
|--------------------------------------|
| Baseline to 16-week Treatment Period |
|--------------------------------------|

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 97 | 286 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | -0.57 (± 3.35) | -0.85 (± 3.62) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Hospital Depression score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in Hospital Depression score |
|-----------------|---|

End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate Anxiety and Depression. The HADS was developed as a self-administered scale to assess the presence and severity of Anxiety and Depression. It consists of 14 items that are scored on a 4-point severity scale ranging from 0 to 3. A score per dimension was calculated with each score ranging from 0 to 21 (higher scores indicating greater problems). A negative value in change from Baseline indicates an improvement from Baseline.

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

End point timeframe:

| |
|--------------------------------------|
| Baseline to 16-week Treatment Period |
|--------------------------------------|

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 97 | 285 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 0.3 (± 3.08) | -0.41 (± 3.54) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's Global Evaluation Scale (P-GES) evaluated at last visit or early discontinuation visit

| | |
|-----------------|--|
| End point title | Patient's Global Evaluation Scale (P-GES) evaluated at last visit or early discontinuation visit |
|-----------------|--|

End point description:

The Patient's Global Evaluation Scale (P-GES) is a global assessment of the disease evolution which was performed using a seven-point scale (1= Marked worsening to 7= Marked improvement) with the start of the study medication as the reference time point. The subject completed it by answering to the following: 'Overall, has there been a change in your seizures since the start of the study medication?'

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

End point timeframe:

Baseline to last visit or early discontinuation visit in the 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 99 | 282 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 4.73 (\pm 1.37) | 5.07 (\pm 1.36) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Global Evaluation Scale (I-GES) evaluated at Last Visit or Early Discontinuation Visit

| | |
|-----------------|---|
| End point title | Investigator's Global Evaluation Scale (I-GES) evaluated at Last Visit or Early Discontinuation Visit |
|-----------------|---|

End point description:

The Investigator's Global Evaluation Scale (I-GES) is a global assessment of the disease evolution which was performed using a seven-point scale (1= Marked worsening to 7= Marked improvement) with the start of the study medication as the reference time point. The Investigator completed it by answering to the following: 'Assess the overall change in the severity of patient's illness, compared to start of study medication.'

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

End point timeframe:

Baseline to Last Visit or Early Discontinuation Visit in the 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 108 | 319 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 4.79 (\pm 1.14) | 5 (\pm 1.22) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Energy/Fatigue Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

| | |
|--|--|
| End point title | Change from Baseline to the 16-week Treatment Period in Energy/Fatigue Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
| End point description: | |
| <p>The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to 16-week Treatment Period | |

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 99 | 286 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 2.98 (\pm 18) | 3.34 (\pm 19.06) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Emotional Well-being Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in |
|-----------------|---|

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type Secondary

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 99 | 287 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 1.97 (± 19.29) | 2.84 (± 18.07) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Cognitive Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title Change from Baseline to the 16-week Treatment Period in Cognitive Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type Secondary

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 99 | 290 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 2.28 (± 19.88) | 5.51 (± 18.55) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in overall Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in overall Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

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

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 | 291 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | -0.48 (± 17.4) | 4.08 (± 19.23) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Medication effects Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

| | |
|-----------------|---|
| End point title | Change from Baseline to the 16-week Treatment Period in Medication effects Patient Weighted Quality of Life in Epilepsy |
|-----------------|---|

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type

Secondary

End point timeframe:

Baseline to 16-week Treatment Period

| End point values | Placebo | Brivaracetam | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 99 | 290 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Arithmetic Mean (Standard Deviation) | 2.83 (\pm 27.21) | -0.24 (\pm 25.84) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected up to 24 weeks from Visit 1 (Week -4) to the Safety Visit (Week 20).

Adverse event reporting additional description:

Adverse Events (AEs) refer to the Safety Population, including all randomized subjects who received at least 1 dose of study medication.

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|-----|
| Dictionary version | 9.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Brivaracetam |
|-----------------------|--------------|

Reporting group description:

A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day

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

Reporting group description:

Matching Placebo tablets administered twice a day

| Serious adverse events | Brivaracetam | Placebo | |
|---|------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 359 (5.57%) | 9 / 121 (7.44%) | |
| number of deaths (all causes) | 1 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Drug toxicity | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Burns second degree | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Face injury | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin laceration | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Tremor | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postictal state | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 7 / 359 (1.95%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 5 / 9 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 2 / 359 (0.56%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drowning | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Hepatitis B | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 359 (0.00%) | 1 / 121 (0.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 359 (0.28%) | 0 / 121 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Brivaracetam | Placebo | |
|--|--------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 139 / 359 (38.72%) | 40 / 121 (33.06%) | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 31 / 359 (8.64%) | 7 / 121 (5.79%) | |
| occurrences (all) | 36 | 9 | |
| Headache | | | |
| subjects affected / exposed | 52 / 359 (14.48%) | 24 / 121 (19.83%) | |
| occurrences (all) | 79 | 45 | |
| Somnolence | | | |
| subjects affected / exposed | 40 / 359 (11.14%) | 5 / 121 (4.13%) | |
| occurrences (all) | 47 | 7 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 27 / 359 (7.52%) | 5 / 121 (4.13%) | |
| occurrences (all) | 31 | 5 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 20 / 359 (5.57%) 26 | 11 / 121 (9.09%) 14 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 11 / 359 (3.06%) 11 | 8 / 121 (6.61%) 9 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 14 / 359 (3.90%) 16 | 8 / 121 (6.61%) 10 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|--|
| 08 May 2007 | <p>A global protocol amendment was issued on 08 May 2007 in response to Food and Drug Administration (FDA) feedback on the N01253 final protocol. The following changes were implemented; no subjects were enrolled at the time:</p> <ul style="list-style-type: none">• One step was added in the Down-Titration Scheme to reduce subjects from BRV 50 mg/day to BRV 20 mg/day before entering the Study Drug-Free Period. For subjects not entering the LTFU study and taking doses of BRV 50 mg/day, 100 mg/day, or 150 mg/day (or corresponding matching PBO) a down-titration of 1, 2, or 3 weeks, respectively, was required prior to entering the Study Drug-Free Period.• Addition of a clinic visit requiring a complete safety evaluation, including laboratory safety assessments and electrocardiogram (ECG), at 2-weeks after randomization.• Addition of microscopy evaluations for all urinalysis assessments. |
| 08 May 2007 | <p>In order to harmonize the 3 studies for the BRV POS Phase 3 program, the following changes were applied for N01254:</p> <ul style="list-style-type: none">• One step was added in the Down-Titration Scheme to reduce subjects from BRV 50 mg/day to BRV 20 mg/day before entering the Study Drug-Free Period.• An ECG was added at Visit (V) 3 (2 weeks after randomization).• Laboratory safety assessments, pregnancy test (if applicable), AED plasma level, and BRV plasma level were added at V3 (2 weeks after randomization).• Weight was also measured at V3. <p>Other changes implemented in this amendment include:</p> <ul style="list-style-type: none">• Details of the statistical methods used to analyze the Type IC/Type I seizure frequency ratio were removed from the protocol. A reference to the statistical analysis plan (SAP) was added.• The definition of a completed subject was clarified. A subject completed the study if either he/she was randomized, underwent the Evaluation Visit (V8), did not have any Early Discontinuation Visit (EDV), and entered the LTFU study; or was randomized, underwent the V8 and Safety Visit (SV), did not have any EDV, and did not enter the LTFU study. Otherwise, the subject was considered discontinued.• Specifications for the handling of missing data for primary efficacy analysis on the Intent-to-Treat (ITT) Population were added. The primary efficacy analysis assumes that subjects who prematurely withdrew from the Treatment Period had the same seizure frequency for the remaining unobserved period. In addition, a sensitivity analysis was further described in the SAP.• Additional instructions for blood sampling volumes for laboratory assessments and genotyping were added. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24116853>