



Clinical trial results:

An open-label, multi-center, follow-up trial to evaluate long term safety and efficacy of brivaracetam used as adjunctive treatment at a flexible dose up to a maximum of 200 mg/day in subjects aged 16 years or older suffering from epilepsy

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-004397-42 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 18 September 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 25 November 2018 |
| First version publication date | 05 April 2018 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | N01199 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00150800 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | UCB Pharma Inc. |
| Sponsor organisation address | 1950 Lake Park Drive, Smyrna, United States, 30080 |
| Public contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com |
| Scientific contact | Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 November 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses with a maximum of 200 mg/day in subjects suffering from epilepsy.

Protection of trial subjects:

During the conduct of the study all subjects were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 23 January 2006 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 30 |
| Country: Number of subjects enrolled | Brazil: 115 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | India: 202 |
| Country: Number of subjects enrolled | Mexico: 96 |
| Country: Number of subjects enrolled | United States: 211 |
| Worldwide total number of subjects | 667 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |

| | |
|---------------------------|-----|
| Adolescents (12-17 years) | 30 |
| Adults (18-64 years) | 632 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in January 2006 and concluded in September 2017. 668 subjects were included in the Enrolled Set but 1 subject from India lost to follow up and was excluded from the Safety Analysis Set due to lack of medical data.

Pre-assignment

Screening details:

The Participant Flow refers to the Safety Analysis Set which included all subjects who took at least 1 dose of study drug.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

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

Arm description:

Brivaracetam (BRV) used as adjunctive treatment, flexible dosing up to 200 mg /day in b.i.d (twice daily) administration. Dose increase or decrease can be made in increments of maximum 50 mg /day on a weekly basis.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Brivaracetam |
| Investigational medicinal product code | BRV |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Active investigational product (tablets containing 10 or 25 mg BRV) used as adjunctive treatment, flexible dosing up to 200 mg/day in b.i.d (twice daily) administration. Dose increase or decrease could be made in increments of maximum 50 mg/day on a weekly basis.

| Number of subjects in period 1 | Brivaracetam |
|--------------------------------|--------------|
| Started | 667 |
| Completed | 171 |
| Not completed | 496 |
| Adverse event, serious fatal | 18 |
| Neurosurgery | 2 |
| Nobody to accompany patient | 1 |
| Surgical intervention | 4 |
| Distance too long for patient | 1 |
| PI discontinuation request | 1 |
| Subject's choice | 90 |

| | |
|--------------------------|-----|
| No compliance | 18 |
| Site closure | 24 |
| Pregnancy planned | 1 |
| Patient insurance | 1 |
| BRV monotherapy | 1 |
| Sponsor's request | 2 |
| Adverse event, non-fatal | 89 |
| PI retiring | 2 |
| PI leaving site | 2 |
| IP misshandling | 1 |
| Generalized Epilepsy | 1 |
| Lost to follow-up | 58 |
| Moved from area/country | 8 |
| Protocol non-adherence | 2 |
| Lack of efficacy | 166 |
| Visit refusal | 3 |

Baseline characteristics

Reporting groups

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

Reporting group description:

Brivaracetam (BRV) used as adjunctive treatment, flexible dosing up to 200 mg /day in b.i.d (twice daily) administration. Dose increase or decrease can be made in increments of maximum 50 mg /day on a weekly basis.

| Reporting group values | Brivaracetam | Total | |
|---------------------------------------|--------------|-------|--|
| Number of subjects | 667 | 667 | |
| Age categorical Units: Subjects | | | |
| <=18 years | 30 | 30 | |
| Between 18 and 65 years | 632 | 632 | |
| >=65 years | 5 | 5 | |
| Age continuous Units: years | | | |
| arithmetic mean | 34.3 | | |
| standard deviation | ± 12.2 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 303 | 303 | |
| Male | 364 | 364 | |

End points

End points reporting groups

| | |
|---|-----------------------|
| Reporting group title | Brivaracetam |
| Reporting group description: Brivaracetam (BRV) used as adjunctive treatment, flexible dosing up to 200 mg /day in b.i.d (twice daily) administration. Dose increase or decrease can be made in increments of maximum 50 mg /day on a weekly basis. | |
| Subject analysis set title | Brivaracetam (SS) |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Brivaracetam (BRV) used as adjunctive treatment, flexible dosing up to 200 mg /day in b.i.d (twice daily) administration. Dose increase or decrease can be made in increments of maximum 50 mg /day on a weekly basis. | |
| Subject analysis set title | Brivaracetam (POS-ES) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Brivaracetam (BRV) used as adjunctive treatment, flexible dosing up to 200 mg /day in b.i.d (twice daily) administration. Dose increase or decrease can be made in increments of maximum 50 mg /day on a weekly basis. | |

Primary: Percentage of participants with at least one Treatment-Emergent Adverse Event (TEAE) during the Study Period

| | |
|--|---|
| End point title | Percentage of participants with at least one Treatment-Emergent Adverse Event (TEAE) during the Study Period ^[1] |
| End point description: Treatment-Emergent Adverse Events (TEAEs) are any untoward medical incidence in a subject during administered study treatment, whether or not these events are related to study treatment. | |
| End point type | Primary |
| End point timeframe: Visit 1 through last Evaluation Period, Down-Titration, or Post-Treatment Periods (up to 11 years) | |
| 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 as descriptive statistics only. | |

| End point values | Brivaracetam (SS) | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 667 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 91.2 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants who withdrew due to an Adverse Event (AE) during the Study Period

| | |
|-----------------|---|
| End point title | Percentage of participants who withdrew due to an Adverse Event (AE) during the Study Period ^[2] |
|-----------------|---|

End point description:

Adverse Events (AE) are any untoward medical incidence in a subject during administered study treatment, whether or not these events are related to study treatment.

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

End point timeframe:

Visit 1 through last Evaluation Period, Down-Titration, or Post-Treatment Periods (up to 11 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

| End point values | Brivaracetam (SS) | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 667 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 14.8 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with a Serious Adverse Event (SAE) during the Study Period

| | |
|-----------------|--|
| End point title | Percentage of participants with a Serious Adverse Event (SAE) during the Study Period ^[3] |
|-----------------|--|

End point description:

A Serious Adverse Event (SAE) is any untoward medical incidence that occurs at any dose.

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

End point timeframe:

Visit 1 through last Evaluation Period, Down-Titration, or Post-Treatment Periods (up to 11 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized as descriptive statistics only.

| End point values | Brivaracetam (SS) | | | |
|-----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 667 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 22.8 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Partial Onset Seizure (POS) (type I) frequency per 28 days during the

Evaluation Period

| | |
|-----------------|---|
| End point title | Partial Onset Seizure (POS) (type I) frequency per 28 days during the Evaluation Period |
|-----------------|---|

End point description:

Baseline is the Baseline from subject's previous study of enrollment period.

N01193 [NCT00175825], N01252 [NCT00490035], N01253 [NCT00464269], N01254 [NCT00504881].

A 28 day Type 1 seizure frequency is the total number of Type 1 seizures divided by the total number of days evaluated multiplied by 28.

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

End point timeframe:

From Baseline of the previous study to the Evaluation Period (up to 11 years)

| | | | | |
|---------------------------------------|-----------------------|--|--|--|
| End point values | Brivaracetam (POS-ES) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 648 | | | |
| Units: Seizures per 28 days | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| baseline | 9.2 (5.5 to 20.2) | | | |
| on treatment | 4.2 (1.6 to 11.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Partial Onset Seizure (POS) (type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period

| | |
|-----------------|---|
| End point title | Percent change in Partial Onset Seizure (POS) (type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period |
|-----------------|---|

End point description:

The percent change from the previous study baselines, in Partial Onset Seizure (POS) (Type I) frequency per 28 days is defined as:

(the value at the previous study baselines) minus (the value at each time-points during the evaluation period) divided by the value at the previous study baselines.

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

End point timeframe:

From Baseline of the previous study to the Evaluation Period (up to 11 years)

| | | | | |
|---------------------------------------|-----------------------|--|--|--|
| End point values | Brivaracetam (POS-ES) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 648 | | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | 57.3 (18.6 to 82.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with response for Partial Onset Seizure (POS) (type I) frequency over the Evaluation Period

| | |
|-----------------|--|
| End point title | Percentage of participants with response for Partial Onset Seizure (POS) (type I) frequency over the Evaluation Period |
|-----------------|--|

End point description:

A responder is defined as a subject with a higher than or equal to (\geq) 50 % change in seizure frequency from Baseline period of the previous study.

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

End point timeframe:

From Baseline of the previous study to the Evaluation Period (up to 11 years)

| | | | | |
|-----------------------------------|-----------------------|--|--|--|
| End point values | Brivaracetam (POS-ES) | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 648 | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 55.6 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Visit 1 through last Evaluation Period, Down-Titration, or Post-Treatment Periods (up to 11 years)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Brivaracetam (BRV) used as adjunctive treatment, flexible dosing up to 200 mg /day in b.i.d (twice daily) administration. Dose increase or decrease can be made in increments of maximum 50 mg /day on a weekly basis.

| Serious adverse events | Brivaracetam | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 152 / 667 (22.79%) | | |
| number of deaths (all causes) | 18 | | |
| number of deaths resulting from adverse events | 2 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Brain cancer metastatic | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain neoplasm | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colon cancer metastatic | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Gastrointestinal tract adenoma | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lipoma | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung adenocarcinoma metastatic | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Malignant pleural effusion | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metastatic bronchial carcinoma | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Non-small cell lung cancer | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Ocular neoplasm | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophageal cancer metastatic | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Ovarian epithelial cancer | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Ovarian germ cell teratoma benign | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small cell lung cancer stage unspecified | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestine carcinoma metastatic | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Foetal death | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy | | | |
| subjects affected / exposed | 5 / 667 (0.75%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy on oral contraceptive | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy on contraceptive | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|-----------------|--|--|
| Unintended pregnancy | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug ineffective | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden unexplained death in epilepsy | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Unevaluable event | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysfunctional uterine bleeding | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal disorder | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asphyxia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aggression | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Completed suicide | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 1 / 2 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hallucination | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paranoia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Major depression | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Self-injurious ideation | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Schizophrenia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 7 / 667 (1.05%) | | |
| occurrences causally related to treatment / all | 5 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Anticonvulsant drug level increased | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight increased | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |

| | | | | |
|---|-----------------|--|--|--|
| Abdominal injury | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Accident | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Anastomotic ulcer | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Animal bite | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ankle fracture | | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Brain contusion | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Burns third degree | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Comminuted fracture | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Craniocerebral injury | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 3 / 667 (0.45%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Foot fracture | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip fracture | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus fracture | | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ligament sprain | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Post procedural haematoma | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Procedural hypotension | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thermal burn | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 4 / 667 (0.60%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ulna fracture | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper limb fracture | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Angina unstable | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Central nervous system lesion | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cerebral infarction | | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Complicated migraine | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Convulsion | | | | |
| subjects affected / exposed | 15 / 667 (2.25%) | | | |
| occurrences causally related to treatment / all | 4 / 20 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epilepsy | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Grand mal convulsion | | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hemiparesis | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolic encephalopathy | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Partial seizures | | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Postictal state | | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure cluster | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Somnolence | | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Status epilepticus | | | | |
| subjects affected / exposed | 6 / 667 (0.90%) | | | |
| occurrences causally related to treatment / all | 4 / 7 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transient ischaemic attack | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 667 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric fistula | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Gastrooesophageal reflux disease subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoids subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal perforation subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Splenic artery aneurysm subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders Cholecystitis acute subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Calculus ureteric | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus urinary | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc degeneration | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|
| Joint instability | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coccidioidomycosis | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dengue fever | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disseminated tuberculosis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Encephalitis herpes | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia sepsis | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis viral | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lobar pneumonia | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infection | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malaria | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mastoiditis | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningitis tuberculous | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neurocysticercosis | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic inflammatory disease | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periorbital cellulitis | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 7 / 667 (1.05%) | | | |
| occurrences causally related to treatment / all | 0 / 9 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rickettsiosis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 667 (0.45%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperammonaemia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 667 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 1 / 667 (0.15%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Brivaracetam | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 521 / 667 (78.11%) | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 40 / 667 (6.00%) | | |
| occurrences (all) | 72 | | |
| Contusion | | | |
| subjects affected / exposed | 34 / 667 (5.10%) | | |
| occurrences (all) | 68 | | |
| Laceration | | | |
| subjects affected / exposed | 34 / 667 (5.10%) | | |
| occurrences (all) | 65 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 46 / 667 (6.90%) | | |
| occurrences (all) | 55 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 165 / 667 (24.74%) | | |
| occurrences (all) | 420 | | |

| | | | |
|--|--------------------|--|--|
| Dizziness | | | |
| subjects affected / exposed | 142 / 667 (21.29%) | | |
| occurrences (all) | 254 | | |
| Somnolence | | | |
| subjects affected / exposed | 91 / 667 (13.64%) | | |
| occurrences (all) | 116 | | |
| Convulsion | | | |
| subjects affected / exposed | 70 / 667 (10.49%) | | |
| occurrences (all) | 99 | | |
| Tremor | | | |
| subjects affected / exposed | 38 / 667 (5.70%) | | |
| occurrences (all) | 48 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 69 / 667 (10.34%) | | |
| occurrences (all) | 132 | | |
| Fatigue | | | |
| subjects affected / exposed | 51 / 667 (7.65%) | | |
| occurrences (all) | 63 | | |
| Irritability | | | |
| subjects affected / exposed | 42 / 667 (6.30%) | | |
| occurrences (all) | 50 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 67 / 667 (10.04%) | | |
| occurrences (all) | 93 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 65 / 667 (9.75%) | | |
| occurrences (all) | 86 | | |
| Vomiting | | | |
| subjects affected / exposed | 58 / 667 (8.70%) | | |
| occurrences (all) | 109 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 39 / 667 (5.85%) | | |
| occurrences (all) | 55 | | |
| Toothache | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>42 / 667 (6.30%)</p> <p>66</p> <p>38 / 667 (5.70%)</p> <p>48</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>46 / 667 (6.90%)</p> <p>69</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>34 / 667 (5.10%)</p> <p>56</p> | | |
| <p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>70 / 667 (10.49%)</p> <p>85</p> <p>49 / 667 (7.35%)</p> <p>65</p> <p>45 / 667 (6.75%)</p> <p>65</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>64 / 667 (9.60%)</p> <p>88</p> <p>52 / 667 (7.80%)</p> <p>66</p> <p>44 / 667 (6.60%)</p> <p>63</p> | | |
| <p>Infections and infestations</p> | | | |

| | | | |
|--|--------------------------|--|--|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 94 / 667 (14.09%) 154 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 76 / 667 (11.39%) 137 | | |
| Influenza subjects affected / exposed occurrences (all) | 84 / 667 (12.59%) 177 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 64 / 667 (9.60%) 150 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 36 / 667 (5.40%) 41 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 02 June 2006 | Clarified several sections of the protocol, including study title, study drug packaging, flow chart, study procedures and visit description, and Sponsor contact information. |
| 02 March 2007 | Permitted participation of subjects from the brivaracetam (BRV) Phase 3 studies (N01253, N01253, and N01254) and updates of several sections including study title, background information, exclusion criteria, objectives, variables, and the study schematic. Maximum dose of study drug was increased to 150 mg/day. |
| 01 June 2007 | Issued as a follow-up to the Food and Drug Administration (FDA) feedback received on study N01253 where FDA specifically requested to add an additional down-titration step for subjects taking 50 mg/day or more. The use of the 2.5 mg tablets was restricted to subjects taking less than BRV 40 mg/day. Additional clarifications were made to allow for a new Clinical Trial Manager, clarify additional information from Amendment 2, and update some minor typographical errors. |
| 20 May 2008 | Clarified that subjects rolling over from the Phase 2 brivaracetam (BRV) study, N01193, who were on placebo would have access to BRV, updated the inclusion criterion regarding contraceptive methods, and stipulated that dose increments were to be made using only 10 mg or 25 mg tablets beyond the dose of 40 mg/day. |
| 26 June 2011 | Introduced the increased maximum dose of brivaracetam (BRV) of 200 mg/day; provided that conversion to monotherapy would no longer be at the Investigator's discretion; updated procedures for reporting serious adverse events (SAEs) to implement Food and Drug Administration (FDA) Final Rule requirements; updated laboratory assessments (BRV and antiepileptic drug (AED) plasma levels were no longer obtained), statistical analyses, and contact information; reduced the number of study assessments; limited the assessments of exploratory variables (Patient Weighted Quality of Life in Epilepsy Questionnaire [QOLIE-31-P], Hospital Anxiety and Depression Scale [HADS], EuroQoL 5 Dimensions Questionnaire [EQ-5D], hospital stays, healthcare provider consultations not foreseen, school and work days lost, and socioprofessional data) to the first 2 years after study entry; added the Columbia Suicide Severity Rating Scale (C-SSRS) and respective withdrawal criteria; introduced a Partner Pregnancy Consent form; removal of 2.5 mg tablets; removal of references to subjects coming from N01258, since these subjects were no longer to be included in N01199; and made further minor changes for consistency between BRV studies. |
| 15 October 2015 | Aligned efficacy variables in statistics section with current N01199 statistical analysis plan (SAP); the study duration language was revised to include the possibility of a named patient or compassionate use program (or similar) as a reason for ending the study duration; language regarding Investigator deviation from the protocol in the event of a medical emergency was revised to align with current UCB standard language. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported