



## Clinical trial results:

### A Multicenter, Double Blind, Randomized, Placebo-Controlled Trial to Determine the Efficacy and Safety of Ganaxolone as Adjunctive Therapy for Adults With Drug-Resistant Partial-Onset Seizures Followed by Long-term Open-Label Treatment

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2014-004363-21  |
| Trial protocol           | BG DE PL        |
| Global end of trial date | 01 October 2016 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 23 November 2023 |
| First version publication date | 23 November 2023 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | 1042-0603 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01963208 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Marinus Pharmaceuticals, Inc.  |
| Sponsor organisation address | 5 Radnor Corporate Center, 100 Matsonford Road, Suite 500, Radnor, United States, PA 19087           |
| Public contact               | Marinus Pharmaceuticals, Inc., Safety Department, 001 484-801-4670, clinicaltrials@marinuspharma.com |
| Scientific contact           | Marinus Pharmaceuticals, Inc., Safety Department, 001 484-801-4670, clinicaltrials@marinuspharma.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 01 October 2016 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 01 October 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate efficacy of ganaxolone compared to placebo as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalizations.

Protection of trial subjects:

At the first visit, prior to initiation of any study-related procedures, the parent(s) or legal guardian(s) of the subjects gave their written consent to participate in the study after having been informed about the nature and purpose of the study, participation / termination conditions, and risks and benefits. Before the informed consent document was signed, the investigator, or a person designated by the investigator, provided the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial were answered to the satisfaction of the subject or the subject's legally acceptable representative.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 01 October 2013 |
| 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 | Poland: 42             |
| Country: Number of subjects enrolled | Bulgaria: 77           |
| Country: Number of subjects enrolled | Germany: 17            |
| Country: Number of subjects enrolled | Australia: 47          |
| Country: Number of subjects enrolled | Russian Federation: 81 |
| Country: Number of subjects enrolled | United States: 141     |
| Worldwide total number of subjects   | 405                    |
| EEA total number of subjects         | 136                    |

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)                | 0   |
| Adults (18-64 years)                     | 391 |
| From 65 to 84 years                      | 14  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This was a 2-cohort study where each cohort comprised of 2 treatment phases. Phase 1 was a double-blind phase followed by Phase 2, an open-label phase. The study analyzed safety, tolerability and pharmacokinetics (PK) of Ganaxolone when compared with placebo in both the cohorts.

### Pre-assignment

Screening details:

This was a 2-cohort study where each cohort comprised of 2 treatment phases. Phase 1 was a double-blind phase followed by Phase 2, an open-label phase. The study analyzed safety, tolerability and pharmacokinetics (PK) of Ganaxolone when compared with placebo in both the cohorts.

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Treatment Phase 1 (Up to Week 14) |
| Is this the baseline period? | Yes                               |
| Allocation method            | Randomised - controlled           |
| Blinding used                | Double blind                      |
| Roles blinded                | Investigator, Subject             |

### Arms

|                              |                                     |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes                                 |
| <b>Arm title</b>             | Double Blind: Cohort 1 - Ganaxolone |

Arm description:

Participants were administered ganaxolone 1200 milligrams per day (mg/day) and 1800 mg/day + Antiepileptic drug (AED). Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

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

Dosage and administration details:

Ganaxolone was administered

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Double Blind: Cohort 1 - Placebo |
|------------------|----------------------------------|

Arm description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

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

Dosage and administration details:

Placebo was administered.

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | Double Blind: Cohort 2 - Ganaxolone |
|------------------|-------------------------------------|

Arm description:

Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while

participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

|   |                                  |
|---|----------------------------------|
| Arm type  | Experimental                     |
| Investigational medicinal product name                                | Ganaxolone                       |
| Investigational medicinal product code                                |                                  |
| Other name  |                                  |
| Pharmaceutical forms  | Tablet                           |
| Routes of administration  | Oral use                         |
| Dosage and administration details:<br>Ganaxolone will be administered |                                  |
| <b>Arm title</b>  | Double Blind: Cohort 2 - Placebo |

Arm description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

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

Dosage and administration details:

Placebo was administered.

| <b>Number of subjects in period 1</b> | Double Blind: Cohort 1 - Ganaxolone | Double Blind: Cohort 1 - Placebo | Double Blind: Cohort 2 - Ganaxolone |
|---------------------------------------|-------------------------------------|----------------------------------|-------------------------------------|
| Started                               | 24                                  | 22                               | 179                                 |
| Completed                             | 23                                  | 19                               | 135                                 |
| Not completed                         | 1                                   | 3                                | 44                                  |
| Consent withdrawn by subject          | -                                   | 2                                | 8                                   |
| Non-Compliance                        | -                                   | -                                | 4                                   |
| Adverse event, non-fatal              | 1                                   | -                                | 30                                  |
| Protocol violation                    | -                                   | -                                | 1                                   |
| Insufficient Clinical Response        | -                                   | -                                | -                                   |
| Unspecified                           | -                                   | 1                                | 1                                   |
| Lost to follow-up                     | -                                   | -                                | -                                   |

| <b>Number of subjects in period 1</b> | Double Blind: Cohort 2 - Placebo |
|---------------------------------------|----------------------------------|
| Started                               | 180                              |
| Completed                             | 154                              |
| Not completed                         | 26                               |
| Consent withdrawn by subject          | 9                                |
| Non-Compliance                        | -                                |
| Adverse event, non-fatal              | 11                               |
| Protocol violation                    | 3                                |
| Insufficient Clinical Response        | 1                                |

|                   |   |
|-------------------|---|
| Unspecified       | 1 |
| Lost to follow-up | 1 |

## Period 2

|                              |  |
|------------------------------|--|
| Period 2 title               | Treatment Phase 2 (Up to Week 68)      |
| Is this the baseline period? | No                                     |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

## Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Open Label: Ganaxolone in Double-blind Phase |

### Arm description:

Following the completion of the double-blind phase, participants randomized to ganaxolone remained on the drug at 1800 mg/day + AED. Participants from Double Blind: Cohort 1 - Ganaxolone and Double Blind: Cohort 2 - Ganaxolone were combined to enter in Open Label: Ganaxolone in Double-blind Phase

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

### Dosage and administration details:

Ganaxolone was administered.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Open Label: Placebo in Double-blind Phase |
|------------------|---|

### Arm description:

Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone + AED. Participants from Double Blind: Cohort 1 - Placebo and Double Blind: Cohort 2 - Placebo were combined to enter in Open Label: Placebo in Double-blind Phase

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

### Dosage and administration details:

Placebo was administered

| <b>Number of subjects in period 2</b> | Open Label:<br>Ganaxolone in<br>Double-blind Phase | Open Label: Placebo<br>in Double-blind<br>Phase |
|---------------------------------------|--|---|
| Started                               | 158  | 173   |
| Completed                             | 57   | 44  |
| Not completed                         | 101  | 129   |
| Consent withdrawn by subject          | 7  | 19  |
| Non-Compliance                        | -  | 1   |
| Adverse event, non-fatal              | 16   | 15  |
| Protocol violation                    | -  | 1   |
| Death                                 | -  | 1   |
| Insufficient Clinical Response        | 20   | 17  |
| Unspecified                           | 58   | 75  |

## Baseline characteristics

### Reporting groups

|                                |                                   |
|--------------------------------|-----------------------------------|
| Reporting group title          | Treatment Phase 1 (Up to Week 14) |
| Reporting group description: - |                                   |

| Reporting group values                                | Treatment Phase 1<br>(Up to Week 14) | Total |  |
|---|--------------------------------------|-------|--|
| Number of subjects                                    | 405                                  | 405   |  |
| Age categorical<br>Units: Subjects                    |                                      |       |  |
| In utero  | 0                                    | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                    | 0     |  |
| Newborns (0-27 days)                                  | 0                                    | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0                                    | 0     |  |
| Children (2-11 years)                                 | 0                                    | 0     |  |
| Adolescents (12-17 years)                             | 0                                    | 0     |  |
| Adults (18-64 years)                                  | 391                                  | 391   |  |
| From 65-84 years                                      | 14                                   | 14    |  |
| 85 years and over                                     | 0                                    | 0     |  |
| Age continuous<br>Units: years                        |                                      |       |  |
| arithmetic mean                                       | 40.99                                |       |  |
| standard deviation                                    | ± 12.379                             | -     |  |
| Gender categorical<br>Units: Subjects                 |                                      |       |  |
| Female  | 243                                  | 243   |  |
| Male  | 162                                  | 162   |  |

### Subject analysis sets

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Double Blind: Cohort 1 – Ganaxolone |
| Subject analysis set type  | Modified intention-to-treat         |

Subject analysis set description:

Participants were administered ganaxolone 1200 mg/day and 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Double Blind: Cohort 1 - Placebo |
| Subject analysis set type  | Modified intention-to-treat      |

Subject analysis set description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | Double Blind: Cohort 2 - Ganaxolone |
| Subject analysis set type  | Modified intention-to-treat         |



Subject analysis set description:

Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Double Blind: Cohort 2 - Placebo |
| Subject analysis set type  | Modified intention-to-treat      |

Subject analysis set description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

| Reporting group values  | Double Blind: Cohort 1 – Ganaxolone | Double Blind: Cohort 1 - Placebo | Double Blind: Cohort 2 - Ganaxolone |
|---|-------------------------------------|----------------------------------|-------------------------------------|
| Number of subjects  | 24                                  | 21                               | 178                                 |
| Age categorical<br>Units: Subjects  |                                     |                                  |                                     |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                     |                                  |                                     |
| Age continuous<br>Units: years  |                                     |                                  |                                     |
| arithmetic mean   | 35.1                                | 41.1                             | 40.6                                |
| standard deviation  | ± 10.25                             | ± 11.83                          | ± 12.48                             |
| Gender categorical<br>Units: Subjects   |                                     |                                  |                                     |
| Female  | 13                                  | 12                               | 113                                 |
| Male  | 11                                  | 9                                | 65                                  |

| Reporting group values  | Double Blind: Cohort 2 - Placebo |  |  |
|---|----------------------------------|--|--|
| Number of subjects  | 172                              |  |  |
| Age categorical<br>Units: Subjects  |                                  |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                  |  |  |
| Age continuous<br>Units: years  |                                  |  |  |
| arithmetic mean   | 42.1                             |  |  |

|                    |             |  |  |
|--------------------|-------------|--|--|
| standard deviation | $\pm 12.37$ |  |  |
|--------------------|-------------|--|--|

|                    |    |  |  |
|--------------------|----|--|--|
| Gender categorical |    |  |  |
| Units: Subjects    |    |  |  |
| Female             | 97 |  |  |
| Male               | 75 |  |  |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Double Blind: Cohort 1 - Ganaxolone          |
| Reporting group description:<br>Participants were administered ganaxolone 1200 milligrams per day (mg/day) and 1800 mg/day + Antiepileptic drug (AED). Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.  |  |
| Reporting group title   | Double Blind: Cohort 1 - Placebo             |
| Reporting group description:<br>Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.   |  |
| Reporting group title   | Double Blind: Cohort 2 - Ganaxolone          |
| Reporting group description:<br>Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.  |  |
| Reporting group title   | Double Blind: Cohort 2 - Placebo             |
| Reporting group description:<br>Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase  |  |
| Reporting group title   | Open Label: Ganaxolone in Double-blind Phase |
| Reporting group description:<br>Following the completion of the double-blind phase, participants randomized to ganaxolone remained on the drug at 1800 mg/day + AED. Participants from Double Blind: Cohort 1 - Ganaxolone and Double Blind: Cohort 2 - Ganaxolone were combined to enter in Open Label: Ganaxolone in Double-blind Phase   |  |
| Reporting group title   | Open Label: Placebo in Double-blind Phase    |
| Reporting group description:<br>Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone + AED. Participants from Double Blind: Cohort 1 - Placebo and Double Blind: Cohort 2 - Placebo were combined to enter in Open Label: Placebo in Double-blind Phase   |  |
| Subject analysis set title  | Double Blind: Cohort 1 - Ganaxolone          |
| Subject analysis set type   | Modified intention-to-treat                  |
| Subject analysis set description:<br>Participants were administered ganaxolone 1200 mg/day and 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase  |  |
| Subject analysis set title  | Double Blind: Cohort 1 - Placebo             |
| Subject analysis set type   | Modified intention-to-treat                  |
| Subject analysis set description:<br>Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.<br>Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at |  |
| Subject analysis set title  | Double Blind: Cohort 2 - Ganaxolone          |
| Subject analysis set type   | Modified intention-to-treat                  |
| Subject analysis set description:<br>Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.   |  |
| Subject analysis set title  | Double Blind: Cohort 2 - Placebo             |

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

#### Subject analysis set description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

### Primary: Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period <sup>[1]</sup> |
|-----------------|---|

#### End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period ( $\leq 56$  days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose. Primary analysis was performed using a rank analysis of covariance (ANCOVA). Modified intent to treat (mITT) population: all randomized participants who received at least 1 dose of study medication and provided any post Baseline seizure outcome data.

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

#### End point timeframe:

Baseline and Week 14

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                 | Double Blind: Cohort 2 - Ganaxolone | Double Blind: Cohort 2 - Placebo |  |  |
|----------------------------------|-------------------------------------|----------------------------------|--|--|
| Subject group type               | Reporting group                     | Reporting group                  |  |  |
| Number of subjects analysed      | 178                                 | 172                              |  |  |
| Units: Percent change            |                                     |                                  |  |  |
| median (confidence interval 95%) | -21.28 (-29.60 to -14.29)           | -10.25 (-20.14 to -1.28)         |  |  |

### Statistical analyses

|                            |         |
|----------------------------|---------|
| Statistical analysis title | Week 14 |
|----------------------------|---------|

#### Statistical analysis description:

Double Blind: Cohort 2 - Ganaxolone, Double Blind: Cohort 2 - Placebo

|   |  |
|---|--|
| Comparison groups                       | Double Blind: Cohort 2 - Ganaxolone v Double Blind: Cohort 2 - Placebo |
| Number of subjects included in analysis | 350  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.1788 <sup>[2]</sup>  |
| Method                                  | Rank ANCOVA  |
| Parameter estimate                      | Median difference (final values)                                       |
| Point estimate                          | -7.06  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -17.44  |
| upper limit         | 3.52    |

Notes:

[2] - The null hypothesis is that there is no difference between the distributions of the two treatment groups with respect to percent change in seizure frequency.

### Secondary: Double Blind: Cohort 2: Number of Participants With $\geq 50\%$ Responder Rate During Titration + Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Number of Participants With $\geq 50\%$ Responder Rate During Titration + Maintenance Period <sup>[3]</sup> |
|-----------------|---|

End point description:

A 50% responder was a participant who experienced at least a 50% decrease in 28-day seizure frequency compared to Baseline

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

End point timeframe:

Up to Week 14

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values            | Double Blind: Cohort 2 - Ganaxolone | Double Blind: Cohort 2 - Placebo |  |  |
|-----------------------------|-------------------------------------|----------------------------------|--|--|
| Subject group type          | Reporting group                     | Reporting group                  |  |  |
| Number of subjects analysed | 178                                 | 172                              |  |  |
| Units: Participants         |                                     |                                  |  |  |
| number (not applicable)     | 50                                  | 39                               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Titration + Maintenance Period

|                 |  |
|-----------------|--|
| End point title | Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Titration + Maintenance Period <sup>[4]</sup> |
|-----------------|--|

End point description:

Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire Baseline period ( $\leq 56$  days) divided by the number of days with available seizure data in the baseline period and multiplied by 28. Post-Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire treatment period divided by the number of days with available seizure data in the treatment period and multiplied by 28. Change from Baseline in number of seizure free days per 28-day period from Baseline was calculated as: Post-Baseline number of seizure free days per 28-day period minus Baseline number of seizure free days per 28-day period. Baseline was defined as non-missing value of last assessment before first dose.

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

End point timeframe:

Baseline and Week 14

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed          | 178                                       | 172                                    |  |  |
| Units: Seizure free days             |   |  |  |  |
| arithmetic mean (standard deviation) | 1.47 ( $\pm$ 4.396)                       | 1.01 ( $\pm$ 4.223)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 14

|                 |  |
|-----------------|--|
| End point title | Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 14 <sup>[5]</sup> |
|-----------------|--|

End point description:

The CGI-I scale is a clinician-rated 7-point Likert scale used to assess the degree to which the participant's epilepsy symptoms have changed relative to Baseline. It was rated as 1. "very much improved"; 2. "much improved"; 3. "minimally improved"; 4. "no change"; 5. "minimally worse"; 6. "much worse"; 7. "very much worse". Higher scores indicated worse condition. Baseline was defined as non-missing value of last assessment before first dose.

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

End point timeframe:

At Week 14

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values            | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed | 140                                       | 159                                    |  |  |
| Units: Participants         |   |  |  |  |
| number (not applicable)     |   |  |  |  |
| Very much improved          | 7   | 5                                      |  |  |
| Much improved               | 28  | 30                                     |  |  |
| Minimally improved          | 41  | 47                                     |  |  |
| No change                   | 56  | 67                                     |  |  |
| Minimally worse             | 6   | 8                                      |  |  |
| Much worse                  | 2   | 2                                      |  |  |
| Very much worse             | 0   | 0                                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Maintenance Period <sup>[6]</sup> |
|-----------------|---|

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period ( $\leq 56$  days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose.

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

End point timeframe:

Baseline and Week 2 to Week 14

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                 | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed      | 166                                       | 169                                    |  |  |
| Units: Percent change            |   |  |  |  |
| median (confidence interval 95%) | -20.56 (-31.56<br>to -12.69)              | -12.50 (-20.78<br>to -3.03)            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period <sup>[7]</sup> |
|-----------------|---|

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period ( $\leq 56$  days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value.

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

End point timeframe:

Baseline and Week 14

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed          | 178                                       | 172                                    |  |  |
| Units: Seizures per 28 days          |   |  |  |  |
| arithmetic mean (standard deviation) | -1.46 (±<br>9.650)                        | -0.33 (±<br>11.040)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Maintenance Period <sup>[8]</sup> |
|-----------------|---|

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period ( $\leq 56$  days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value

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

End point timeframe:

Baseline and Week 2 to Week 14

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed          | 166                                       | 169                                    |  |  |
| Units: Seizures per 28 days          |   |  |  |  |
| arithmetic mean (standard deviation) | -1.67 (±<br>11.809)                       | -0.64 (±<br>12.153)                    |  |  |

## Statistical analyses



**Secondary: Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Maintenance Period**

|                 |  |
|-----------------|--|
| End point title | Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Maintenance Period <sup>[9]</sup> |
|-----------------|--|

## End point description:

Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire Baseline period ( $\leq 56$  days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Post-Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire treatment period divided by the number of days with available seizure data in the treatment period and multiplied by 28. Change from Baseline in number of seizure free days per 28-day period from Baseline was calculated as: Post-Baseline number of seizure free days per 28-day period minus Baseline number of seizure free days per 28-day period. Baseline was defined as non-missing value of last assessment before first dose.

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

## End point timeframe:

Baseline and Week 2 to Week 14

## Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed          | 166                                       | 169                                    |  |  |
| Units: Seizure free days             |   |  |  |  |
| arithmetic mean (standard deviation) | 1.63 ( $\pm 4.824$ )                      | 1.20 ( $\pm 4.462$ )                   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Double Blind: Cohort 2: Percentage of Responders Experiencing a  $\geq R\%$  (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Titration + Maintenance Period**

|                 |  |
|-----------------|--|
| End point title | Double Blind: Cohort 2: Percentage of Responders Experiencing a $\geq R\%$ (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Titration + Maintenance Period <sup>[10]</sup> |
|-----------------|--|

## End point description:

Percentage of participants who had reductions of  $\geq 80\%$ ,  $\geq 60\%$ ,  $\geq 40\%$ , and  $\geq 20\%$  in 28-day seizure frequency from Baseline is presented. A responder is an individual whose reduction of percent change from Baseline in 28-day seizure frequency was  $\geq 50\%$ . Baseline was defined as non-missing value of last assessment before first dose.

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

## End point timeframe:

Up to Week 14

## Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                  | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed       | 178                                       | 172                                    |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (not applicable)           |   |  |  |  |
| Reduction $\geq$ 80%              | 7.3                                       | 2.33                                   |  |  |
| Reduction $\geq$ 60%              | 20.79                                     | 16.86                                  |  |  |
| Reduction $\geq$ 40%              | 33.15                                     | 29.65                                  |  |  |
| Reduction $\geq$ 20%              | 51.69                                     | 43.6                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double Blind: Cohort 2: Percentage of Responders Experiencing a $\geq$ R% (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Percentage of Responders Experiencing a $\geq$ R% (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Maintenance Period <sup>[11]</sup> |
|-----------------|---|

End point description:

Percentage of participants who had reductions of  $\geq$  80%,  $\geq$  60%,  $\geq$  40%, and  $\geq$  20% in 28-day seizure frequency from Baseline is presented. A responder is an individual whose reduction of percent change from Baseline in 28-day seizure frequency was  $\geq$  50%. Baseline was defined as non-missing value of last assessment before first dose.

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

End point timeframe:

Week 2 to Week 14

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                  | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed       | 178                                       | 172                                    |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (not applicable)           |   |  |  |  |
| Reduction $\geq$ 80%              | 8.43                                      | 5.81                                   |  |  |
| Reduction $\geq$ 60%              | 24.16                                     | 18.02                                  |  |  |
| Reduction $\geq$ 40%              | 33.71                                     | 31.4                                   |  |  |
| Reduction $\geq$ 20%              | 47.19                                     | 42.44                                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Double Blind: Cohort 2: Percentage of Seizure Free Participants During the Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Percentage of Seizure Free Participants During the Maintenance Period <sup>[12]</sup> |
|-----------------|---|

End point description:

Percentage of participants who completed the study without any seizures is presented

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

End point timeframe:

Week 2 to Week 14

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                  | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed       | 178                                       | 172                                    |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (not applicable)           | 1.12                                      | 0                                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Double Blind: Cohort 2: Percentage of Participants Who Experienced at Least One 28-day Seizure Free Period During Titration + Maintenance Phase

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Percentage of Participants Who Experienced at Least One 28-day Seizure Free Period During Titration + Maintenance Phase <sup>[13]</sup> |
|-----------------|---|

End point description:

Percentage of participants who experienced at least one 28-day seizure free period is presented

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

End point timeframe:

Up to Week 14

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                  | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed       | 178                                       | 172                                    |  |  |
| Units: Percentage of participants |   |  |  |  |
| number (not applicable)           | 17.98                                     | 18.02                                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double Blind: Cohort 2: Longest Percent of Time Spent Seizure-free During Titration + Maintenance Period

|                 |  |
|-----------------|--|
| End point title | Double Blind: Cohort 2: Longest Percent of Time Spent Seizure-free During Titration + Maintenance Period <sup>[14]</sup> |
|-----------------|--|

End point description:

The longest period of time seizure-free was defined as the percent of the longest seizure-free period (days) divided by the days with available seizure data, and then multiplied by 100%.

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

End point timeframe:

Up to Week 14

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|--------------------------------------|---|--|--|--|
| Subject group type                   | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed          | 178                                       | 172                                    |  |  |
| Units: Percentage of time spent      |   |  |  |  |
| arithmetic mean (standard deviation) | 24.00 (±<br>22.457)                       | 17.58 (±<br>12.743)                    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency for Different Subtypes of Seizures During Titration + Maintenance Period

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency for Different Subtypes of Seizures During Titration + Maintenance Period <sup>[15]</sup> |
|-----------------|---|

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. The analysis was conducted for Partial-Onset Seizure (POS) only which included seizure subtypes: Complex partial seizures (CPS), secondarily generalized tonic-clonic (SGTC) seizures, simple partial seizure with motor/observable component (SPS-Motor) and Simple partial seizure (SPS) without motor/observable component. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period ( $\leq 56$  days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose.

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

End point timeframe:

Baseline and Week 14

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values                     | Double Blind: Cohort 2 - Ganaxolone | Double Blind: Cohort 2 - Placebo |  |  |
|--------------------------------------|-------------------------------------|----------------------------------|--|--|
| Subject group type                   | Reporting group                     | Reporting group                  |  |  |
| Number of subjects analysed          | 150                                 | 152                              |  |  |
| Units: Percent change                |                                     |                                  |  |  |
| arithmetic mean (standard deviation) |                                     |                                  |  |  |
| CPS (n= 150, 152)                    | -4.70 ( $\pm$ 92.373)               | -6.52 ( $\pm$ 59.126)            |  |  |
| SGTC (n= 69, 82)                     | -27.42 ( $\pm$ 69.394)              | 1.02 ( $\pm$ 118.444)            |  |  |
| SPS-Motor (n= 44, 32)                | -5.52 ( $\pm$ 93.228)               | -21.97 ( $\pm$ 52.473)           |  |  |
| SPS (n= 33, 31)                      | 12.57 ( $\pm$ 129.979)              | -3.53 ( $\pm$ 87.071)            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double Blind: Cohort 2: Number of Participants With Patient Global Impression of Change – Improvement (PGI-I) at Week 8 and Week 14

|                 |   |
|-----------------|---|
| End point title | Double Blind: Cohort 2: Number of Participants With Patient Global Impression of Change – Improvement (PGI-I) at Week 8 and Week 14 <sup>[16]</sup> |
|-----------------|---|

End point description:

The PGI-I scale was a 7-point Likert scale completed by the Patient or Caregiver representing the degree to which the participant's epilepsy symptoms had changed relative to Baseline. It was rated as 1. "very much improved"; 2. "much improved"; 3. "minimally improved"; 4. "no change"; 5. "minimally worse"; 6. "much worse"; 7. "very much worse". Higher score indicated worse condition. Baseline was defined as non-missing value of last assessment before first dose.

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

End point timeframe:

Week 8 and Week 14

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| End point values            | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed | 166                                       | 161                                    |  |  |
| Units: Participants         |   |  |  |  |
| number (not applicable)     |   |  |  |  |
| Week 8: Very Much Improved  | 7   | 5                                      |  |  |
| Week 8: Much Improved       | 30  | 21                                     |  |  |
| Week 8: Minimally Improved  | 44  | 51                                     |  |  |
| Week 8: No Change           | 59  | 65                                     |  |  |
| Week 8: Minimally Worse     | 12  | 11                                     |  |  |
| Week 8: Much Worse          | 8   | 4                                      |  |  |
| Week 8: Very Much Worse     | 6   | 4                                      |  |  |
| Week 14: Very Much Improved | 7   | 10                                     |  |  |
| Week 14: Much Improved      | 33  | 29                                     |  |  |
| Week 14: Minimally Improved | 43  | 43                                     |  |  |
| Week 14: No Change          | 46  | 60                                     |  |  |
| Week 14: Minimally Worse    | 7   | 12                                     |  |  |
| Week 14: Much Worse         | 3   | 4                                      |  |  |
| Week 14: Very Much Worse    | 1   | 1                                      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 8

|                 |  |
|-----------------|--|
| End point title | Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 8 <sup>[17]</sup> |
|-----------------|--|

End point description:

The CGI-I scale is a clinician-rated 7-point Likert scale used to assess the degree to which the participant's epilepsy symptoms have changed relative to Baseline. It was rated as 1. "very much improved"; 2. "much improved"; 3. "minimally improved"; 4. "no change"; 5. "minimally worse"; 6. "much worse"; 7. "very much worse". Higher scores indicated worse condition. Baseline was defined as non-missing value of last assessment before first dose.

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

End point timeframe:

At Week 8

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, statistical analysis was not planned for this endpoint.

| <b>End point values</b>     | Double Blind:<br>Cohort 2 -<br>Ganaxolone | Double Blind:<br>Cohort 2 -<br>Placebo |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                           | Reporting group                        |  |  |
| Number of subjects analysed | 166                                       | 162                                    |  |  |
| Units: Participants         |   |  |  |  |
| number (not applicable)     |   |  |  |  |
| Very much improved          | 3   | 4                                      |  |  |
| Much improved               | 27  | 20                                     |  |  |
| Minimally improved          | 50  | 49                                     |  |  |
| No change                   | 68  | 71                                     |  |  |
| Minimally worse             | 8   | 12                                     |  |  |
| Much worse                  | 9   | 5                                      |  |  |
| Very much worse             | 1   | 1                                      |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Week -8 through Week 14 in Double blind phase and from Week 16 to Week 68 in open label phase

Adverse event reporting additional description:

Safety Population: included all randomized participants who received at least 1 dose of study medication.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Open Label: Ganaxolone in Double-blind Phase |
|-----------------------|--|

Reporting group description:

Following the completion of the double-blind phase, participants randomized to ganaxolone remained on the drug at 1800 mg/day + AED. Participants from Double Blind: Cohort 1 - Ganaxolone and Double Blind: Cohort 2 - Ganaxolone were combined to enter in Open Label: Ganaxolone in Double-blind Phase

|                       |   |
|-----------------------|---|
| Reporting group title | Open Label: Placebo in Double-blind Phase |
|-----------------------|---|

Reporting group description:

Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone + AED. Participants from Double Blind: Cohort 1 - Placebo and Double Blind: Cohort 2 - Placebo were combined to enter in Open Label: Placebo in Double-blind Phase

|                       |   |
|-----------------------|---|
| Reporting group title | Double Blind: Cohort 1 and Cohort 2- Ganaxolone |
|-----------------------|---|

Reporting group description:

Participants were administered ganaxolone 1200 milligrams per day (mg/day) and 1800 mg/day + Antiepileptic drug (AED) in Cohort 1 and Participants were administered Ganaxolone 1800 mg/day + AED in Cohort 2. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

|                       |   |
|-----------------------|---|
| Reporting group title | Double Blind: Cohort 1 and Cohort 2 - Placebo |
|-----------------------|---|

Reporting group description:

Participants were administered Placebo + AED in Cohort 1 and Cohort 2. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

| <b>Serious adverse events</b>                                       | Open Label:<br>Ganaxolone in<br>Double-blind Phase | Open Label: Placebo<br>in Double-blind<br>Phase | Double Blind: Cohort<br>1 and Cohort 2-<br>Ganaxolone |
|---|--|---|---|
| Total subjects affected by serious adverse events                   |  |   |   |
| subjects affected / exposed   | 12 / 158 (7.59%)                                   | 12 / 173 (6.94%)                                | 9 / 203 (4.43%)                                       |
| number of deaths (all causes)                                       | 0  | 1   | 0   |
| number of deaths resulting from adverse events                      |  |   | 0   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |   |   |
| Breast cancer   |  |   |   |
| subjects affected / exposed   | 0 / 158 (0.00%)                                    | 0 / 173 (0.00%)                                 | 1 / 203 (0.49%)                                       |
| occurrences causally related to treatment / all                     | 0 / 0  | 0 / 0   | 0 / 1   |
| deaths causally related to treatment / all                          | 0 / 0  | 0 / 0   | 0 / 1   |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Clavicle fracture                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Accidental overdose                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Tongue injury                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Ligament rupture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Spinal column injury                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cardiac disorders                               |                 |                 |                 |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Convulsion                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 4 / 173 (2.31%) | 2 / 203 (0.99%) |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 4           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 4           | 0 / 2           |
| Epilepsy  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Toxic encephalopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Seizure cluster                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Status epilepticus                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Speech disorder                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Somnolence                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Postictal psychosis                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Grand mal convulsion                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 2           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Asthenia   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           | 0 / 0           |
| Gait disturbance                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 2           | 0 / 1           |
| Gastrointestinal disorders                           |                 |                 |                 |
| Small intestinal obstruction                         |                 |                 |                 |
| subjects affected / exposed                          | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 1           |
| Oesophageal obstruction                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |
| Respiratory failure                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 1           |
| Psychiatric disorders                                |                 |                 |                 |
| Psychogenic seizure                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Suicidal ideation                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Suicide attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Mental status changes                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Hallucination                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Delusion  |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 1           | 0 / 0           |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |                 |                 |
| Rhabdomyolysis   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 1           | 0 / 0           |
| <b>Infections and infestations</b>                     |                 |                 |                 |
| Pulmonary tuberculosis                                 |                 |                 |                 |
| subjects affected / exposed                            | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |
| Appendicitis   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Clostridium difficile colitis                          |                 |                 |                 |
| subjects affected / exposed                            | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 1           | 0 / 0           |
| Lung abscess   |                 |                 |                 |
| subjects affected / exposed                            | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Meningitis viral                                       |                 |                 |                 |
| subjects affected / exposed                            | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |
| Pneumonia  |                 |                 |                 |
| subjects affected / exposed                            | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Metabolism and nutrition disorders              |                 |                 |                 |
| Hypokalaemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |

|   |   |  |  |
|---|---|--|--|
| <b>Serious adverse events</b>                                       | Double Blind: Cohort 1 and Cohort 2 - Placebo |  |  |
| Total subjects affected by serious adverse events                   |   |  |  |
| subjects affected / exposed   | 9 / 197 (4.57%)                               |  |  |
| number of deaths (all causes)                                       | 0   |  |  |
| number of deaths resulting from adverse events                      | 0   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| Breast cancer   |   |  |  |
| subjects affected / exposed   | 0 / 197 (0.00%)                               |  |  |
| occurrences causally related to treatment / all                     | 0 / 0   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Injury, poisoning and procedural complications                      |   |  |  |
| Fall  |   |  |  |
| subjects affected / exposed   | 1 / 197 (0.51%)                               |  |  |
| occurrences causally related to treatment / all                     | 0 / 1   |  |  |
| deaths causally related to treatment / all                          | 0 / 1   |  |  |
| Foot fracture   |   |  |  |
| subjects affected / exposed   | 0 / 197 (0.00%)                               |  |  |
| occurrences causally related to treatment / all                     | 0 / 0   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Clavicle fracture   |   |  |  |
| subjects affected / exposed   | 0 / 197 (0.00%)                               |  |  |
| occurrences causally related to treatment / all                     | 0 / 0   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Accidental overdose   |   |  |  |
| subjects affected / exposed   | 0 / 197 (0.00%)                               |  |  |
| occurrences causally related to treatment / all                     | 0 / 0   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Tongue injury   |   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ligament rupture                                |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Ankle fracture                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal column injury                            |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Coronary artery disease                         |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Nervous system disorders                        |                 |  |  |
| Convulsion                                      |                 |  |  |
| subjects affected / exposed                     | 2 / 197 (1.02%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 2           |  |  |
| Epilepsy  |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Toxic encephalopathy                            |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Seizure cluster                                 |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Status epilepticus                                   |                 |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Speech disorder                                      |                 |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Somnolence   |                 |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Postictal psychosis                                  |                 |  |  |
| subjects affected / exposed                          | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Grand mal convulsion                                 |                 |  |  |
| subjects affected / exposed                          | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia   |                 |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Gait disturbance                                     |                 |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Gastrointestinal disorders                           |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Small intestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Oesophageal obstruction                         |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Psychogenic seizure                             |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Suicidal ideation                               |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Anxiety   |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Confusional state                               |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Suicide attempt                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mental status changes                           |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hallucination                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Delusion  |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Rhabdomyolysis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Pulmonary tuberculosis                          |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Appendicitis                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Clostridium difficile colitis                   |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Lung abscess                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Meningitis viral                                |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (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: 0 %

| <b>Non-serious adverse events</b>                                   | Open Label:<br>Ganaxolone in<br>Double-blind Phase | Open Label: Placebo<br>in Double-blind<br>Phase | Double Blind: Cohort<br>1 and Cohort 2-<br>Ganaxolone |
|---|--|---|---|
| Total subjects affected by non-serious adverse events               |  |   |   |
| subjects affected / exposed   | 42 / 158 (26.58%)                                  | 67 / 173 (38.73%)                               | 134 / 203 (66.01%)                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |   |   |
| Benign hepatic neoplasm   |  |   |   |
| subjects affected / exposed   | 0 / 158 (0.00%)                                    | 0 / 173 (0.00%)                                 | 0 / 203 (0.00%)                                       |
| occurrences (all)   | 0  | 0   | 0   |
| Cervical polyp  |  |   |   |
| subjects affected / exposed   | 0 / 158 (0.00%)                                    | 0 / 173 (0.00%)                                 | 1 / 203 (0.49%)                                       |
| occurrences (all)   | 0  | 0   | 1   |
| Intraductal papilloma of breast                                     |  |   |   |
| subjects affected / exposed   | 0 / 158 (0.00%)                                    | 0 / 173 (0.00%)                                 | 1 / 203 (0.49%)                                       |
| occurrences (all)   | 0  | 0   | 1   |
| Fibroadenoma of breast  |  |   |   |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)        | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Vascular disorders                                      |                      |                      |                      |
| Cardiovascular disorder                                 |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 0 / 173 (0.00%)      | 1 / 203 (0.49%)      |
| occurrences (all)                                       | 0                    | 0                    | 1                    |
| Hypertension  |                      |                      |                      |
| subjects affected / exposed                             | 4 / 158 (2.53%)      | 2 / 173 (1.16%)      | 1 / 203 (0.49%)      |
| occurrences (all)                                       | 4                    | 2                    | 1                    |
| Aortic disorder   |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 0 / 173 (0.00%)      | 0 / 203 (0.00%)      |
| occurrences (all)                                       | 0                    | 0                    | 0                    |
| Ecchymosis  |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 0 / 173 (0.00%)      | 0 / 203 (0.00%)      |
| occurrences (all)                                       | 0                    | 0                    | 0                    |
| Venous thrombosis                                       |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 0 / 173 (0.00%)      | 0 / 203 (0.00%)      |
| occurrences (all)                                       | 0                    | 0                    | 0                    |
| Haemorrhoids  |                      |                      |                      |
| subjects affected / exposed                             | 1 / 158 (0.63%)      | 0 / 173 (0.00%)      | 0 / 203 (0.00%)      |
| occurrences (all)                                       | 1                    | 0                    | 0                    |
| Hypertensive crisis                                     |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 1 / 173 (0.58%)      | 0 / 203 (0.00%)      |
| occurrences (all)                                       | 0                    | 1                    | 0                    |
| Haematoma   |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 2 / 173 (1.16%)      | 0 / 203 (0.00%)      |
| occurrences (all)                                       | 0                    | 4                    | 0                    |
| Surgical and medical procedures                         |                      |                      |                      |
| Tooth extraction  |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 0 / 173 (0.00%)      | 1 / 203 (0.49%)      |
| occurrences (all)                                       | 0                    | 0                    | 1                    |
| Open reduction of fracture                              |                      |                      |                      |
| subjects affected / exposed                             | 0 / 158 (0.00%)      | 0 / 173 (0.00%)      | 1 / 203 (0.49%)      |
| occurrences (all)                                       | 0                    | 0                    | 1                    |
| General disorders and administration<br>site conditions |                      |                      |                      |

|                             |                 |                  |                   |
|-----------------------------|-----------------|------------------|-------------------|
| Night sweats                |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%)  | 0 / 203 (0.00%)   |
| occurrences (all)           | 0               | 0                | 0                 |
| Fatigue                     |                 |                  |                   |
| subjects affected / exposed | 9 / 158 (5.70%) | 15 / 173 (8.67%) | 23 / 203 (11.33%) |
| occurrences (all)           | 10              | 19               | 30                |
| Gait disturbance            |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%)  | 5 / 203 (2.46%)   |
| occurrences (all)           | 0               | 1                | 5                 |
| Asthenia                    |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%)  | 1 / 203 (0.49%)   |
| occurrences (all)           | 0               | 1                | 1                 |
| Chest pain                  |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%)  | 1 / 203 (0.49%)   |
| occurrences (all)           | 0               | 0                | 1                 |
| Chills                      |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%)  | 1 / 203 (0.49%)   |
| occurrences (all)           | 0               | 1                | 1                 |
| Cyst                        |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%)  | 0 / 203 (0.00%)   |
| occurrences (all)           | 0               | 0                | 0                 |
| Hyperhidrosis               |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%)  | 1 / 203 (0.49%)   |
| occurrences (all)           | 0               | 0                | 1                 |
| Injection site pain         |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%)  | 1 / 203 (0.49%)   |
| occurrences (all)           | 0               | 0                | 1                 |
| Lethargy                    |                 |                  |                   |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 173 (0.58%)  | 1 / 203 (0.49%)   |
| occurrences (all)           | 1               | 1                | 1                 |
| Non-cardiac chest pain      |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%)  | 0 / 203 (0.00%)   |
| occurrences (all)           | 0               | 0                | 0                 |
| Pyrexia                     |                 |                  |                   |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%)  | 0 / 203 (0.00%)   |
| occurrences (all)           | 0               | 1                | 0                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 158 (1.27%)<br>2 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Feeling abnormal<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Feeling cold<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 1 / 158 (0.63%)<br>2 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 2 / 173 (1.16%)<br>2 | 0 / 203 (0.00%)<br>0 |
| Immune system disorders<br>Dermatitis allergic<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Social circumstances<br>Stress at work<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Reproductive system and breast disorders<br>Menopausal symptoms<br>subjects affected / exposed<br>occurrences (all) | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |

|                              |                 |                 |                 |
|------------------------------|-----------------|-----------------|-----------------|
| Vaginal haemorrhage          |                 |                 |                 |
| subjects affected / exposed  | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 2 / 203 (0.99%) |
| occurrences (all)            | 0               | 1               | 3               |
| Breast cyst                  |                 |                 |                 |
| subjects affected / exposed  | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)            | 0               | 0               | 0               |
| Dysmenorrhoea                |                 |                 |                 |
| subjects affected / exposed  | 0 / 158 (0.00%) | 3 / 173 (1.73%) | 0 / 203 (0.00%) |
| occurrences (all)            | 0               | 3               | 0               |
| Erectile dysfunction         |                 |                 |                 |
| subjects affected / exposed  | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)            | 0               | 0               | 0               |
| Menorrhagia                  |                 |                 |                 |
| subjects affected / exposed  | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)            | 0               | 0               | 0               |
| Metrorrhagia                 |                 |                 |                 |
| subjects affected / exposed  | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)            | 0               | 0               | 1               |
| Polymenorrhoea               |                 |                 |                 |
| subjects affected / exposed  | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)            | 1               | 1               | 0               |
| Amenorrhoea                  |                 |                 |                 |
| subjects affected / exposed  | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)            | 1               | 0               | 0               |
| Benign prostatic hyperplasia |                 |                 |                 |
| subjects affected / exposed  | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)            | 1               | 0               | 0               |
| Breast tenderness            |                 |                 |                 |
| subjects affected / exposed  | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)            | 0               | 1               | 0               |
| Vaginal inflammation         |                 |                 |                 |
| subjects affected / exposed  | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)            | 1               | 0               | 0               |
| Uterine polyp                |                 |                 |                 |
| subjects affected / exposed  | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)            | 1               | 0               | 0               |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Menstruation irregular<br>subjects affected / exposed<br>occurrences (all)       | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Uterine haemorrhage<br>subjects affected / exposed<br>occurrences (all)          | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders                                  |                      |                      |                      |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 3 / 203 (1.48%)<br>3 |
| Asthma<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 158 (0.63%)<br>1 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)             | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Cough<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 158 (1.27%)<br>2 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Nasal inflammation<br>subjects affected / exposed<br>occurrences (all)           | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)           | 1 / 158 (0.63%)<br>1 | 3 / 173 (1.73%)<br>3 | 1 / 203 (0.49%)<br>1 |
| Respiratory disorder<br>subjects affected / exposed<br>occurrences (all)         | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Respiratory tract congestion<br>subjects affected / exposed<br>occurrences (all) | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Wheezing   |                      |                      |                      |



|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Rhinorrhoea                 |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 2               | 1               | 0               |
| Dysphonia                   |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Musculoskeletal chest pain  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Rhonchi                     |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Sleep apnoea syndrome       |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Sneezing                    |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Psychiatric disorders       |                 |                 |                 |
| Euphoric mood               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Mood swings                 |                 |                 |                 |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Anger                       |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Panic attack                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Sleep disorder              |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Stress                      |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Suicidal ideation           |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 1               | 0               | 1               |
| Affective disorder          |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Nervousness                 |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 3               |
| Confusional state           |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 2 / 203 (0.99%) |
| occurrences (all)           | 1               | 1               | 2               |
| Irritability                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 3 / 173 (1.73%) | 2 / 203 (0.99%) |
| occurrences (all)           | 0               | 3               | 2               |
| Anxiety                     |                 |                 |                 |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 173 (0.00%) | 3 / 203 (1.48%) |
| occurrences (all)           | 2               | 0               | 3               |
| Mood altered                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Mental status changes       |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Libido decreased            |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Depression                  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 2 / 173 (1.16%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 2               | 3               |
| Suicide attempt             |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Psychotic disorder<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Emotional distress<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Aggression<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Abnormal behaviour<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 2 / 203 (0.99%)<br>2 |
| Investigations  |                      |                      |                      |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Blood alkaline phosphatase abnormal<br>subjects affected / exposed<br>occurrences (all) | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Biopsy skin<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 158 (0.00%)<br>0 | 3 / 173 (1.73%)<br>3 | 0 / 203 (0.00%)<br>0 |
| Blood potassium increased<br>subjects affected / exposed<br>occurrences (all)           | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Blood glucose abnormal  |                      |                      |                      |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Diagnostic procedure                 |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Blood triglycerides increased        |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Blood sodium decreased               |                 |                 |                 |
| subjects affected / exposed          | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Blood pressure increased             |                 |                 |                 |
| subjects affected / exposed          | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Blood creatinine increased           |                 |                 |                 |
| subjects affected / exposed          | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Blood alkaline phosphatase increased |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Aspartate aminotransferase abnormal  |                 |                 |                 |
| subjects affected / exposed          | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Arthroscopy                          |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Transaminases increased              |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 0               | 0               |
| Neutrophil count increased           |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 0               | 0               |
| Neurological examination abnormal    |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                    | 0               | 0               | 1               |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Liver function test abnormal<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Electrocardiogram repolarisation<br>abnormality<br>subjects affected / exposed<br>occurrences (all) | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Blood iron increased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Platelet count increased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Injury, poisoning and procedural<br>complications   |                      |                      |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 158 (0.00%)<br>0 | 4 / 173 (2.31%)<br>8 | 3 / 203 (1.48%)<br>3 |
| Fall<br>subjects affected / exposed<br>occurrences (all)  | 1 / 158 (0.63%)<br>1 | 3 / 173 (1.73%)<br>6 | 1 / 203 (0.49%)<br>2 |
| Head injury<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 158 (0.63%)<br>1 | 1 / 173 (0.58%)<br>1 | 2 / 203 (0.99%)<br>2 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 158 (0.63%)<br>1 | 2 / 173 (1.16%)<br>2 | 2 / 203 (0.99%)<br>2 |
| Rib fracture  |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Facial bones fracture       |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Laceration                  |                 |                 |                 |
| subjects affected / exposed | 3 / 158 (1.90%) | 2 / 173 (1.16%) | 1 / 203 (0.49%) |
| occurrences (all)           | 3               | 5               | 2               |
| Excoriation                 |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 3               | 1               |
| Joint injury                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Limb injury                 |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Muscle contusion            |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Periorbital contusion       |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Foot fracture               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Eye contusion               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Wound haemorrhage           |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Tibia fracture              |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Tendon injury               |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Road traffic accident       |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Incision site erythema      |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Hand fracture               |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Procedural pain             |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 1               | 0               | 1               |
| Soft tissue injury          |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Thermal burn                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Upper limb fracture         |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Wrist fracture              |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Burns third degree          |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Clavicle fracture           |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Concussion                  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Cardiac disorders           |                 |                 |                 |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Coronary artery disease<br>subjects affected / exposed<br>occurrences (all)             | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Paroxysmal arrhythmia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Silent myocardial infarction<br>subjects affected / exposed<br>occurrences (all)        | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Atrioventricular block first degree<br>subjects affected / exposed<br>occurrences (all) | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Bundle branch block left<br>subjects affected / exposed<br>occurrences (all)            | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>2 | 0 / 203 (0.00%)<br>0 |
| Left ventricular hypertrophy<br>subjects affected / exposed<br>occurrences (all)        | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Cardiac failure congestive<br>subjects affected / exposed<br>occurrences (all)          | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Nervous system disorders<br>Somnolence  |                      |                      |                      |



|                             |                  |                   |                   |
|-----------------------------|------------------|-------------------|-------------------|
| subjects affected / exposed | 12 / 158 (7.59%) | 29 / 173 (16.76%) | 46 / 203 (22.66%) |
| occurrences (all)           | 13               | 33                | 56                |
| Dizziness                   |                  |                   |                   |
| subjects affected / exposed | 8 / 158 (5.06%)  | 27 / 173 (15.61%) | 38 / 203 (18.72%) |
| occurrences (all)           | 16               | 29                | 50                |
| Headache                    |                  |                   |                   |
| subjects affected / exposed | 9 / 158 (5.70%)  | 11 / 173 (6.36%)  | 18 / 203 (8.87%)  |
| occurrences (all)           | 15               | 12                | 19                |
| Ataxia                      |                  |                   |                   |
| subjects affected / exposed | 2 / 158 (1.27%)  | 2 / 173 (1.16%)   | 6 / 203 (2.96%)   |
| occurrences (all)           | 2                | 3                 | 7                 |
| Balance disorder            |                  |                   |                   |
| subjects affected / exposed | 3 / 158 (1.90%)  | 1 / 173 (0.58%)   | 7 / 203 (3.45%)   |
| occurrences (all)           | 3                | 1                 | 7                 |
| Aphasia                     |                  |                   |                   |
| subjects affected / exposed | 1 / 158 (0.63%)  | 2 / 173 (1.16%)   | 5 / 203 (2.46%)   |
| occurrences (all)           | 1                | 2                 | 5                 |
| Convulsion                  |                  |                   |                   |
| subjects affected / exposed | 5 / 158 (3.16%)  | 4 / 173 (2.31%)   | 5 / 203 (2.46%)   |
| occurrences (all)           | 5                | 5                 | 5                 |
| Tremor                      |                  |                   |                   |
| subjects affected / exposed | 2 / 158 (1.27%)  | 2 / 173 (1.16%)   | 4 / 203 (1.97%)   |
| occurrences (all)           | 24               | 2                 | 4                 |
| Dysarthria                  |                  |                   |                   |
| subjects affected / exposed | 2 / 158 (1.27%)  | 4 / 173 (2.31%)   | 3 / 203 (1.48%)   |
| occurrences (all)           | 2                | 4                 | 3                 |
| Memory impairment           |                  |                   |                   |
| subjects affected / exposed | 1 / 158 (0.63%)  | 2 / 173 (1.16%)   | 1 / 203 (0.49%)   |
| occurrences (all)           | 1                | 2                 | 1                 |
| Sedation                    |                  |                   |                   |
| subjects affected / exposed | 1 / 158 (0.63%)  | 1 / 173 (0.58%)   | 4 / 203 (1.97%)   |
| occurrences (all)           | 1                | 2                 | 4                 |
| Cerebellar syndrome         |                  |                   |                   |
| subjects affected / exposed | 0 / 158 (0.00%)  | 0 / 173 (0.00%)   | 1 / 203 (0.49%)   |
| occurrences (all)           | 0                | 0                 | 1                 |
| Agitation                   |                  |                   |                   |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Hypoaesthesia               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Slow speech                 |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 2 / 203 (0.99%) |
| occurrences (all)           | 0               | 1               | 2               |
| Amnesia                     |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 1               | 1               |
| Insomnia                    |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 3 / 203 (1.48%) |
| occurrences (all)           | 0               | 0               | 3               |
| Coordination abnormal       |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Disorientation              |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Disturbance in attention    |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 2 / 173 (1.16%) | 1 / 203 (0.49%) |
| occurrences (all)           | 1               | 2               | 1               |
| Dyskinesia                  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Essential tremor            |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Migraine                    |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Grand mal convulsion        |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Hypoaesthesia oral          |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Loss of consciousness       |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Mental impairment           |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Gait disturbance            |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 2               | 0               |
| Psychomotor hyperactivity   |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Psychomotor skills impaired |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Sleep terror                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Speech disorder             |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 2 / 173 (1.16%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 2               | 1               |
| Vertigo                     |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Seizure cluste              |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 4               | 0               |
| Restless legs syndrome      |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Dementia Alzheimer''s type  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Initial insomnia            |                 |                 |                 |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Lethargy                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Paraesthesia                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Postictal state                      |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 2               | 0               |
| Radicular pain                       |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Delayed sleep phase                  |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Sciatica                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |
| Slow response to stimuli             |                 |                 |                 |
| subjects affected / exposed          | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Blood and lymphatic system disorders |                 |                 |                 |
| Lymphadenopathy                      |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Splenomegaly                         |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 0               | 0               |
| Anaemia                              |                 |                 |                 |
| subjects affected / exposed          | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 2               | 0               | 0               |
| Thrombocytopenia                     |                 |                 |                 |
| subjects affected / exposed          | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                    | 0               | 1               | 0               |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Ear and labyrinth disorders |                 |                 |                 |
| Vertigo                     |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 5 / 173 (2.89%) | 4 / 203 (1.97%) |
| occurrences (all)           | 0               | 7               | 4               |
| Ear pain                    |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Tinnitus                    |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Eye disorders               |                 |                 |                 |
| Nystagmus                   |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 2 / 203 (0.99%) |
| occurrences (all)           | 1               | 1               | 2               |
| Diplopia                    |                 |                 |                 |
| subjects affected / exposed | 2 / 158 (1.27%) | 4 / 173 (2.31%) | 2 / 203 (0.99%) |
| occurrences (all)           | 2               | 4               | 2               |
| Vision blurred              |                 |                 |                 |
| subjects affected / exposed | 3 / 158 (1.90%) | 1 / 173 (0.58%) | 7 / 203 (3.45%) |
| occurrences (all)           | 11              | 1               | 14              |
| Eye swelling                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Eye pruritus                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Photophobia                 |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Visual impairment           |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 2 / 203 (0.99%) |
| occurrences (all)           | 0               | 0               | 2               |
| Dry eye                     |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Eye allergy                 |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Blepharospasm               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Ocular dysmetria            |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Gastrointestinal disorders  |                 |                 |                 |
| Flatulence                  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 2 / 203 (0.99%) |
| occurrences (all)           | 0               | 0               | 2               |
| Nausea                      |                 |                 |                 |
| subjects affected / exposed | 5 / 158 (3.16%) | 4 / 173 (2.31%) | 1 / 203 (0.49%) |
| occurrences (all)           | 13              | 5               | 1               |
| Diarrhoea                   |                 |                 |                 |
| subjects affected / exposed | 2 / 158 (1.27%) | 3 / 173 (1.73%) | 3 / 203 (1.48%) |
| occurrences (all)           | 2               | 5               | 3               |
| Vomiting                    |                 |                 |                 |
| subjects affected / exposed | 2 / 158 (1.27%) | 7 / 173 (4.05%) | 1 / 203 (0.49%) |
| occurrences (all)           | 2               | 7               | 1               |
| Constipation                |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 2 / 173 (1.16%) | 3 / 203 (1.48%) |
| occurrences (all)           | 1               | 2               | 3               |
| Dry mouth                   |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Abdominal pain              |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Oral pruritus               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Haematochezia               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| Toothache                        |                 |                 |                 |
| subjects affected / exposed      | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)                | 2               | 1               | 1               |
| Gastrooesophageal reflux disease |                 |                 |                 |
| subjects affected / exposed      | 1 / 158 (0.63%) | 3 / 173 (1.73%) | 0 / 203 (0.00%) |
| occurrences (all)                | 1               | 3               | 0               |
| Dyspepsia                        |                 |                 |                 |
| subjects affected / exposed      | 0 / 158 (0.00%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)                | 0               | 2               | 0               |
| Gastroenteritis                  |                 |                 |                 |
| subjects affected / exposed      | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                | 1               | 2               | 0               |
| Dental caries                    |                 |                 |                 |
| subjects affected / exposed      | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Disbacteriosis                   |                 |                 |                 |
| subjects affected / exposed      | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Abdominal distension             |                 |                 |                 |
| subjects affected / exposed      | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                | 0               | 0               | 0               |
| Abdominal pain upper             |                 |                 |                 |
| subjects affected / exposed      | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)                | 1               | 1               | 1               |
| Eructation                       |                 |                 |                 |
| subjects affected / exposed      | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                | 0               | 0               | 0               |
| Abdominal discomfort             |                 |                 |                 |
| subjects affected / exposed      | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                | 0               | 0               | 1               |
| Bowel movement irregularity      |                 |                 |                 |
| subjects affected / exposed      | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                | 0               | 0               | 1               |
| Gastritis                        |                 |                 |                 |
| subjects affected / exposed      | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                | 0               | 0               | 0               |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Gingivitis                             |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 0               | 0               | 0               |
| Paraesthesia oral                      |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                      | 0               | 0               | 1               |
| Epigastric discomfort                  |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 0               | 1               | 0               |
| Oesophagitis                           |                 |                 |                 |
| subjects affected / exposed            | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 1               | 0               | 0               |
| Retching                               |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 0               | 1               | 0               |
| Hepatobiliary disorders                |                 |                 |                 |
| Hepatic steatosis                      |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 0               | 0               | 0               |
| Cholecystitis chronic                  |                 |                 |                 |
| subjects affected / exposed            | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 1               | 0               | 0               |
| Skin and subcutaneous tissue disorders |                 |                 |                 |
| Rash macular                           |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 0               | 1               | 0               |
| Rash pruritic                          |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 0               | 1               | 0               |
| Skin lesion                            |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                      | 0               | 0               | 1               |
| Skin irritation                        |                 |                 |                 |
| subjects affected / exposed            | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                      | 0               | 0               | 0               |
| Skin hypopigmentation                  |                 |                 |                 |



|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Rash maculo-papular         |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Pain of skin                |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Eczema                      |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 1               | 0               | 1               |
| Acne                        |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Pruritus                    |                 |                 |                 |
| subjects affected / exposed | 2 / 158 (1.27%) | 1 / 173 (0.58%) | 3 / 203 (1.48%) |
| occurrences (all)           | 2               | 1               | 3               |
| Alopecia                    |                 |                 |                 |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 173 (0.00%) | 4 / 203 (1.97%) |
| occurrences (all)           | 2               | 0               | 4               |
| Rash                        |                 |                 |                 |
| subjects affected / exposed | 3 / 158 (1.90%) | 2 / 173 (1.16%) | 5 / 203 (2.46%) |
| occurrences (all)           | 3               | 2               | 5               |
| Dermatitis contact          |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Swelling face               |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Renal and urinary disorders |                 |                 |                 |
| Nephrolithiasis             |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Dysuria                     |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Micturition urgency<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Urinary incontinence<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Endocrine disorders<br>Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Menstruation irregular<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 2 / 203 (0.99%)<br>2 |
| Adrenal cyst<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Gynaecomastia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 1 / 158 (0.63%)<br>2 | 1 / 173 (0.58%)<br>2 | 0 / 203 (0.00%)<br>0 |
| Musculoskeletal stiffness  |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Musculoskeletal chest pain  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 1               | 1               |
| Muscle fatigue              |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Ligament sprain             |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Joint swelling              |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 1               | 0               | 1               |
| Hypertonia                  |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Exostosis                   |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Arthralgia                  |                 |                 |                 |
| subjects affected / exposed | 3 / 158 (1.90%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)           | 4               | 2               | 0               |
| Neck pain                   |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 1               | 2               |
| Myalgia                     |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Musculoskeletal pain        |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 2 / 203 (0.99%) |
| occurrences (all)           | 0               | 1               | 2               |
| Muscle spasms               |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 2 / 173 (1.16%) | 2 / 203 (0.99%) |
| occurrences (all)           | 1               | 2               | 2               |
| Back pain                   |                 |                 |                 |

|                                |                 |                 |                 |
|--------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed    | 1 / 158 (0.63%) | 4 / 173 (2.31%) | 1 / 203 (0.49%) |
| occurrences (all)              | 1               | 6               | 2               |
| Sensation of heaviness         |                 |                 |                 |
| subjects affected / exposed    | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)              | 0               | 0               | 1               |
| Arthritis                      |                 |                 |                 |
| subjects affected / exposed    | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)              | 1               | 0               | 0               |
| Spinal pain                    |                 |                 |                 |
| subjects affected / exposed    | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)              | 1               | 0               | 0               |
| Sciatica                       |                 |                 |                 |
| subjects affected / exposed    | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)              | 0               | 1               | 0               |
| Osteochondrosis                |                 |                 |                 |
| subjects affected / exposed    | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)              | 0               | 1               | 0               |
| Muscular weakness              |                 |                 |                 |
| subjects affected / exposed    | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)              | 1               | 0               | 0               |
| Lumbar spinal stenosis         |                 |                 |                 |
| subjects affected / exposed    | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)              | 0               | 1               | 0               |
| Intervertebral disc protrusion |                 |                 |                 |
| subjects affected / exposed    | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)              | 1               | 0               | 0               |
| Flank pain                     |                 |                 |                 |
| subjects affected / exposed    | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)              | 1               | 0               | 0               |
| Contusion                      |                 |                 |                 |
| subjects affected / exposed    | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)              | 1               | 0               | 0               |
| Infections and infestations    |                 |                 |                 |
| Localised infection            |                 |                 |                 |
| subjects affected / exposed    | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)              | 0               | 0               | 1               |

|                                   |                 |                 |                 |
|-----------------------------------|-----------------|-----------------|-----------------|
| Nasopharyngitis                   |                 |                 |                 |
| subjects affected / exposed       | 6 / 158 (3.80%) | 9 / 173 (5.20%) | 5 / 203 (2.46%) |
| occurrences (all)                 | 6               | 9               | 5               |
| Upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed       | 4 / 158 (2.53%) | 5 / 173 (2.89%) | 6 / 203 (2.96%) |
| occurrences (all)                 | 6               | 5               | 6               |
| Urinary tract infection           |                 |                 |                 |
| subjects affected / exposed       | 3 / 158 (1.90%) | 8 / 173 (4.62%) | 3 / 203 (1.48%) |
| occurrences (all)                 | 3               | 9               | 3               |
| Sinusitis                         |                 |                 |                 |
| subjects affected / exposed       | 2 / 158 (1.27%) | 3 / 173 (1.73%) | 2 / 203 (0.99%) |
| occurrences (all)                 | 2               | 4               | 2               |
| Pharyngitis                       |                 |                 |                 |
| subjects affected / exposed       | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                 | 0               | 0               | 0               |
| Influenza                         |                 |                 |                 |
| subjects affected / exposed       | 2 / 158 (1.27%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                 | 2               | 0               | 0               |
| Pharyngitis streptococcal         |                 |                 |                 |
| subjects affected / exposed       | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                 | 0               | 0               | 1               |
| Bronchitis                        |                 |                 |                 |
| subjects affected / exposed       | 6 / 158 (3.80%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)                 | 6               | 2               | 0               |
| Corneal infection                 |                 |                 |                 |
| subjects affected / exposed       | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                 | 0               | 0               | 1               |
| Cystitis                          |                 |                 |                 |
| subjects affected / exposed       | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                 | 0               | 0               | 1               |
| Ear infection                     |                 |                 |                 |
| subjects affected / exposed       | 2 / 158 (1.27%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                 | 2               | 0               | 0               |
| Gastroenteritis                   |                 |                 |                 |
| subjects affected / exposed       | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                 | 0               | 0               | 1               |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Gastroenteritis viral                   |                 |                 |                 |
| subjects affected / exposed             | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                       | 0               | 0               | 1               |
| Lower respiratory tract infection       |                 |                 |                 |
| subjects affected / exposed             | 1 / 158 (0.63%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)                       | 1               | 2               | 0               |
| Infected bites                          |                 |                 |                 |
| subjects affected / exposed             | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                       | 1               | 0               | 0               |
| Rash pustular                           |                 |                 |                 |
| subjects affected / exposed             | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                       | 0               | 0               | 0               |
| Respiratory tract infection viral       |                 |                 |                 |
| subjects affected / exposed             | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)                       | 1               | 1               | 1               |
| Rhinitis                                |                 |                 |                 |
| subjects affected / exposed             | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)                       | 0               | 0               | 0               |
| Rotavirus infection                     |                 |                 |                 |
| subjects affected / exposed             | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                       | 0               | 0               | 1               |
| Sinusitis bacterial                     |                 |                 |                 |
| subjects affected / exposed             | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                       | 1               | 0               | 1               |
| Tooth infection                         |                 |                 |                 |
| subjects affected / exposed             | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 1 / 203 (0.49%) |
| occurrences (all)                       | 0               | 1               | 1               |
| Viral upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed             | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)                       | 0               | 0               | 1               |
| Viral infection                         |                 |                 |                 |
| subjects affected / exposed             | 2 / 158 (1.27%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)                       | 2               | 3               | 0               |
| Fungal infection                        |                 |                 |                 |
| subjects affected / exposed             | 1 / 158 (0.63%) | 2 / 173 (1.16%) | 0 / 203 (0.00%) |
| occurrences (all)                       | 2               | 2               | 0               |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Gastrointestinal viral infection<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 158 (0.63%)<br>1 | 2 / 173 (1.16%)<br>2 | 0 / 203 (0.00%)<br>0 |
| Laryngitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 2 / 173 (1.16%)<br>2 | 0 / 203 (0.00%)<br>0 |
| Impetigo<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 0 / 173 (0.00%)<br>0 | 1 / 203 (0.49%)<br>1 |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Skin infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Tonsillitis bacterial<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)  | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Viral diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 158 (0.00%)<br>0 | 1 / 173 (0.58%)<br>1 | 0 / 203 (0.00%)<br>0 |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 158 (0.63%)<br>1 | 0 / 173 (0.00%)<br>0 | 0 / 203 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 2 / 158 (1.27%)<br>2 | 1 / 173 (0.58%)<br>1 | 1 / 203 (0.49%)<br>1 |
| Hypercholesterolaemia  |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 0               | 1               |
| Hyponatraemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 4 / 173 (2.31%) | 1 / 203 (0.49%) |
| occurrences (all)           | 0               | 4               | 1               |
| Thirst                      |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Vitamin D deficiency        |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 1 / 203 (0.49%) |
| occurrences (all)           | 1               | 0               | 1               |
| Increased appetite          |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Hyperkalaemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Hypochloraemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 173 (0.58%) | 0 / 203 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Hypoglycaemia               |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hypokalaemia                |                 |                 |                 |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 173 (0.00%) | 0 / 203 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>                                   | Double Blind: Cohort 1 and Cohort 2 - Placebo |  |  |
| Total subjects affected by non-serious adverse events               |   |  |  |
| subjects affected / exposed   | 98 / 197 (49.75%)                             |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| Benign hepatic neoplasm   |   |  |  |
| subjects affected / exposed   | 1 / 197 (0.51%)                               |  |  |
| occurrences (all)   | 1   |  |  |
| Cervical polyp  |   |  |  |



|                                 |                 |  |  |
|---------------------------------|-----------------|--|--|
| subjects affected / exposed     | 0 / 197 (0.00%) |  |  |
| occurrences (all)               | 0               |  |  |
| Intraductal papilloma of breast |                 |  |  |
| subjects affected / exposed     | 0 / 197 (0.00%) |  |  |
| occurrences (all)               | 0               |  |  |
| Fibroadenoma of breast          |                 |  |  |
| subjects affected / exposed     | 1 / 197 (0.51%) |  |  |
| occurrences (all)               | 1               |  |  |
| Vascular disorders              |                 |  |  |
| Cardiovascular disorder         |                 |  |  |
| subjects affected / exposed     | 0 / 197 (0.00%) |  |  |
| occurrences (all)               | 0               |  |  |
| Hypertension                    |                 |  |  |
| subjects affected / exposed     | 1 / 197 (0.51%) |  |  |
| occurrences (all)               | 1               |  |  |
| Aortic disorder                 |                 |  |  |
| subjects affected / exposed     | 1 / 197 (0.51%) |  |  |
| occurrences (all)               | 1               |  |  |
| Ecchymosis                      |                 |  |  |
| subjects affected / exposed     | 1 / 197 (0.51%) |  |  |
| occurrences (all)               | 1               |  |  |
| Venous thrombosis               |                 |  |  |
| subjects affected / exposed     | 1 / 197 (0.51%) |  |  |
| occurrences (all)               | 1               |  |  |
| Haemorrhoids                    |                 |  |  |
| subjects affected / exposed     | 0 / 197 (0.00%) |  |  |
| occurrences (all)               | 0               |  |  |
| Hypertensive crisis             |                 |  |  |
| subjects affected / exposed     | 0 / 197 (0.00%) |  |  |
| occurrences (all)               | 0               |  |  |
| Haematoma                       |                 |  |  |
| subjects affected / exposed     | 1 / 197 (0.51%) |  |  |
| occurrences (all)               | 1               |  |  |
| Surgical and medical procedures |                 |  |  |
| Tooth extraction                |                 |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed                          | 1 / 197 (0.51%)  |  |  |
| occurrences (all)                                    | 1                |  |  |
| Open reduction of fracture                           |                  |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%)  |  |  |
| occurrences (all)                                    | 0                |  |  |
| General disorders and administration site conditions |                  |  |  |
| Night sweats   |                  |  |  |
| subjects affected / exposed                          | 1 / 197 (0.51%)  |  |  |
| occurrences (all)                                    | 1                |  |  |
| Fatigue  |                  |  |  |
| subjects affected / exposed                          | 12 / 197 (6.09%) |  |  |
| occurrences (all)                                    | 12               |  |  |
| Gait disturbance                                     |                  |  |  |
| subjects affected / exposed                          | 1 / 197 (0.51%)  |  |  |
| occurrences (all)                                    | 1                |  |  |
| Asthenia   |                  |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%)  |  |  |
| occurrences (all)                                    | 0                |  |  |
| Chest pain   |                  |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%)  |  |  |
| occurrences (all)                                    | 0                |  |  |
| Chills   |                  |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%)  |  |  |
| occurrences (all)                                    | 0                |  |  |
| Cyst   |                  |  |  |
| subjects affected / exposed                          | 1 / 197 (0.51%)  |  |  |
| occurrences (all)                                    | 1                |  |  |
| Hyperhidrosis  |                  |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%)  |  |  |
| occurrences (all)                                    | 0                |  |  |
| Injection site pain                                  |                  |  |  |
| subjects affected / exposed                          | 0 / 197 (0.00%)  |  |  |
| occurrences (all)                                    | 0                |  |  |
| Lethargy   |                  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Non-cardiac chest pain      |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 2               |  |  |
| Pyrexia                     |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Procedural pain             |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Feeling abnormal            |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Feeling cold                |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Influenza like illness      |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Malaise                     |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Pain                        |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Immune system disorders     |                 |  |  |
| Dermatitis allergic         |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Drug hypersensitivity       |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Seasonal allergy            |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Social circumstances                     |                 |  |  |
| Stress at work                           |                 |  |  |
| subjects affected / exposed              | 0 / 197 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Reproductive system and breast disorders |                 |  |  |
| Menopausal symptoms                      |                 |  |  |
| subjects affected / exposed              | 0 / 197 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Vaginal haemorrhage                      |                 |  |  |
| subjects affected / exposed              | 0 / 197 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Breast cyst                              |                 |  |  |
| subjects affected / exposed              | 1 / 197 (0.51%) |  |  |
| occurrences (all)                        | 1               |  |  |
| Dysmenorrhoea                            |                 |  |  |
| subjects affected / exposed              | 1 / 197 (0.51%) |  |  |
| occurrences (all)                        | 1               |  |  |
| Erectile dysfunction                     |                 |  |  |
| subjects affected / exposed              | 1 / 197 (0.51%) |  |  |
| occurrences (all)                        | 1               |  |  |
| Menorrhagia                              |                 |  |  |
| subjects affected / exposed              | 1 / 197 (0.51%) |  |  |
| occurrences (all)                        | 1               |  |  |
| Metrorrhagia                             |                 |  |  |
| subjects affected / exposed              | 0 / 197 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Polymenorrhoea                           |                 |  |  |
| subjects affected / exposed              | 0 / 197 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Amenorrhoea                              |                 |  |  |
| subjects affected / exposed              | 0 / 197 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Benign prostatic hyperplasia             |                 |  |  |
| subjects affected / exposed              | 0 / 197 (0.00%) |  |  |
| occurrences (all)                        | 0               |  |  |
| Breast tenderness                        |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Vaginal inflammation                            |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Uterine polyp                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Menstruation irregular                          |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Uterine haemorrhage                             |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Asthma  |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences (all)                               | 1               |  |  |
| Chest discomfort                                |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Cough   |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences (all)                               | 1               |  |  |
| Nasal inflammation                              |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences (all)                               | 1               |  |  |
| Oropharyngeal pain                              |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Respiratory disorder                            |                 |  |  |

|                              |                 |  |  |
|------------------------------|-----------------|--|--|
| subjects affected / exposed  | 1 / 197 (0.51%) |  |  |
| occurrences (all)            | 1               |  |  |
| Respiratory tract congestion |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Sinusitis                    |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Wheezing                     |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Rhinorrhoea                  |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Dysphonia                    |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Musculoskeletal chest pain   |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Rhonchi                      |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Sleep apnoea syndrome        |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Sneezing                     |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Psychiatric disorders        |                 |  |  |
| Euphoric mood                |                 |  |  |
| subjects affected / exposed  | 0 / 197 (0.00%) |  |  |
| occurrences (all)            | 0               |  |  |
| Mood swings                  |                 |  |  |
| subjects affected / exposed  | 1 / 197 (0.51%) |  |  |
| occurrences (all)            | 1               |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Anger                       |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Panic attack                |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Sleep disorder              |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Stress                      |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Suicidal ideation           |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Affective disorder          |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Nervousness                 |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Confusional state           |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Irritability                |                 |  |  |
| subjects affected / exposed | 2 / 197 (1.02%) |  |  |
| occurrences (all)           | 2               |  |  |
| Anxiety                     |                 |  |  |
| subjects affected / exposed | 3 / 197 (1.52%) |  |  |
| occurrences (all)           | 3               |  |  |
| Mood altered                |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Mental status changes       |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |

|                                     |                 |  |  |
|-------------------------------------|-----------------|--|--|
| Libido decreased                    |                 |  |  |
| subjects affected / exposed         | 1 / 197 (0.51%) |  |  |
| occurrences (all)                   | 1               |  |  |
| Depression                          |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Suicide attempt                     |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Psychotic disorder                  |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Emotional distress                  |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Agitation                           |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Aggression                          |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Abnormal behaviour                  |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Depressed mood                      |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Investigations                      |                 |  |  |
| Blood glucose increased             |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Blood alkaline phosphatase abnormal |                 |  |  |
| subjects affected / exposed         | 1 / 197 (0.51%) |  |  |
| occurrences (all)                   | 1               |  |  |
| Biopsy skin                         |                 |  |  |



|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Weight increased                     |                 |  |  |
| subjects affected / exposed          | 2 / 197 (1.02%) |  |  |
| occurrences (all)                    | 2               |  |  |
| Blood potassium increased            |                 |  |  |
| subjects affected / exposed          | 2 / 197 (1.02%) |  |  |
| occurrences (all)                    | 2               |  |  |
| Blood glucose abnormal               |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Diagnostic procedure                 |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood triglycerides increased        |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood sodium decreased               |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood pressure increased             |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood creatinine increased           |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood alkaline phosphatase increased |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Aspartate aminotransferase abnormal  |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Arthroscopy                          |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 197 (0.51%)<br>1 |  |  |
| Neutrophil count increased<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 197 (0.51%)<br>1 |  |  |
| Neurological examination abnormal<br>subjects affected / exposed<br>occurrences (all)               | 0 / 197 (0.00%)<br>0 |  |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 197 (0.51%)<br>1 |  |  |
| Liver function test abnormal<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 197 (0.00%)<br>0 |  |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 197 (0.00%)<br>0 |  |  |
| Electrocardiogram repolarisation<br>abnormality<br>subjects affected / exposed<br>occurrences (all) | 0 / 197 (0.00%)<br>0 |  |  |
| Blood iron increased<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 197 (0.51%)<br>1 |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 197 (0.00%)<br>0 |  |  |
| Platelet count increased<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 197 (0.00%)<br>0 |  |  |
| Injury, poisoning and procedural<br>complications   |                      |  |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                                       | 4 / 197 (2.03%)<br>4 |  |  |
| Fall  |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 3 / 197 (1.52%) |  |  |
| occurrences (all)           | 3               |  |  |
| Head injury                 |                 |  |  |
| subjects affected / exposed | 2 / 197 (1.02%) |  |  |
| occurrences (all)           | 2               |  |  |
| Ligament sprain             |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Rib fracture                |                 |  |  |
| subjects affected / exposed | 3 / 197 (1.52%) |  |  |
| occurrences (all)           | 3               |  |  |
| Facial bones fracture       |                 |  |  |
| subjects affected / exposed | 2 / 197 (1.02%) |  |  |
| occurrences (all)           | 2               |  |  |
| Laceration                  |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Excoriation                 |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Joint injury                |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Limb injury                 |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Muscle contusion            |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Periorbital contusion       |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Foot fracture               |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Eye contusion               |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Wound haemorrhage           |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Tibia fracture              |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Tendon injury               |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Road traffic accident       |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Incision site erythema      |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Hand fracture               |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Procedural pain             |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Soft tissue injury          |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Thermal burn                |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Upper limb fracture         |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Wrist fracture              |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Burns third degree          |                 |  |  |

|                                     |                 |  |  |
|-------------------------------------|-----------------|--|--|
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Clavicle fracture                   |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Concussion                          |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Cardiac disorders                   |                 |  |  |
| Coronary artery disease             |                 |  |  |
| subjects affected / exposed         | 1 / 197 (0.51%) |  |  |
| occurrences (all)                   | 1               |  |  |
| Palpitations                        |                 |  |  |
| subjects affected / exposed         | 1 / 197 (0.51%) |  |  |
| occurrences (all)                   | 1               |  |  |
| Paroxysmal arrhythmia               |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Silent myocardial infarction        |                 |  |  |
| subjects affected / exposed         | 1 / 197 (0.51%) |  |  |
| occurrences (all)                   | 1               |  |  |
| Atrioventricular block first degree |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Bradycardia                         |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Bundle branch block left            |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Chest pain                          |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |
| Left ventricular hypertrophy        |                 |  |  |
| subjects affected / exposed         | 0 / 197 (0.00%) |  |  |
| occurrences (all)                   | 0               |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Tachycardia                 |                  |  |  |
| subjects affected / exposed | 0 / 197 (0.00%)  |  |  |
| occurrences (all)           | 0                |  |  |
| Cardiac failure congestive  |                  |  |  |
| subjects affected / exposed | 1 / 197 (0.51%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Nervous system disorders    |                  |  |  |
| Somnolence                  |                  |  |  |
| subjects affected / exposed | 10 / 197 (5.08%) |  |  |
| occurrences (all)           | 10               |  |  |
| Dizziness                   |                  |  |  |
| subjects affected / exposed | 9 / 197 (4.57%)  |  |  |
| occurrences (all)           | 9                |  |  |
| Headache                    |                  |  |  |
| subjects affected / exposed | 15 / 197 (7.61%) |  |  |
| occurrences (all)           | 15               |  |  |
| Ataxia                      |                  |  |  |
| subjects affected / exposed | 0 / 197 (0.00%)  |  |  |
| occurrences (all)           | 0                |  |  |
| Balance disorder            |                  |  |  |
| subjects affected / exposed | 1 / 197 (0.51%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Aphasia                     |                  |  |  |
| subjects affected / exposed | 2 / 197 (1.02%)  |  |  |
| occurrences (all)           | 2                |  |  |
| Convulsion                  |                  |  |  |
| subjects affected / exposed | 5 / 197 (2.54%)  |  |  |
| occurrences (all)           | 5                |  |  |
| Tremor                      |                  |  |  |
| subjects affected / exposed | 1 / 197 (0.51%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Dysarthria                  |                  |  |  |
| subjects affected / exposed | 1 / 197 (0.51%)  |  |  |
| occurrences (all)           | 1                |  |  |
| Memory impairment           |                  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 3 / 197 (1.52%) |  |  |
| occurrences (all)           | 3               |  |  |
| Sedation                    |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Cerebellar syndrome         |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Agitation                   |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Hypoaesthesia               |                 |  |  |
| subjects affected / exposed | 2 / 197 (1.02%) |  |  |
| occurrences (all)           | 2               |  |  |
| Slow speech                 |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Amnesia                     |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Insomnia                    |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Coordination abnormal       |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Disorientation              |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Disturbance in attention    |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Dyskinesia                  |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Essential tremor            |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Migraine                    |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Grand mal convulsion        |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Hypoaesthesia oral          |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Loss of consciousness       |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Mental impairment           |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Gait disturbance            |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Psychomotor hyperactivity   |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Psychomotor skills impaired |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Sleep terror                |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Speech disorder             |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Vertigo                     |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Seizure cluste              |                 |  |  |



|                                      |                 |  |  |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Restless legs syndrome               |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Dementia Alzheimer's type            |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Initial insomnia                     |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Lethargy                             |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Paraesthesia                         |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Postictal state                      |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Radicular pain                       |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Delayed sleep phase                  |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Sciatica                             |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Slow response to stimuli             |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |
| Blood and lymphatic system disorders |                 |  |  |
| Lymphadenopathy                      |                 |  |  |
| subjects affected / exposed          | 0 / 197 (0.00%) |  |  |
| occurrences (all)                    | 0               |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Splenomegaly                |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Anaemia                     |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Thrombocytopenia            |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Ear and labyrinth disorders |                 |  |  |
| Vertigo                     |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Ear pain                    |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Tinnitus                    |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Eye disorders               |                 |  |  |
| Nystagmus                   |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Diplopia                    |                 |  |  |
| subjects affected / exposed | 2 / 197 (1.02%) |  |  |
| occurrences (all)           | 2               |  |  |
| Vision blurred              |                 |  |  |
| subjects affected / exposed | 2 / 197 (1.02%) |  |  |
| occurrences (all)           | 2               |  |  |
| Eye swelling                |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Eye pruritus                |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Photophobia                 |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Visual impairment           |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Dry eye                     |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Eye allergy                 |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Blepharospasm               |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Ocular dysmetria            |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Gastrointestinal disorders  |                 |  |  |
| Flatulence                  |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Nausea                      |                 |  |  |
| subjects affected / exposed | 8 / 197 (4.06%) |  |  |
| occurrences (all)           | 8               |  |  |
| Diarrhoea                   |                 |  |  |
| subjects affected / exposed | 5 / 197 (2.54%) |  |  |
| occurrences (all)           | 5               |  |  |
| Vomiting                    |                 |  |  |
| subjects affected / exposed | 5 / 197 (2.54%) |  |  |
| occurrences (all)           | 5               |  |  |
| Constipation                |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Dry mouth                   |                 |  |  |
| subjects affected / exposed | 3 / 197 (1.52%) |  |  |
| occurrences (all)           | 3               |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| Abdominal pain                   |                 |  |  |
| subjects affected / exposed      | 3 / 197 (1.52%) |  |  |
| occurrences (all)                | 3               |  |  |
| Oral pruritus                    |                 |  |  |
| subjects affected / exposed      | 1 / 197 (0.51%) |  |  |
| occurrences (all)                | 1               |  |  |
| Haematochezia                    |                 |  |  |
| subjects affected / exposed      | 0 / 197 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Toothache                        |                 |  |  |
| subjects affected / exposed      | 0 / 197 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Gastrooesophageal reflux disease |                 |  |  |
| subjects affected / exposed      | 0 / 197 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Dyspepsia                        |                 |  |  |
| subjects affected / exposed      | 0 / 197 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Gastroenteritis                  |                 |  |  |
| subjects affected / exposed      | 0 / 197 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Dental caries                    |                 |  |  |
| subjects affected / exposed      | 0 / 197 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Disbacteriosis                   |                 |  |  |
| subjects affected / exposed      | 0 / 197 (0.00%) |  |  |
| occurrences (all)                | 0               |  |  |
| Abdominal distension             |                 |  |  |
| subjects affected / exposed      | 2 / 197 (1.02%) |  |  |
| occurrences (all)                | 2               |  |  |
| Abdominal pain upper             |                 |  |  |
| subjects affected / exposed      | 1 / 197 (0.51%) |  |  |
| occurrences (all)                | 1               |  |  |
| Eructation                       |                 |  |  |
| subjects affected / exposed      | 2 / 197 (1.02%) |  |  |
| occurrences (all)                | 2               |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 197 (0.00%)<br>0 |  |  |
| Bowel movement irregularity<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 197 (0.00%)<br>0 |  |  |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 197 (0.51%)<br>1 |  |  |
| Gingivitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 197 (0.51%)<br>1 |  |  |
| Paraesthesia oral<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 197 (0.00%)<br>0 |  |  |
| Epigastric discomfort<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 197 (0.00%)<br>0 |  |  |
| Oesophagitis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 197 (0.00%)<br>0 |  |  |
| Retching<br>subjects affected / exposed<br>occurrences (all)   | 0 / 197 (0.00%)<br>0 |  |  |
| Hepatobiliary disorders<br>Hepatic steatosis<br>subjects affected / exposed<br>occurrences (all)           | 1 / 197 (0.51%)<br>1 |  |  |
| Cholecystitis chronic<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 197 (0.00%)<br>0 |  |  |
| Skin and subcutaneous tissue disorders<br>Rash macular<br>subjects affected / exposed<br>occurrences (all) | 0 / 197 (0.00%)<br>0 |  |  |
| Rash pruritic  |                      |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Skin lesion                 |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Skin irritation             |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Skin hypopigmentation       |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Rash maculo-papular         |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Pain of skin                |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Eczema                      |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Acne                        |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Pruritus                    |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Alopecia                    |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Rash                        |                 |  |  |
| subjects affected / exposed | 2 / 197 (1.02%) |  |  |
| occurrences (all)           | 2               |  |  |
| Dermatitis contact          |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Swelling face               |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Renal and urinary disorders |                 |  |  |
| Nephrolithiasis             |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Dysuria                     |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Micturition urgency         |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Pollakiuria                 |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Urinary incontinence        |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Haematuria                  |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Proteinuria                 |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Endocrine disorders         |                 |  |  |
| Hyperglycaemia              |                 |  |  |
| subjects affected / exposed | 1 / 197 (0.51%) |  |  |
| occurrences (all)           | 1               |  |  |
| Menstruation irregular      |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Adrenal cyst                |                 |  |  |
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |
| Hypoglycaemia               |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Gynaecomastia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Pain in extremity                               |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences (all)                               | 3               |  |  |
| Musculoskeletal stiffness                       |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Musculoskeletal chest pain                      |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Muscle fatigue                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Ligament sprain                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Joint swelling                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Hypertonia                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 197 (0.00%) |  |  |
| occurrences (all)                               | 0               |  |  |
| Exostosis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences (all)                               | 1               |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 197 (0.51%) |  |  |
| occurrences (all)                               | 2               |  |  |
| Neck pain                                       |                 |  |  |



|                                |                 |  |  |
|--------------------------------|-----------------|--|--|
| subjects affected / exposed    | 1 / 197 (0.51%) |  |  |
| occurrences (all)              | 1               |  |  |
| Myalgia                        |                 |  |  |
| subjects affected / exposed    | 2 / 197 (1.02%) |  |  |
| occurrences (all)              | 2               |  |  |
| Musculoskeletal pain           |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Muscle spasms                  |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Back pain                      |                 |  |  |
| subjects affected / exposed    | 2 / 197 (1.02%) |  |  |
| occurrences (all)              | 2               |  |  |
| Sensation of heaviness         |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Arthritis                      |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Spinal pain                    |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Sciatica                       |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Osteochondrosis                |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Muscular weakness              |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Lumbar spinal stenosis         |                 |  |  |
| subjects affected / exposed    | 0 / 197 (0.00%) |  |  |
| occurrences (all)              | 0               |  |  |
| Intervertebral disc protrusion |                 |  |  |

|                                   |                 |  |  |
|-----------------------------------|-----------------|--|--|
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Flank pain                        |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Contusion                         |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Infections and infestations       |                 |  |  |
| Localised infection               |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Nasopharyngitis                   |                 |  |  |
| subjects affected / exposed       | 9 / 197 (4.57%) |  |  |
| occurrences (all)                 | 9               |  |  |
| Upper respiratory tract infection |                 |  |  |
| subjects affected / exposed       | 3 / 197 (1.52%) |  |  |
| occurrences (all)                 | 3               |  |  |
| Urinary tract infection           |                 |  |  |
| subjects affected / exposed       | 2 / 197 (1.02%) |  |  |
| occurrences (all)                 | 2               |  |  |
| Sinusitis                         |                 |  |  |
| subjects affected / exposed       | 2 / 197 (1.02%) |  |  |
| occurrences (all)                 | 2               |  |  |
| Pharyngitis                       |                 |  |  |
| subjects affected / exposed       | 3 / 197 (1.52%) |  |  |
| occurrences (all)                 | 3               |  |  |
| Influenza                         |                 |  |  |
| subjects affected / exposed       | 2 / 197 (1.02%) |  |  |
| occurrences (all)                 | 2               |  |  |
| Pharyngitis streptococcal         |                 |  |  |
| subjects affected / exposed       | 1 / 197 (0.51%) |  |  |
| occurrences (all)                 | 2               |  |  |
| Bronchitis                        |                 |  |  |
| subjects affected / exposed       | 1 / 197 (0.51%) |  |  |
| occurrences (all)                 | 1               |  |  |

|                                   |                 |  |  |
|-----------------------------------|-----------------|--|--|
| Corneal infection                 |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Cystitis                          |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Ear infection                     |                 |  |  |
| subjects affected / exposed       | 1 / 197 (0.51%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Gastroenteritis                   |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Gastroenteritis viral             |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Lower respiratory tract infection |                 |  |  |
| subjects affected / exposed       | 1 / 197 (0.51%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Infected bites                    |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Rash pustular                     |                 |  |  |
| subjects affected / exposed       | 1 / 197 (0.51%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Respiratory tract infection viral |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Rhinitis                          |                 |  |  |
| subjects affected / exposed       | 1 / 197 (0.51%) |  |  |
| occurrences (all)                 | 1               |  |  |
| Rotavirus infection               |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |
| Sinusitis bacterial               |                 |  |  |
| subjects affected / exposed       | 0 / 197 (0.00%) |  |  |
| occurrences (all)                 | 0               |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Tooth infection                         |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Viral upper respiratory tract infection |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Viral infection                         |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Fungal infection                        |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Gastrointestinal viral infection        |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Laryngitis                              |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Impetigo                                |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Oral herpes                             |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Pneumonia                               |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Skin infection                          |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Tonsillitis bacterial                   |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |
| Tooth abscess                           |                 |  |  |
| subjects affected / exposed             | 0 / 197 (0.00%) |  |  |
| occurrences (all)                       | 0               |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| Viral diarrhoea                    |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Respiratory tract infection        |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Metabolism and nutrition disorders |                 |  |  |
| Decreased appetite                 |                 |  |  |
| subjects affected / exposed        | 2 / 197 (1.02%) |  |  |
| occurrences (all)                  | 2               |  |  |
| Hypercholesterolaemia              |                 |  |  |
| subjects affected / exposed        | 1 / 197 (0.51%) |  |  |
| occurrences (all)                  | 1               |  |  |
| Hyponatraemia                      |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Thirst                             |                 |  |  |
| subjects affected / exposed        | 1 / 197 (0.51%) |  |  |
| occurrences (all)                  | 1               |  |  |
| Vitamin D deficiency               |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Increased appetite                 |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Hyperkalaemia                      |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Hypochloraemia                     |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Hypoglycaemia                      |                 |  |  |
| subjects affected / exposed        | 0 / 197 (0.00%) |  |  |
| occurrences (all)                  | 0               |  |  |
| Hypokalaemia                       |                 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 197 (0.00%) |  |  |
| occurrences (all)           | 0               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 03 December 2013 | <p>Inclusion criterion 6.e was added: "Perampanel: The use of perampanel was allowed provided that the subject had been maintained on a stable dose of perampanel for <math>\geq 3</math> months and had not experienced any serious psychiatric and behavioral reactions such as hostility- or aggression related adverse reactions. Section 9.4.10 (Background antiepileptic drug [AED] Medications) was modified state that perampanel was permitted as a concomitant medication only if the subject had been on a stable dose for at least 3 months prior to screening and had not experienced any serious psychiatric and behavioral reactions, and was expected to remain on a constant dose through the double-blind phase of the study. An exclusion criterion was added (#12) and existing exclusion criteria #12 through #24 were re-numbered one number higher. The new exclusion criterion was: "Current use of ezogabine (retigabine; Potiga®; Trobalt®) was not permitted. Subjects who may have used this agent in the past were to have been off this medication for at least 3 months prior to screening and were to have had a documented normal fundoscopic examination by an ophthalmologist. Section 9.4.10 (Background AED Medications) was modified state that current use of ezogabine (retigabine) was not permitted, and that subjects who may have used this agent in the past were to have been off this medication for at least 3 months prior to screening and were to have had a documented normal fundoscopic exam by an ophthalmologist. Exclusion criterion #16 (history of drug abuse) was re-numbered to #17 and revised as follows: "The subject had a positive urine drug screen at screening or met criteria for current or historical Substance Use Disorder (Diagnostic and Statistical Manual of Mental Disorders [DSM]-V criteria) within the past 5 years. As with other AEDs, the use of alcohol was not advised.</p>   |
| 10 March 2014    | <p>The original treatment scheme was 4 weeks of prospective baseline plus 63 weeks of treatment: 1 week of titration, 4 weeks at 1200 milligrams per day (mg/day), 4 weeks at 1800 mg/day for the double-blind phase, 1-week transition to open-label, and 51 weeks at 1800 mg/day for the open-label phase. Treatment was then de-escalated over 2 weeks. A second treatment scheme was added and called 'Cohort 2,' as follows: 4 weeks of prospective baseline plus 68 weeks of treatment: 2 weeks of titration, 12 weeks at 1800 mg/day for the double-blind phase, 2 weeks of transition to open-label, and 50 weeks at 1800 mg/day for the open-label phase. Treatment was then de-escalated over 2 weeks. The protocol was revised in other sections as appropriate to support the addition of the second treatment scheme (i.e., Cohort 2), as follows: A new secondary objective was added: "To evaluate serum levels of ganaxolone at 1200 mg/day and 1800 mg/day after chronic dosing."; The planned sample size was increased from 150 subjects to 200 subjects, with approximately 50 subjects being enrolled into Cohort 1 and 150 subjects being enrolled into Cohort 2. Randomization remained at 1:1 ganaxolone or placebo in both cohorts; A schedule of events was added for Cohort 2; The primary efficacy endpoint was the change from baseline in 28-day seizure frequency during the double-blind phase for subjects in Cohort 2; A graphic illustration of the study design for Cohort 2 was added; A table showing the dosing schedule for Cohort 2 was added. Inclusion criterion #5 and exclusion criterion #9 were clarified. Randomization was modified to be stratified by country. The Per Protocol (PP) population was re-defined to require that subjects receive at least 12 weeks of treatment, rather than 9 weeks, without major protocol violations. The analysis method for the primary efficacy variable was revised from an ANCOVA with treatment and pooled countries as factors to an ANCOVA with treatment and country as factors.</p> |

|                   |  |
|-------------------|--|
| 23 September 2014 | The planned sample size for Cohort 2 was increased from 150 subjects to 292 subjects. The time period for determination of the baseline seizure frequency was modified from a 4-week retrospective period plus a 4-week prospective period to an 8-week prospective period. The number of study sites was increased from 30 to 55 (both approximately), and the estimate of the time required for enrollment of study subjects was increased from 20 months to 26 months. Inclusion criterion #5 and exclusion criterion #6 were clarified. Section 9.4.11 (Excluded Prior and Concomitant Medications) was modified to add that treatment with the 5- $\alpha$ -reductase inhibitor finasteride may not be initiated during the study because it affects endogenous levels of allopregnanolone, which could affect seizure frequency.   |
| 08 April 2016     | The planned sample size for Cohort 1 was decreased from 50 subjects to 46 subjects. The planned sample size for Cohort 2 was increased from 292 subjects to 359 subjects. Instead of the single primary efficacy endpoint of percent change from baseline in 28-day seizure frequency, two co-primary efficacy endpoints were defined because of the difference in registration requirements in the US and the EU. The original primary endpoint was unchanged, and was to be used to support a US submission, and a second co-primary endpoint of 50% responder rate during the Maintenance Period was added to support an EU submission. This change was made throughout the study protocol. In addition to the second co-primary efficacy endpoint, three key secondary efficacy endpoints were identified, and a fixed sequence analysis procedure was established to protect the familywise error rate at 0.05. These endpoints were: 50% responder rate during the Titration + Maintenance Period (Cohort 2), change from baseline in the number of seizure-free days per 28-day period during the Titration + Maintenance Period (Cohort 2), and CGI-I at Week 14 of the double-blind phase (Cohort 2). It was stated that all remaining secondary efficacy endpoints would be tested at an alpha of 0.05 and that those p-values would be nominal. Exploratory efficacy endpoints of weekly seizure frequency for each week after randomization during the double-blind phase in Cohort 2 and 28-day seizure frequency for each 4-week period in the open-label phase of the study were added. For inclusion criterion #6, it was added that AEDs could be adjusted during the open-label phase of the study. A criterion for withdrawal from the study (liver function test abnormalities) was added to Section 9.3.4.1 of the study protocol. Specific values of liver function test elevations had to be met to fulfill this criterion, and these were defined in the study protocol. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: