



## Clinical trial results:

### A Multi-center, Double-blind, Parallel-group, Placebo-Controlled, Randomized Study: Evaluation of the Efficacy and Safety of Brivaracetam in Subjects ( $\geq 16$ to 70 Years Old) With Partial Onset Seizures

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2006-006344-59             |
| Trial protocol           | BE NL FR GB HU FI IT DE ES |
| Global end of trial date | 09 February 2009           |

#### 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 | N01252 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00490035 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | UCB Pharma SA   |
| Sponsor organisation address | Allée de la Recherche 60, Brussels, Belgium, B-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:

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**Results analysis stage**

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|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 16 April 2009 |
| Is this the analysis of the primary completion data? | No            |

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|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 09 February 2009 |
| Was the trial ended prematurely? | No               |

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of Brivaracetam (BRV) at doses of 20, 50, and 100 mg/day in reducing seizure frequency in subjects with partial onset seizures not fully controlled despite optimal treatment with 1 to 2 concomitant antiepileptic drug(s) (AED(s)), compared with Placebo (PBO).

Protection of trial subjects:

Standard measures to minimize pain and distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 10 September 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                |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Belgium: 6        |
| Country: Number of subjects enrolled | Finland: 11       |
| Country: Number of subjects enrolled | France: 60        |
| Country: Number of subjects enrolled | Germany: 41       |
| Country: Number of subjects enrolled | Hungary: 12       |
| Country: Number of subjects enrolled | India: 91         |
| Country: Number of subjects enrolled | Italy: 20         |
| Country: Number of subjects enrolled | Netherlands: 7    |
| Country: Number of subjects enrolled | Poland: 108       |
| Country: Number of subjects enrolled | Spain: 22         |
| Country: Number of subjects enrolled | Switzerland: 15   |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Worldwide total number of subjects   | 399               |
| EEA total number of subjects         | 293               |

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Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                 | 5   |
| Adults (18-64 years)                      | 383 |
| From 65 to 84 years                       | 11  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study started to enroll subjects in September 2007 and concluded in February 2009.

### Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set.

### 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     |
| <b>Arm title</b>             | 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.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Brivaracetam 20 mg/day |
|------------------|------------------------|

Arm description:

Brivaracetam 20 mg/day, 10 mg administered twice a 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:

10 mg and 25 mg tablets. Two equal intakes, morning and evening, in a double-blinded way for the 12-week Treatment Period.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Brivaracetam 50 mg/day |
|------------------|------------------------|

Arm description:

Brivaracetam 50 mg/day, 25 mg administered twice a 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:**

10 mg and 25 mg tablets. Two equal intakes, morning and evening, in a double-blinded way for the 12-week Treatment Period.

|   |                         |
|---|-------------------------|
| <b>Arm title</b>  | Brivaracetam 100 mg/day |
| Arm description:<br>Brivaracetam 100 mg/day, 50 mg administered twice a 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:**

10 mg and 25 mg tablets. Two equal intakes, morning and evening, in a double-blinded way for the 12-week Treatment Period.

| <b>Number of subjects in period 1</b> | Placebo | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day |
|---------------------------------------|---------|------------------------|------------------------|
| Started                               | 100     | 99                     | 100                    |
| Completed                             | 92      | 93                     | 88                     |
| Not completed                         | 8       | 6                      | 12                     |
| AE, serious fatal                     | 1       | -                      | -                      |
| Consent withdrawn by subject          | 2       | 1                      | 1                      |
| AE, non-serious non-fatal             | 3       | 4                      | 4                      |
| AE of unknown type                    | -       | -                      | 2                      |
| Other reason                          | -       | 1                      | 3                      |
| Lost to follow-up                     | 2       | -                      | 1                      |
| SAE, non-fatal                        | -       | -                      | 1                      |

| <b>Number of subjects in period 1</b> | Brivaracetam 100 mg/day |
|---------------------------------------|-------------------------|
| Started                               | 100                     |
| Completed                             | 94                      |
| Not completed                         | 6                       |
| AE, serious fatal                     | -                       |
| Consent withdrawn by subject          | -                       |
| AE, non-serious non-fatal             | 5                       |
| AE of unknown type                    | -                       |
| Other reason                          | 1                       |
| Lost to follow-up                     | -                       |
| SAE, non-fatal                        | -                       |



## Baseline characteristics

### Reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Placebo                 |
| Reporting group description:<br>Matching Placebo tablets administered twice a day       |                         |
| Reporting group title   | Brivaracetam 20 mg/day  |
| Reporting group description:<br>Brivaracetam 20 mg/day, 10 mg administered twice a day  |                         |
| Reporting group title   | Brivaracetam 50 mg/day  |
| Reporting group description:<br>Brivaracetam 50 mg/day, 25 mg administered twice a day  |                         |
| Reporting group title   | Brivaracetam 100 mg/day |
| Reporting group description:<br>Brivaracetam 100 mg/day, 50 mg administered twice a day |                         |

| Reporting group values                  | Placebo | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day |
|---|---------|------------------------|------------------------|
| Number of subjects                      | 100     | 99                     | 100                    |
| Age Categorical<br>Units: Subjects      |         |                        |                        |
| <18 years                               | 2       | 2                      | 0                      |
| Between 18 and 65 years                 | 96      | 94                     | 97                     |
| >=65 years                              | 2       | 3                      | 3                      |
| Age Continuous<br>Units: years          |         |                        |                        |
| arithmetic mean                         | 36.4    | 35.7                   | 39                     |
| standard deviation                      | ± 13    | ± 12.5                 | ± 13.5                 |
| Gender Categorical<br>Units: Subjects   |         |                        |                        |
| Female                                  | 46      | 38                     | 45                     |
| Male                                    | 54      | 61                     | 55                     |
| Region of Enrollment<br>Units: Subjects |         |                        |                        |
| Hungary                                 | 4       | 2                      | 3                      |
| Poland                                  | 26      | 28                     | 27                     |
| India                                   | 23      | 22                     | 23                     |
| Belgium                                 | 3       | 0                      | 3                      |
| Finland                                 | 3       | 3                      | 1                      |
| France                                  | 17      | 17                     | 11                     |
| Germany                                 | 8       | 10                     | 14                     |
| Italy                                   | 4       | 8                      | 3                      |
| Netherlands                             | 3       | 0                      | 1                      |
| Spain                                   | 8       | 4                      | 6                      |
| Switzerland                             | 1       | 3                      | 6                      |
| United Kingdom                          | 0       | 2                      | 2                      |

| Reporting group values | Brivaracetam 100 mg/day | Total |  |
|------------------------|-------------------------|-------|--|
| Number of subjects     | 100                     | 399   |  |

|   |        |     |  |
|---|--------|-----|--|
| Age Categorical<br>Units: Subjects      |        |     |  |
| <18 years                               | 1      | 5   |  |
| Between 18 and 65 years                 | 96     | 383 |  |
| >=65 years                              | 3      | 11  |  |
| Age Continuous<br>Units: years          |        |     |  |
| arithmetic mean                         | 38     |     |  |
| standard deviation                      | ± 13.1 | -   |  |
| Gender Categorical<br>Units: Subjects   |        |     |  |
| Female                                  | 42     | 171 |  |
| Male                                    | 58     | 228 |  |
| Region of Enrollment<br>Units: Subjects |        |     |  |
| Hungary                                 | 3      | 12  |  |
| Poland                                  | 27     | 108 |  |
| India                                   | 23     | 91  |  |
| Belgium                                 | 0      | 6   |  |
| Finland                                 | 4      | 11  |  |
| France                                  | 15     | 60  |  |
| Germany                                 | 9      | 41  |  |
| Italy                                   | 5      | 20  |  |
| Netherlands                             | 3      | 7   |  |
| Spain                                   | 4      | 22  |  |
| Switzerland                             | 5      | 15  |  |
| United Kingdom                          | 2      | 6   |  |



## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Placebo                 |
| Reporting group description:<br>Matching Placebo tablets administered twice a day       |                         |
| Reporting group title   | Brivaracetam 20 mg/day  |
| Reporting group description:<br>Brivaracetam 20 mg/day, 10 mg administered twice a day  |                         |
| Reporting group title   | Brivaracetam 50 mg/day  |
| Reporting group description:<br>Brivaracetam 50 mg/day, 25 mg administered twice a day  |                         |
| Reporting group title   | Brivaracetam 100 mg/day |
| Reporting group description:<br>Brivaracetam 100 mg/day, 50 mg administered twice a day |                         |

### Primary: Partial Onset Seizure (Type I) frequency per week over the 12-week Treatment Period

|   |   |
|---|---|
| End point title   | Partial Onset Seizure (Type I) frequency per week over the 12-week Treatment Period |
| End point description:<br>Partial (Type I) Seizures can be classified into one of the following three groups: Simple Partial Seizures, Complex Partial Seizures, Partial Seizures evolving to Secondarily Generalized Seizures. |   |
| End point type  | Primary   |
| End point timeframe:<br>From Baseline to 12-week Treatment Period   |   |

| End point values                      | Placebo             | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|---------------------------------------|---------------------|------------------------|------------------------|-------------------------|
| Subject group type                    | Reporting group     | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed           | 100                 | 99                     | 99                     | 100                     |
| Units: Seizure Frequency per Week     |                     |                        |                        |                         |
| median (inter-quartile range (Q1-Q3)) |                     |                        |                        |                         |
| Median (Q1-Q3)                        | 1.75 (0.76 to 5.12) | 1.34 (0.7 to 3.12)     | 1.49 (0.69 to 2.78)    | 1.26 (0.52 to 2.93)     |

### Statistical analyses

|  |                                  |
|--|----------------------------------|
| Statistical analysis title   | BRV 50 mg/day versus PBO         |
| Statistical analysis description:<br>In order to control the Type I error testing was performed in sequence starting with 50 mg, then 100 mg and finally 20 mg Brivaracetam per day versus Placebo, only moving to the next test if the previous one was significant at the 5 % level. |                                  |
| Comparison groups  | Placebo v Brivaracetam 50 mg/day |

|   |                                   |
|---|-----------------------------------|
| Number of subjects included in analysis | 199                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | superiority                       |
| P-value                                 | = 0.261                           |
| Method                                  | ANCOVA                            |
| Parameter estimate                      | Percentage Reduction over Placebo |
| Point estimate                          | 6.5                               |
| Confidence interval                     |                                   |
| level                                   | 95 %                              |
| sides                                   | 2-sided                           |
| lower limit                             | -5.2                              |
| upper limit                             | 16.9                              |

### Secondary: Responder rate for partial onset seizures (Type I) frequency per week over the 12-week Treatment Period

|   |   |
|---|---|
| End point title   | Responder rate for partial onset seizures (Type I) frequency per week over the 12-week Treatment Period |
| End point description:  |   |
| <p>Responders are those subjects with at least 50 % reduction from Baseline to Treatment Period in Partial Onset Seizure frequency per week.</p> <p>The Responder Rate for Partial Onset Seizures (Type I) is the proportion of subjects who have a <math>\geq 50</math> % reduction in seizure frequency per week from Baseline.</p> |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| From Baseline to 12-week Treatment Period   |   |

| End point values                  | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|-----------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed       | 100             | 99                     | 99                     | 100                     |
| Units: Percentage of Participants |                 |                        |                        |                         |
| number (not applicable)           |                 |                        |                        |                         |
| Non-responders                    | 80              | 72.7                   | 72.7                   | 64                      |
| Responders                        | 20              | 27.3                   | 27.3                   | 36                      |

### Statistical analyses

No statistical analyses for this end point

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

|  |  |
|--|--|
| End point title  | All seizure frequency (Type I+II+III) per week over the 12-week Treatment Period |
| End point description:   |  |
| <p>There are three types of Epilepsy: Partial Epilepsies (Type I), Generalized Epilepsies (Type II) and uncertain classification of Epilepsies (Type III).</p> |  |

|   |           |
|---|-----------|
| End point type                            | Secondary |
| End point timeframe:                      |           |
| From Baseline to 12-week Treatment Period |           |

| End point values                      | Placebo             | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|---------------------------------------|---------------------|------------------------|------------------------|-------------------------|
| Subject group type                    | Reporting group     | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed           | 100                 | 99                     | 99                     | 100                     |
| Units: Times per week                 |                     |                        |                        |                         |
| median (inter-quartile range (Q1-Q3)) |                     |                        |                        |                         |
| Median (Q1-Q3)                        | 1.75 (0.76 to 5.61) | 1.34 (0.7 to 3.12)     | 1.49 (0.69 to 2.78)    | 1.26 (0.52 to 2.93)     |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent change from Baseline to the 12-week Treatment Period in Partial Onset Seizure (Type I) Frequency per week

|  |   |
|--|---|
| End point title  | Percent change from Baseline to the 12-week Treatment Period in Partial Onset Seizure (Type I) Frequency per week |
| End point description:   |   |
| The percent change from Baseline was computed as: Weekly Seizure Frequency (Treatment) - Weekly Seizure Frequency (Baseline) / Weekly Seizure Frequency (Baseline) * 100. Negative values indicate a reduction from Baseline with higher negative values showing higher reduction. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From Baseline to 12-week Treatment Period  |   |

| End point values                           | Placebo                  | Brivaracetam 20 mg/day   | Brivaracetam 50 mg/day  | Brivaracetam 100 mg/day |
|--|--------------------------|--------------------------|-------------------------|-------------------------|
| Subject group type                         | Reporting group          | Reporting group          | Reporting group         | Reporting group         |
| Number of subjects analysed                | 100                      | 99                       | 99                      | 100                     |
| Units: Percent change in seizures per week |                          |                          |                         |                         |
| median (inter-quartile range (Q1-Q3))      |                          |                          |                         |                         |
| Median (Q1-Q3)                             | -17.03 (-40.27 to 17.59) | -30.03 (-55.99 to -2.11) | -26.83 (-60.05 to 6.32) | -32.45 (-72.51 to 0.04) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Categorized percentage change from Baseline in seizure frequency for

**Partial Onset Seizure (Type I) over the 12-week Treatment Period**

|                 |   |
|-----------------|---|
| End point title | Categorized percentage change from Baseline in seizure frequency for Partial Onset Seizure (Type I) over the 12-week Treatment Period |
|-----------------|---|

End point description:

The categories are:

- ≤ 25 %
- 25 % to < 50 %
- 50 % to < 75 %
- 75 % to < 100 %
- 100 %

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

End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                  | Placebo         | Brivaracetam<br>20 mg/day | Brivaracetam<br>50 mg/day | Brivaracetam<br>100 mg/day |
|-----------------------------------|-----------------|---------------------------|---------------------------|----------------------------|
| Subject group type                | Reporting group | Reporting group           | Reporting group           | Reporting group            |
| Number of subjects analysed       | 100             | 99                        | 99                        | 100                        |
| Units: Percentage of Participants |                 |                           |                           |                            |
| number (not applicable)           |                 |                           |                           |                            |
| ≤ 25 %                            | 19              | 10.1                      | 15.2                      | 10                         |
| 25 % to < 50 %                    | 41              | 35.4                      | 33.3                      | 33                         |
| 50 % to < 75 %                    | 20              | 27.3                      | 24.2                      | 21                         |
| 75 % to < 100 %                   | 12              | 18.2                      | 17.2                      | 14                         |
| 100 %                             | 8               | 7.1                       | 9.1                       | 18                         |
|                                   | 0               | 2                         | 1                         | 4                          |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Seizure Freedom Rate (all seizure types) over the 12-week Treatment Period**

|                 |  |
|-----------------|--|
| End point title | Seizure Freedom Rate (all seizure types) over the 12-week Treatment Period |
|-----------------|--|

End point description:

Subjects were considered seizure free if their seizure counts for every day over the entire Treatment Period was zero and if they completed the Treatment Period.

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

End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                  | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|-----------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed       | 100             | 99                     | 99                     | 100                     |
| Units: Percentage of Participants |                 |                        |                        |                         |
| number (not applicable)           |                 |                        |                        |                         |
| Seizure free                      | 0               | 2                      | 0                      | 4                       |
| No Seizures but non-completer     | 0               | 0                      | 1                      | 0                       |
| Not Seizure-free                  | 100             | 98                     | 99                     | 96                      |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to first Type I Seizure during the 12-week Treatment Period

|  |  |
|--|--|
| End point title  | Time to first Type I Seizure during the 12-week Treatment Period |
| End point description:<br>The time to first Type I Seizure during the 12-week Treatment Period was measured in days. |  |
| End point type   | Secondary  |
| End point timeframe:<br>From Baseline to 12-week Treatment Period  |  |

| End point values                 | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|----------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type               | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed      | 100             | 99                     | 99                     | 100                     |
| Units: Days                      |                 |                        |                        |                         |
| median (confidence interval 95%) |                 |                        |                        |                         |
| Median (95 % CI)                 | 4 (3 to 5)      | 6 (3 to 8)             | 6 (4 to 10)            | 4 (3 to 5)              |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Fifth Type I Seizure during the 12-week Treatment Period

|  |  |
|--|--|
| End point title  | Time to Fifth Type I Seizure during the 12-week Treatment Period |
| End point description:<br>The time to Fifth Type I Seizure during the 12-week Treatment Period was measured in days. |  |
| End point type   | Secondary  |
| End point timeframe:<br>From Baseline to 12-week Treatment Period  |  |

| End point values                 | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|----------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type               | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed      | 100             | 99                     | 99                     | 100                     |
| Units: Days                      |                 |                        |                        |                         |
| median (confidence interval 95%) |                 |                        |                        |                         |
| Median (95 % CI)                 | 19 (14 to 25)   | 25 (20 to 34)          | 24 (20 to 32)          | 24 (18 to 34)           |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to tenth Type I seizure during the 12-week Treatment Period

|                        |  |
|------------------------|--|
| End point title        | Time to tenth Type I seizure during the 12-week Treatment Period                           |
| End point description: | The time to tenth Type I Seizure during the 12-week Treatment Period was measured in days. |
| End point type         | Secondary  |
| End point timeframe:   | From Baseline to 12-week Treatment Period  |

| End point values                 | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|----------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type               | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed      | 100             | 99                     | 99                     | 100                     |
| Units: Days                      |                 |                        |                        |                         |
| median (confidence interval 95%) |                 |                        |                        |                         |
| Median (95 % CI)                 | 39 (24 to 50)   | 49 (36 to 64)          | 40 (33 to 49)          | 46 (34 to 66)           |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Reduction of Type IC/Type I Seizure frequency ratio from Baseline to the 12- week Treatment Period.

|                        |  |
|------------------------|--|
| End point title        | Reduction of Type IC/Type I Seizure frequency ratio from Baseline to the 12- week Treatment Period.  |
| End point description: | Reduction of Type IC/Type I Seizure frequency ratio from Baseline to the 12- week Treatment Period. This variable was not analyzed and no results are available. |
| End point type         | Secondary  |

End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo          | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|------------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group  | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 0 <sup>[1]</sup> | 0 <sup>[2]</sup>       | 0 <sup>[3]</sup>       | 0 <sup>[4]</sup>        |
| Units: units on a scale              |                  |                        |                        |                         |
| arithmetic mean (standard deviation) |                  |                        |                        |                         |
| Not applicable                       | ()               | ()                     | ()                     | ()                      |

Notes:

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

[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.

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

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

End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 86              | 91                     | 94                     | 80                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 2.29 (± 14.03)  | 4.5 (± 12.71)          | 3.09 (± 14.43)         | 1.78 (± 13.95)          |

### Statistical analyses

**Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Seizure Worry Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

## End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

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

## End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 88              | 93                     | 96                     | 86                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 8.25 (± 22.01)  | 6.23 (± 17.97)         | 5.34 (± 23.81)         | 8.04 (± 26.26)          |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline to the 12-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 12-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 QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

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

## End point timeframe:

From Baseline to 12-week Treatment Period



| End point values                     | Placebo              | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|----------------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group      | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 88                   | 93                     | 96                     | 85                      |
| Units: units on a scale              |                      |                        |                        |                         |
| arithmetic mean (standard deviation) |                      |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | -2.09 ( $\pm$ 20.26) | 3.35 ( $\pm$ 19.72)    | 3.09 ( $\pm$ 20.79)    | 3.5 ( $\pm$ 22.52)      |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to the 12-week Treatment Period in Hospital Anxiety Score

|                 |  |
|-----------------|--|
| End point title | Change from Baseline to the 12-week Treatment Period in Hospital Anxiety Score |
|-----------------|--|

End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression simultaneously. The HADS was developed as a self-administered scale that has been designed to assess the presence and severity of both 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 and higher scores indicating higher depression / anxiety. Negative values in Change from Baseline indicate a decrease of HADS from Baseline to Treatment Period.

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

End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo             | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|---------------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group     | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 86                  | 91                     | 95                     | 83                      |
| Units: units on a scale              |                     |                        |                        |                         |
| arithmetic mean (standard deviation) |                     |                        |                        |                         |
| Anxiety                              | -1.54 ( $\pm$ 3.89) | -0.59 ( $\pm$ 3.89)    | -0.41 ( $\pm$ 3.82)    | 0.08 ( $\pm$ 3.6)       |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to the 12-week Treatment Period in Hospital Depression Score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to the 12-week Treatment Period in |
|-----------------|---|

## End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression simultaneously. The HADS was developed as a self-administered scale that has been designed to assess the presence and severity of both 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 and higher scores indicating higher depression / anxiety. Negative values in Change from Baseline indicate a decrease of HADS from Baseline to Treatment Period.

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

## End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 86              | 91                     | 95                     | 83                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Depression                           | -0.65 (± 3.58)  | -0.1 (± 3.67)          | 0.26 (± 3.84)          | -0.24 (± 3.69)          |

## 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 not mentally impaired had to complete it by answering the following question: "Overall, has there been a change in your seizures since the start of the study medication?"

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

## End point timeframe:

Last Visit or Early Discontinuation Visit in the 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 81              | 90                     | 90                     | 85                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 4.93 (± 1.39)   | 5.17 (± 1.27)          | 5.04 (± 1.29)          | 5.47 (± 1.16)           |

## 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 reference time point. The Investigator was to complete it by answering the following question: "Assess the Overall change in the severity of patient's illness, compared to start of study medication."

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

End point timeframe:

Last Visit or Early Discontinuation Visit in the 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam<br>20 mg/day | Brivaracetam<br>50 mg/day | Brivaracetam<br>100 mg/day |
|--------------------------------------|-----------------|---------------------------|---------------------------|----------------------------|
| Subject group type                   | Reporting group | Reporting group           | Reporting group           | Reporting group            |
| Number of subjects analysed          | 96              | 99                        | 98                        | 100                        |
| Units: units on a scale              |                 |                           |                           |                            |
| arithmetic mean (standard deviation) |                 |                           |                           |                            |
| Arithmetic Mean (Standard Deviation) | 4.78 (± 1.2)    | 4.99 (± 1.15)             | 4.99 (± 1.1)              | 5.34 (± 1.12)              |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Energy/Fatigue Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|--|

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

|   |           |
|---|-----------|
| End point type                            | Secondary |
| End point timeframe:                      |           |
| From Baseline to 12-week Treatment Period |           |

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 86              | 92                     | 95                     | 83                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 3.49 (± 19.22)  | 3.53 (± 17.04)         | 1.95 (± 20.74)         | 1.99 (± 20.42)          |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Emotional Well-Being Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|--|

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

|   |           |
|---|-----------|
| End point type                            | Secondary |
| End point timeframe:                      |           |
| From Baseline to 12-week Treatment Period |           |

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 88              | 93                     | 96                     | 84                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 3.8 (± 18.71)   | 3.75 (± 15.94)         | 3.13 (± 19.35)         | -2.45 (± 18.55)         |

### Statistical analyses

**Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Cognitive Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

## End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

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

## End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 88              | 93                     | 96                     | 85                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 1.8 (± 19.16)   | 5.36 (± 20.69)         | 1.02 (± 19.95)         | 0.69 (± 16.66)          |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Medication Effects Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|--|

## End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

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

## End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 88              | 92                     | 96                     | 86                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 0.92 (± 28.93)  | 3.64 (± 29.24)         | -0.85 (± 24.36)        | 3 (± 28.22)             |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to the 12-week Treatment Period in Overall Quality of Life Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline to the 12-week Treatment Period in Overall Quality of Life Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

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

End point timeframe:

From Baseline to 12-week Treatment Period

| End point values                     | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 88              | 93                     | 95                     | 86                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 5.11 (± 18.48)  | 4.52 (± 16.73)         | 4.55 (± 18.93)         | 2.24 (± 18.45)          |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline to the 12-week Treatment Period in Health Status

---

**of Life Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score**

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|                 |   |
|-----------------|---|
| End point title | Change from Baseline to the 12-week Treatment Period in Health Status of Life Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score |
|-----------------|---|

---

**End point description:**

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

---

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

---

**End point timeframe:**

From Baseline to 12-week Treatment Period

---

| <b>End point values</b>              | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day | Brivaracetam 100 mg/day |
|--------------------------------------|-----------------|------------------------|------------------------|-------------------------|
| Subject group type                   | Reporting group | Reporting group        | Reporting group        | Reporting group         |
| Number of subjects analysed          | 88              | 93                     | 95                     | 84                      |
| Units: units on a scale              |                 |                        |                        |                         |
| arithmetic mean (standard deviation) |                 |                        |                        |                         |
| Arithmetic Mean (Standard Deviation) | 6.6 (± 16.3)    | 6.9 (± 20.1)           | 9.7 (± 19.8)           | 4.9 (± 18.1)            |

---

**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected up to 23 weeks from Visit 1 (Week -8) to the Safety Visit (Week 15).

Adverse event reporting additional description:

Adverse Events (AEs) refer to the Safety Set (SS) population which contains the same set of subjects as the Intention-To-Treat (ITT) population.

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

### Dictionary used

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

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

### Reporting groups

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

Reporting group description:

Matching Placebo tablets administered twice a day

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Brivaracetam 20 mg/day |
|-----------------------|------------------------|

Reporting group description:

Brivaracetam 20 mg/day, 10 mg administered twice a day

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Brivaracetam 50 mg/day |
|-----------------------|------------------------|

Reporting group description:

Brivaracetam 50 mg/day, 25 mg administered twice a day

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

Reporting group description:

Brivaracetam 100 mg/day, 50 mg administered twice a day

| Serious adverse events                            | Placebo         | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day |
|---|-----------------|------------------------|------------------------|
| Total subjects affected by serious adverse events |                 |                        |                        |
| subjects affected / exposed                       | 6 / 100 (6.00%) | 2 / 99 (2.02%)         | 4 / 99 (4.04%)         |
| number of deaths (all causes)                     | 1               | 0                      | 0                      |
| number of deaths resulting from adverse events    | 0               | 0                      | 0                      |
| Injury, poisoning and procedural complications    |                 |                        |                        |
| Humerus fracture                                  |                 |                        |                        |
| subjects affected / exposed                       | 0 / 100 (0.00%) | 0 / 99 (0.00%)         | 0 / 99 (0.00%)         |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 0                  | 0 / 0                  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0                  | 0 / 0                  |
| Jaw fracture                                      |                 |                        |                        |
| subjects affected / exposed                       | 0 / 100 (0.00%) | 1 / 99 (1.01%)         | 0 / 99 (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                  |



|   |                 |                |                |
|---|-----------------|----------------|----------------|
| Cardiac disorders                               |                 |                |                |
| Angina pectoris                                 |                 |                |                |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 99 (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          |
| Pregnancy, puerperium and perinatal conditions  |                 |                |                |
| Abortion spontaneous                            |                 |                |                |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 99 (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          |
| Pregnancy                                       |                 |                |                |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 99 (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                        |                 |                |                |
| Convulsion                                      |                 |                |                |
| subjects affected / exposed                     | 3 / 100 (3.00%) | 0 / 99 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Grand mal convulsion                            |                 |                |                |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Status epilepticus                              |                 |                |                |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                      |                 |                |                |
| Gastritis erosive                               |                 |                |                |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders        |                 |                |                |
| Vaginal hemorrhage                              |                 |                |                |

|   |                 |                |                |
|---|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 99 (1.01%) | 0 / 99 (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          |
| <b>Psychiatric disorders</b>                    |                 |                |                |
| Amnesia   |                 |                |                |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| <b>Psychotic Disorder</b>                       |                 |                |                |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 0 / 99 (0.00%) | 1 / 99 (1.01%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| <b>Infections and infestations</b>              |                 |                |                |
| Sepsis  |                 |                |                |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 99 (0.00%) | 0 / 99 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |

|  |                         |  |  |
|--|-------------------------|--|--|
| <b>Serious adverse events</b>                            | Brivaracetam 100 mg/day |  |  |
| <b>Total subjects affected by serious adverse events</b> |                         |  |  |
| subjects affected / exposed                              | 2 / 100 (2.00%)         |  |  |
| number of deaths (all causes)                            | 0                       |  |  |
| number of deaths resulting from adverse events           | 0                       |  |  |
| <b>Injury, poisoning and procedural complications</b>    |                         |  |  |
| Humerus fracture   |                         |  |  |
| subjects affected / exposed                              | 1 / 100 (1.00%)         |  |  |
| occurrences causally related to treatment / all          | 0 / 1                   |  |  |
| deaths causally related to treatment / all               | 0 / 0                   |  |  |
| <b>Jaw fracture</b>                                      |                         |  |  |
| subjects affected / exposed                              | 0 / 100 (0.00%)         |  |  |
| occurrences causally related to treatment / all          | 0 / 0                   |  |  |
| deaths causally related to treatment / all               | 0 / 0                   |  |  |
| <b>Cardiac disorders</b>                                 |                         |  |  |
| Angina pectoris  |                         |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pregnancy, puerperium and perinatal conditions  |                 |  |  |
| Abortion spontaneous                            |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pregnancy                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Convulsion                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Grand mal convulsion                            |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Status epilepticus                              |                 |  |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Gastritis erosive                               |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast disorders        |                 |  |  |
| Vaginal hemorrhage                              |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Amnesia   |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychotic Disorder                              |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| Non-serious adverse events                            | Placebo           | Brivaracetam 20 mg/day | Brivaracetam 50 mg/day |
|---|-------------------|------------------------|------------------------|
| Total subjects affected by non-serious adverse events |                   |                        |                        |
| subjects affected / exposed                           | 22 / 100 (22.00%) | 31 / 99 (31.31%)       | 35 / 99 (35.35%)       |
| Nervous system disorders                              |                   |                        |                        |
| Convulsion  |                   |                        |                        |
| subjects affected / exposed                           | 1 / 100 (1.00%)   | 5 / 99 (5.05%)         | 1 / 99 (1.01%)         |
| occurrences (all)                                     | 1                 | 7                      | 1                      |
| Dizziness   |                   |                        |                        |
| subjects affected / exposed                           | 5 / 100 (5.00%)   | 5 / 99 (5.05%)         | 7 / 99 (7.07%)         |
| occurrences (all)                                     | 11                | 8                      | 12                     |
| Headache  |                   |                        |                        |
| subjects affected / exposed                           | 10 / 100 (10.00%) | 14 / 99 (14.14%)       | 18 / 99 (18.18%)       |
| occurrences (all)                                     | 14                | 19                     | 31                     |
| Somnolence  |                   |                        |                        |

|  |                      |                      |                     |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 6 / 100 (6.00%)<br>6 | 8 / 99 (8.08%)<br>10 | 6 / 99 (6.06%)<br>7 |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 2 / 100 (2.00%)<br>2 | 3 / 99 (3.03%)<br>4  | 4 / 99 (4.04%)<br>5 |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                             | 3 / 100 (3.00%)<br>5 | 1 / 99 (1.01%)<br>2  | 2 / 99 (2.02%)<br>2 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                               | 4 / 100 (4.00%)<br>4 | 0 / 99 (0.00%)<br>0  | 1 / 99 (1.01%)<br>1 |
| Psychiatric disorders<br>Irritability<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 100 (0.00%)<br>0 | 0 / 99 (0.00%)<br>0  | 5 / 99 (5.05%)<br>5 |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 100 (1.00%)<br>1 | 8 / 99 (8.08%)<br>8  | 1 / 99 (1.01%)<br>1 |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>   | Brivaracetam 100<br>mg/day  |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 37 / 100 (37.00%)   |  |  |
| Nervous system disorders<br>Convulsion<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Somnolence | 2 / 100 (2.00%)<br>2<br><br>5 / 100 (5.00%)<br>5<br><br>9 / 100 (9.00%)<br>15 |  |  |

|  |                       |  |  |
|--|-----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 8 / 100 (8.00%)<br>8  |  |  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 8 / 100 (8.00%)<br>9  |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                             | 8 / 100 (8.00%)<br>26 |  |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                               | 6 / 100 (6.00%)<br>7  |  |  |
| Psychiatric disorders<br>Irritability<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 100 (1.00%)<br>1  |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 100 (2.00%)<br>2  |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 02 February 2007 | <p>Protocol amendment 1 was issued on 02 Feb 2007. The following changes were implemented; no subjects were enrolled at the time:</p> <ul style="list-style-type: none"><li>• A storage period of up to 20 years was proposed for the DNA samples in order to have the possibility to re-evaluate a possible correlation between SV2 (A, B, and C) gene variations and treatment response if, and when, new mutations are found to be relevant to SV2 pharmacogenomics. The initial genotyping will occur during the conduct of the study, but there is high likelihood that new mutations in SV2A, B or C will be found over the subsequent years as this is a rapidly evolving area. In addition, it will be of interest to examine the genetic variability in other disease-related genes of possible relevance for epileptic disorders and in genes related to SV2 biology.</li><li>• The rationale for collecting the race has been added according to legal requirement in some countries.</li><li>• Clarification of the electrocardiogram (ECG) tracings retrieval has been added to include the following text: Copies of all ECG tracings will be retrieved for all subjects presenting treatment-emergent, clinically significant abnormalities during the study.</li></ul>  |
| 08 May 2007      | <p>A protocol amendment was issued on 08 May 2007 in response to Food and Drug Administration (FDA) feedback on the N01253 final protocol, which was identical in design to N01252. The following changes were implemented; no subjects were enrolled at the time:</p> <ul style="list-style-type: none"><li>• An additional 1 week step at 20 mg/day was added to the Down-Titration Period for subjects on 50 mg/day or on 100 mg/day.</li><li>• A clinic visit was added 2 weeks after randomization which included a complete safety evaluation (including laboratory analysis and ECGs).</li><li>• Microscopy evaluations for all urinalysis assessments were added at clinic visits when urinalysis samples were taken.</li></ul> <p>Other changes implemented in this amendment included:</p> <ul style="list-style-type: none"><li>• 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.</li><li>• The definition of a completed subject was clarified. A subject completed the study if either he/she was randomized, underwent the Evaluation Visit (V) (V7), did not have any Early Discontinuation Visit (EDV), and entered the LTFU; or was randomized, underwent the Evaluation Visit (V7) and Safety Visit (SV), did not have any EDV, and did not enter the LTFU. Otherwise the subject was to be considered discontinued.</li><li>• Specifications for the handling of missing data for primary efficacy analysis on the Intent-to-Treat (ITT) Population analyses 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.</li><li>• Additional instructions for blood sampling volumes for laboratory assessments and genotyping were added.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24256083>