# Clinical trial results:
# A Phase 3b Multicenter, Double-Blind, Randomized, Placebo-Controlled, 2-Way Crossover Study of Pregabalin in the Treatment of Fibromyalgia With Concurrent Antidepressant Therapy for Comorbid Depression

## Summary

| | |
|---|---|
| EudraCT number | 2011-002480-19 |
| Trial protocol | ES IT |
| Global end of trial date | 22 July 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 30 May 2016 |
| First version publication date | 25 July 2015 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | A0081275 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01432236 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Pfizer Inc. |
| Sponsor organisation address | 235 East 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001 8007181021, clinicaltrials.govcallcenter@pfizer.com |
| Scientific contact | Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001 8007181021, clinicaltrials.govcallcenter@pfizer.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 | 07 January 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 22 July 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of pregabalin compared with placebo in subjects with fibromyalgia and comorbid depression currently on a stable selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenalin reuptake inhibitor (SNRI) primarily being used to treat the depression.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on
Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 17 November 2011 |
| 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 | Spain: 39 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | United States: 120 |
| Country: Number of subjects enrolled | Canada: 22 |
| Worldwide total number of subjects | 193 |
| EEA total number of subjects | 51 |

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) | 180 |

| | |
|---|---|
| From 65 to 84 years | 13 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

In this double blind, crossover study, a total of 197 subjects were randomized to either pregabalin/placebo or placebo/pregabalin treatment sequence. Of these, 193 took at least one dose of study medication. Four randomized subjects never took study medication. Randomized subjects were recruited from 4 countries at 38 study centers.

### Pre-assignment

Screening details:

Subjects with mean Numeric Rating Scale (NRS) pain score of greater than or equal to (>=) 4 at baseline, meeting all other inclusion/exclusion criteria were randomly assigned to receive double blind treatment with either pregabalin followed by placebo with background antidepressant or placebo followed by pregabalin with background antidepressant.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Pregabalin/Placebo |

Arm description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. There was a 2-week single-blind taper/washout period between treatment periods.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Pregabalin |
| Investigational medicinal product code | |
| Other name | Lyrica |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 milligram per day (mg/day) and increased up to 300 - 450 mg/day during the dose optimization process.

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

Dosage and administration details:

Placebo matched to pregabalin.

| | |
|---|---|
| **Arm title** | Placebo/Pregabalin |

Arm description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. There was a 2-week single-blind taper or washout period between treatment periods.

| | |
|---|---|
| Arm type | Experimental |

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

Dosage and administration details:

Placebo matched to pregabalin.

| | |
|---|---|
| Investigational medicinal product name | Pregabalin |
| Investigational medicinal product code | |
| Other name | Lyrica |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Pregabalin was administered as IR capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process.

| **Number of subjects in period 1** | Pregabalin/Placebo | Placebo/Pregabalin |
|---|---|---|
| Started | 96 | 97 |
| Completed | 70 | 79 |
| Not completed | 26 | 18 |
| Consent withdrawn by subject | 4 | 5 |
| Protocol violation | 1 | 1 |
| Adverse event | 11 | 5 |
| Unspecified | 3 | 4 |
| Lost to follow-up | 2 | 2 |
| Lack of efficacy | 5 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Pregabalin/Placebo |
| Reporting group description: | |
| Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. There was a 2-week single-blind taper/washout period between treatment periods. | |
| Reporting group title | Placebo/Pregabalin |
| Reporting group description: | |
| Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. There was a 2-week single-blind taper or washout period between treatment periods. | |

| Reporting group values | Pregabalin/Placebo | Placebo/Pregabalin | Total |
|---|---|---|---|
| Number of subjects | 96 | 97 | 193 |
| Age categorical<br>Units: Subjects | | | |
| Below 18 Years | 0 | 0 | 0 |
| 18-44 years | 22 | 29 | 51 |
| 45-64 years | 69 | 60 | 129 |
| 65 years or above | 5 | 8 | 13 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 87 | 93 | 180 |
| Male | 9 | 4 | 13 |

## End points

### End points reporting groups

| Reporting group title | Pregabalin/Placebo |
|---|---|

Reporting group description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. There was a 2-week single-blind taper/washout period between treatment periods.

| Reporting group title | Placebo/Pregabalin |
|---|---|

Reporting group description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. There was a 2-week single-blind taper or washout period between treatment periods.

| Subject analysis set title | All Subjects |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomized subjects were included in this analysis.

| Subject analysis set title | Pregabalin |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with pregabalin for 6 weeks (3 weeks dose optimization and 3 weeks fixed dose) in period 1 followed by placebo in period 2 with background antidepressants. Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process. There was a 2-week single-blind taper/washout period between treatment periods.

| Subject analysis set title | Placebo |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Subjects were randomized in a 1:1 ratio to double-blind treatment with placebo for 6 weeks in period 1 followed by pregabalin in period 2 (3 weeks dose optimization and 3 weeks fixed dose) with background antidepressants. Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process in period 2. There was a 2-week single-blind taper/washout period between treatment periods

### Primary: Mean Numeric Rating Scale (NRS) Pain Score at End of Period

| End point title | Mean Numeric Rating Scale (NRS) Pain Score at End of Period |
|---|---|

End point description:

The daily pain diary consists of an 11-point numeric scale (NRS) ranging from 0 (“no pain”) to 10 (“worst possible pain”). Subjects describe their pain during the past 24 hours by choosing the appropriate number between 0 and 10. The endpoint mean pain scores for Period 1 and Period 2 are defined as the mean of the last 7 non-missing daily diary pain ratings while taking study medication in the double-blind phase during Period 1 and Period 2, respectively. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of each period, at Weeks 6, Week 14

| End point values | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 173 | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 4.84 (± 0.15) | 5.45 (± 0.16) | | |

### Statistical analyses

| Statistical analysis title | Mean NRS Pain Score at End of Period |
|---|---|

Statistical analysis description:

Analysis was done using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.0001 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.91 |
| upper limit | -0.31 |

Notes:

[1] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 352.
[2] - Primary analysis was two-sided and performed at the 0.05 significance level. Satterthwaite’s approximation was used to estimate denominator degrees of freedom.

### Secondary: Fibromyalgia Impact Questionnaire (FIQ) Score at Baseline

| End point title | Fibromyalgia Impact Questionnaire (FIQ) Score at Baseline |
|---|---|

End point description:

This was a 20-item subjects reported outcome instrument. It contained 10 subscales, which were combined to yield a total score. The first 11 questions were related specifically to physical functioning subscale, ranging from 0 to 10. The remaining 9 questions assessed pain, fatigue, stiffness, difficulty working, and symptoms of anxiety and depression ranging from 0 to 10. The higher values indicated greater impairment. All 20 were combined to form a total score ranging from 0 to 100, provides an estimation of fibromyalgia impact with higher scores indicating more impairment. The severity categorizations for the FIQ are: less than 40 (mild), 40-60 (moderate), and above 60 (severe). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

Baseline

| End point values | Pregabalin/Placebo | Placebo/Pregabalin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 97 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total (N=96, 96) | 63.83 (± 11.58) | 62.75 (± 12.51) | | |
| Physical Impairment (N=96, 97) | 4.58 (± 2.1) | 4.44 (± 2.14) | | |
| Feel Good (N=96, 97) | 7.78 (± 2.47) | 7.43 (± 2.32) | | |
| Work Missed (N=96, 97) | 3.38 (± 2.88) | 3.49 (± 3.21) | | |
| Do Work (N=96, 97) | 6.61 (± 2.03) | 6.38 (± 2.21) | | |
| Pain (N=96, 96) | 6.98 (± 1.25) | 7.09 (± 1.32) | | |
| Fatigue (N=96, 97) | 8.17 (± 1.37) | 8.08 (± 1.58) | | |
| Rested (N=96, 97) | 7.9 (± 1.51) | 7.82 (± 1.96) | | |
| Stiffness (N=96, 97) | 7.56 (± 1.56) | 7.64 (± 1.58) | | |
| Anxiety (N=96, 97) | 5.65 (± 2.73) | 5.6 (± 2.59) | | |
| Depression (N=96, 97) | 5.23 (± 2.64) | 4.84 (± 2.55) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: FIQ Score at End of Period

| End point title | FIQ Score at End of Period |
|---|---|

End point description:

This was a 20-item subject reported outcome instrument. It contained 10 subscales, which were combined to yield a total score. The first 11 questions were related specifically to physical functioning subscale, ranging from 0 to 10. The remaining 9 questions assessed pain, fatigue, stiffness, difficulty working, and symptoms of anxiety and depression ranging from 0 to 10. The higher values indicated greater impairment. All 20 were combined to form a total score ranging from 0 to 100, provides an estimation of fibromyalgia impact with higher scores indicating more impairment. The severity categorizations for the FIQ are: less than 40 (mild), 40-60 (moderate), and above 60 (severe). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation. 'N' for each category represents subjects that were actually treated with pregabalin and placebo during the study.

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

End point timeframe:

End of each period, at Weeks 6, Week 14

| End point values | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 181 | 177 | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Total (N=176, 172) | 43.78 (± 1.42) | 50.38 (± 1.43) | | |
| Physical impairment (N=176, 173) | 3.35 (± 0.17) | 3.77 (± 0.17) | | |
| Feel good (N=176, 173) | 4.69 (± 0.23) | 5.53 (± 0.23) | | |
| Work missed (N=176 , 173) | 2.02 (± 0.21) | 2.62 (± 0.21) | | |

| | | | | |
|---|---|---|---|---|
| Do work (N=176, 172) | 4.56 (± 0.2) | 5.31 (± 0.2) | | |
| Pain (N=176, 173) | 4.91 (± 0.17) | 5.54 (± 0.17) | | |
| Fatigue (N=176, 173) | 6.32 (± 0.19) | 6.76 (± 0.19) | | |
| Rested (N=176, 173) | 5.64 (± 0.19) | 6.41 (± 0.19) | | |
| Stiffness (N=176, 173) | 5.24 (± 0.19) | 5.95 (± 0.19) | | |
| Anxiety (N=176, 173) | 3.8 (± 0.2) | 4.35 (± 0.21) | | |
| Depression (N=176, 173) | 3.2 (± 0.2) | 4.13 (± 0.2) | | |

## Statistical analyses

| **Statistical analysis title** | FIQ Total Score |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | < 0.0001 [4] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.33 |
| upper limit | -3.87 |

Notes:

[3] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[4] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Physical Impairment |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.0078 [6] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.42 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.74 |
| upper limit | -0.11 |

Notes:

[5] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[6] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Feel Good |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.0014 [8] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.36 |
| upper limit | -0.33 |

Notes:

[7] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[8] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Work Missed |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within- subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[9] |
| P-value | = 0.005 [10] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.59 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.01 |
| upper limit | -0.18 |

Notes:

[9] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[10] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Do Work |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | = 0.0002 [12] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.14 |
| upper limit | -0.36 |

Notes:

[11] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[12] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Pain |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[13] |
| P-value | = 0.0006 [14] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | -0.28 |

Notes:

[13] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[14] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Fatigue |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[15] |
| P-value | = 0.0315 [16] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.44 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.85 |
| upper limit | -0.04 |

Notes:

[15] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[16] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Rested |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[17] |
| P-value | = 0.0003 [18] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.17 |
| upper limit | -0.35 |

Notes:

[17] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[18] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Stiffness |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[19] |
| P-value | = 0.0007 [20] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.11 |
| upper limit | -0.31 |

Notes:

[19] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.

[20] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Anxiety |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[21] |
| P-value | = 0.0048 [22] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.93 |
| upper limit | -0.17 |

Notes:

[21] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[22] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | Depression |
|---|---|

Statistical analysis description:

Analysis was performed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 358 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[23] |
| P-value | < 0.0001 [24] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.32 |
| upper limit | -0.53 |

Notes:

[23] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 181, not 358.
[24] - Analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Secondary: Patient Global Impression of Change (PGIC) at the End of Period 1

| End point title | Patient Global Impression of Change (PGIC) at the End of Period 1 |
|---|---|

End point description:

PGIC: Subject rated instrument to measure subject's change in overall status from baseline to the end

of period 1 (Week 6) on a 7-point scale; range from 1 (very much improved) to 7 (very much worse). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of Period 1 at Week 6

| **End point values** | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 93 | 93 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Very much improved | 10.8 | 4.3 | | |
| Much improved | 35.5 | 25.8 | | |
| Minimally improved | 28 | 40.9 | | |
| No change | 17.2 | 21.5 | | |
| Minimally worse | 4.3 | 6.5 | | |
| Much worse | 3.2 | 1.1 | | |
| Very much worse | 1.1 | 0 | | |

## Statistical analyses

| **Statistical analysis title** | PGIC at the End of Period 1 |
|---|---|

Statistical analysis description:

The PGIC variable was analyzed using Cochran Mantel-Haenszel (CMH) test with modified ridit transformation.

| Comparison groups | Pregabalin v Placebo |
|---|---|
| Number of subjects included in analysis | 186 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0637 [25] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[25] - This analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Secondary: Percentage of Subjects with Greater than or Equal to (>=)30 Percent (%) and >=50% Pain Reduction Based on Daily Pain

| End point title | Percentage of Subjects with Greater than or Equal to (>=)30 Percent (%) and >=50% Pain Reduction Based on Daily Pain |
|---|---|

End point description:

Subject with at least a 30% reduction in mean pain score from baseline (at randomization) to the endpoint at the end of each period (Visit 6 and 12) was considered a 30% responder, for the respective period. Similarly, a subject with at least a 50% reduction in mean pain score from baseline (at randomization) to the endpoint at the end of each period (Visit 6 and 12) was considered a 50% responder, for the respective period. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:
Visits 2, 6, 12

| End point values | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 173 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| 30% Responders | 45.3 | 27.7 | | |
| 50% Responders | 26 | 15.8 | | |

**Statistical analyses**

| Statistical analysis title | For 30 Percent Responders |
|---|---|

Statistical analysis description:

Analysis was conducted using a logistic regression model using sequence, period, and treatment as fixed factors and subject within sequence and within subject error as random factors. Log link transformation was used for the model.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[26] |
| P-value | = 0.0007 [27] |
| Method | Regression, Logistic |

Notes:

[26] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.
[27] - This secondary analyses was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| Statistical analysis title | For 50 Percent Responders |
|---|---|

Statistical analysis description:

Analysis was conducted using a logistic regression model using sequence, period, and treatment as fixed factors and subject within sequence and within subject error as random factors. Log link transformation was used for the model.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[28] |
| P-value | = 0.0205 [29] |
| Method | Regression, Logistic |

Notes:

[28] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.
[29] - This secondary analyses was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Secondary: Subjective Sleep Questionnaire - Mean Sleep Quality at End of Period

| End point title | Subjective Sleep Questionnaire - Mean Sleep Quality at End of Period |
|---|---|

End point description:

Subjective sleep questionnaire-mean sleep quality at end of each period (Week 6 and Week 14) included 5 items: subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (NRS) for the previous night. Subjective rating of quality of sleep during the past night was done by selecting a number between 0 (very poor) and 10 (excellent). Mean sleep quality was calculated as the mean of the last seven days, the potential range of responses was therefore 0-10. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of each period, at Weeks 6 and 14

| **End point values** | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 173 | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 6.15 (± 0.14) | 5.57 (± 0.14) | | |

**Statistical analyses**

| **Statistical analysis title** | Subjective Sleep Questionnaire |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| Comparison groups | Pregabalin v Placebo |
|---|---|
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[30] |
| P-value | < 0.0001 [31] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.31 |
| upper limit | 0.84 |

Notes:

[30] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.
[31] - This was done using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

**Secondary: Subjective Sleep Questionnaire - Mean Subjective Wake After Sleep Onset at End of Period**

| End point title | Subjective Sleep Questionnaire - Mean Subjective Wake After Sleep Onset at End of Period |
|---|---|

End point description:

Subjective sleep questionnaire included, subjects report latency (how long it took them to fall asleep),

how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective wake after sleep onset was the subjective estimate of the total amount of time the subject was awake after initial sleep onset until final awakening. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of each period, at Weeks 6 and 14

| **End point values** | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 173 | | |
| Units: Minutes | | | | |
| least squares mean (standard error) | 33.38 (± 2.73) | 41.18 (± 2.76) | | |

## Statistical analyses

| **Statistical analysis title** | Subjective Sleep Questionnaire |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| Comparison groups | Pregabalin v Placebo |
|---|---|
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[32] |
| P-value | = 0.0018 [33] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -7.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.66 |
| upper limit | -2.96 |

Notes:

[32] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[33] - This was done using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Secondary: Subjective Sleep Questionnaire - Mean Latency to Sleep Onset at End of Period

| End point title | Subjective Sleep Questionnaire - Mean Latency to Sleep Onset at End of Period |
|---|---|

End point description:

Subjective sleep questionnaire included, subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective latency to sleep onset was the subjective estimate of the amount of time to fall asleep after lights out. ITT

population defined, as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of each period, at Weeks 6 and 14

| **End point values** | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 173 | | |
| Units: Minutes | | | | |
| least squares mean (standard error) | 33.54 (± 2.68) | 39.33 (± 2.71) | | |

**Statistical analyses**

| **Statistical analysis title** | Subjective Sleep Questionnaire |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| Comparison groups | Pregabalin v Placebo |
|---|---|
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[34] |
| P-value | = 0.0117 [35] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -5.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.29 |
| upper limit | -1.31 |

Notes:

[34] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.
[35] - This was done using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

**Secondary: Subjective Sleep Questionnaire - Mean Subjective Total Sleep Time at End of Period**

| End point title | Subjective Sleep Questionnaire - Mean Subjective Total Sleep Time at End of Period |
|---|---|

End point description:

Subjective Sleep Questionnaire included, subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective total sleep time was the subjective estimate of the total amount of time the subject was asleep after lights out until final awakening. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of each period, at Weeks 6 and 14

| **End point values** | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 173 | | |
| Units: Minutes | | | | |
| least squares mean (standard error) | 422.98 (± 5.42) | 414.63 (± 5.48) | | |

## Statistical analyses

| **Statistical analysis title** | Subjective Sleep Questionnaire |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[36] |
| P-value | = 0.0511 [37] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 8.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 16.74 |

Notes:

[36] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.

[37] - This was done using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Secondary: Subjective Sleep Questionnaire - Parameter Estimates for Subjective Number of Awakenings Per Night After Sleep Onset at End of Period

| End point title | Subjective Sleep Questionnaire - Parameter Estimates for Subjective Number of Awakenings Per Night After Sleep Onset at End of Period |
|---|---|

End point description:

Subjective sleep questionnaire included, subjects report latency (how long it took them to fall asleep), how many hours they slept, the number of times they woke up, the total wake time after sleep onset, and then rate the quality of their sleep (numeric rating scale) for the previous night. Subjective number of awakenings after sleep onset was the subjective estimate of the total number of times the subject awakened during the night until final awakening. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of each period, at Weeks 6 and 14

| **End point values** | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 179 | 173 | | |
| Units: Number of times awakened | | | | |
| least squares mean (standard error) | 0.48 (± 0.07) | 0.61 (± 0.07) | | |

## Statistical analyses

| **Statistical analysis title** | Subjective Sleep Questionnaire |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors. Analyzed as a count variable using a generalized linear model assuming a Poisson distribution and utilizing a log link transformation.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 352 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[38] |
| P-value | = 0.1139 [39] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.29 |
| upper limit | 0.03 |

Notes:

[38] - For 'number of subjects included in the analysis' field: In cross over studies, each subject received both treatments. Total number of subjects were 179, not 352.
[39] - This was done using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Secondary: Hospital Anxiety and Depression Scale (HADS) at Baseline

| End point title | Hospital Anxiety and Depression Scale (HADS) at Baseline |
|---|---|

End point description:

HADS: Subject rated questionnaire with 2 subscales. HADS-A (anxiety) assesses state of generalized anxiety (anxious mood, restlessness, anxious thoughts, panic attacks); HADS-D (depression) assesses state of lost interest and diminished pleasure response (lowering of hedonic tone). Each subscale comprised of 7 items with range 0 (no presence of anxiety or depression) to 3 (severe feeling of anxiety or depression). Total score 0 to 21 for each subscale; higher score indicates greater severity of anxiety and depression symptoms. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

Baseline

| End point values | Pregabalin/Placebo | Placebo/Pregabalin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 97 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| HADS-A (anxiety) | 8.67 (± 3.95) | 7.97 (± 3.77) | | |
| HADS-D (depression) | 8.34 (± 3.59) | 7.73 (± 3.64) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: HADS at End of Period

| End point title | HADS at End of Period |
|---|---|

End point description:

HADS: Subject rated questionnaire with 2 subscales. HADS-A (anxiety) assesses state of generalized anxiety (anxious mood, restlessness, anxious thoughts, panic attacks); HADS-D (depression) assesses state of lost interest and diminished pleasure response (lowering of hedonic tone). Each subscale comprised of 7 items with range 0 (no presence of anxiety or depression) to 3 (severe feeling of anxiety or depression). Total score 0 to 21 for each subscale; higher score indicates greater severity of anxiety and depression symptoms. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

Week 6, Week 14

| End point values | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 176 | 173 | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| HADS-A (anxiety) | 6.01 (± 0.28) | 6.96 (± 0.28) | | |
| HADS-D (depression) | 6.17 (± 0.31) | 7.05 (± 0.31) | | |

## Statistical analyses

| Statistical analysis title | For HADS-A (anxiety) |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 349 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [40] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4 |
| upper limit | -0.5 |

Notes:

[40] - Two-sided test with α=0.05 was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

| **Statistical analysis title** | For HADS-D (depression) |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 349 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 [41] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.37 |
| upper limit | -0.39 |

Notes:

[41] - Two-sided test with α=0.05 was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Secondary: Mean EuroQoL 5-Dimensions (EQ-5D) Score at Baseline

| End point title | Mean EuroQoL 5-Dimensions (EQ-5D) Score at Baseline |
|---|---|

End point description:

EQ-5D is a standardized, subject-administered measure of health outcome. It provides a descriptive profile for 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), using 3 levels (no, moderate, or extreme problems) and a single index value characterizing current health status using a 100-point visual analog scale (0=worst, 100=best). EQ-5D summary index is obtained with a formula that weights each level of the dimensions. The index-based score is interpreted along a continuum of 0 (death) to 1 (perfect health). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

Baseline

| End point values | Pregabalin/Placebo | Placebo/Pregabalin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 97 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.4 (± 0.31) | 0.37 (± 0.33) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: EQ-5D score at End of Period

| End point title | EQ-5D score at End of Period |
|---|---|

End point description:

EQ-5D is a standardized, subject-administered measure of health outcome. It provides a descriptive profile for 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), using 3 levels (no, moderate, or extreme problems) and a single index value characterizing current health status using a 100-point visual analog scale (0=worst, 100=best). EQ-5D summary index is obtained with a formula that weights each level of the dimensions. The index-based score is interpreted along a continuum of 0 (death) to 1 (perfect health). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

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

End point timeframe:

End of each period, at Weeks 6 and 14

| End point values | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 176 | 172 | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 0.58 (± 0.02) | 0.56 (± 0.02) | | |

## Statistical analyses

| Statistical analysis title | For EQ-5D Score at End of Period |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subjectt within sequence and within-subject error as random factors.

| Comparison groups | Pregabalin v Placebo |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 348 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3854 [42] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02 |
| upper limit | 0.06 |

Notes:

[42] - Two-sided test with α=0.05 was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Other pre-specified: PGIC at the End of Period 2

| | |
|---|---|
| End point title | PGIC at the End of Period 2 |

End point description:

PGIC: subject rated instrument to measure subjects's change in overall status from baseline to the end of period 2 (Week 14) on a 7-point scale; range from 1 (very much improved) to 7 (very much worse). Because of the crossover design and PGIC recall period (since starting study medication), the Period 1 PGIC data were felt to provide the clearest comparison across treatments, whereas Period 2 PGIC data were felt to have a more complex interpretation. Thus PGIC at End of Period 2 was separately analyzed from PGIC at End of Period 1. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

| | |
|---|---|
| End point type | Other pre-specified |

End point timeframe:

End of Period 2 at Week 14

| **End point values** | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 82 | 81 | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Very much improved | 18.3 | 8.6 | | |
| Much improved | 34.1 | 25.9 | | |
| Minimally improved | 28 | 38.3 | | |
| No change | 11 | 14.8 | | |
| Minimally worse | 6.1 | 8.6 | | |
| Much worse | 1.2 | 2.5 | | |
| Very much worse | 1.2 | 1.2 | | |

## Statistical analyses

| Statistical analysis title | For PGIC at the End of Period 2 |
|---|---|

Statistical analysis description:

The PGIC variable was analyzed using CMH test with modified ridit transformation.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 163 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.116 [43] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[43] - This analysis was conducted using a two-sided test with α=0.05. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Other pre-specified: Mean Patient Static Global Assessment (PSGA) Score at Baseline

| End point title | Mean Patient Static Global Assessment (PSGA) Score at Baseline |
|---|---|

End point description:

PSGA was a single-item self-rated instrument that measured the subject's overall status on an 11-point NRS ranging from 0 (very poor) to 10 (very good). ITT population defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline

| End point values | Pregabalin/Placebo | Placebo/Pregabalin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 97 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | 4.35 (± 2.04) | 4.46 (± 1.92) | | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Mean PSGA score at End of Period

| End point title | Mean PSGA score at End of Period |
|---|---|

End point description:

PSGA was a single-item self-rated instrument that measured the subject's overall status on an 11-point numeric rating scale (NRS) ranging from 0 (very poor) to 10 (very good). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

End of each period, at Weeks 6 and 14

| End point values | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 176 | 172 | | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 5.83 (± 0.17) | 5.27 (± 0.17) | | |

## Statistical analyses

| Statistical analysis title | Mean PSGA Score at End of Period |
|---|---|

Statistical analysis description:

Analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors and subject within sequence and within-subject error as random factors.

| | |
|---|---|
| Comparison groups | Pregabalin v Placebo |
| Number of subjects included in analysis | 348 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0085 [44] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.14 |
| upper limit | 0.97 |

Notes:

[44] - Two-sided test with α=0.05 was used. No corrections to alpha to control for potential inflation of Type I error resulting from multiple comparisons were made.

## Other pre-specified: Number of Subjects With Categorical Scores on the Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline

| End point title | Number of Subjects With Categorical Scores on the Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline |
|---|---|

End point description:

C-SSRS assessed whether subjects experienced following: completed suicide (1), suicide attempt (2) (response of "Yes" on "actual attempt"), preparatory acts toward imminent suicidal behavior (3) ("Yes" on "preparatory acts or behavior"), suicidal ideation (4) ("Yes" on "wish to be dead", "non-specific active suicidal thoughts", "active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent), any suicidal behavior or ideation, self-injurious behavior (7) ("Yes" on "Has subject engaged in non-suicidal self-injurious behavior"). ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline

| End point values | Pregabalin/Placebo | Placebo/Pregabalin | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 | 97 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Wish to be Dead | 3 | 1 | | |
| Non-Specific Thoughts | 0 | 1 | | |
| Without Intent to Act | 0 | 0 | | |
| Some Intent to Act | 0 | 0 | | |
| Specific Plan and Intent | 0 | 0 | | |
| Actual Attempt | 0 | 0 | | |
| Non-Suicidal Self-Injurious Behavior | 0 | 0 | | |
| Interrupted Attempt | 0 | 0 | | |
| Aborted Attempt | 0 | 0 | | |
| Preparatory Acts or Behavior | 0 | 0 | | |
| Suicidal Behavior Present | 0 | 0 | | |
| Completed Suicide | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of Subjects With Categorical Scores on the Columbia Suicidality Severity Rating Scale (C-SSRS) at Post-Baseline

| End point title | Number of Subjects With Categorical Scores on the Columbia Suicidality Severity Rating Scale (C-SSRS) at Post-Baseline |
|---|---|

End point description:

C-SSRS assessed whether subjects experienced following: completed suicide (1), suicide attempt (2) (response of Yes on "actual attempt"), preparatory acts toward imminent suicidal behavior (3) (Yes on "preparatory acts or behavior"), suicidal ideation (4) (Yes on "wish to be dead", "non-specific active suicidal thoughts", "active suicidal ideation with methods without intent to act or some intent to act, without specific plan or with specific plan and intent), any suicidal behavior or ideation, self-injurious behavior (7) (Yes on "Has subject engaged in non-suicidal self-injurious behavior"). Below table indicated 1 subject treated with Pregabalin reported preparatory act. On study unblinding it was clarified that preparatory act occurred while subject was taking placebo. ITT population, defined as all subject who were randomized, treated (ie, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

From Visit 3 to Visit 14

| End point values | Pregabalin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 181 | 177 | | |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Wish to be Dead | 10 | 8 | | |
| Non-Specific Thoughts | 3 | 1 | | |
| Without Intent to Act | 2 | 0 | | |
| Some Intent to Act | 0 | 0 | | |
| Specific Plan and Intent | 0 | 0 | | |
| Actual Attempt | 0 | 0 | | |
| Non-Suicidal Self-Injurious Behavior | 0 | 0 | | |
| Interrupted Attempt | 0 | 0 | | |
| Aborted Attempt | 0 | 0 | | |
| Preparatory Acts or Behavior | 1 | 0 | | |
| Suicidal Behavior Present | 1 | 0 | | |
| Completed Suicide | 0 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Work Productivity and Activity Index-Specific Health Problem (WPAI-SHP) Questionnaire at Baseline

| End point title | Work Productivity and Activity Index-Specific Health Problem (WPAI-SHP) Questionnaire at Baseline |
|---|---|

End point description:

WPAI-SHP assessed work productivity and impairment. It was a subject-rated, six-item questionnaire regarding current employment, hours missed and actually worked, and degree to which a specified health problem affected work productivity and regular activities over the past 7 days. Subscale scores included percent work time missed due to the health problem; percent impairment while working due to problem; percent overall work impairment due to problem; and percent activity impairment due to problem. Each subscale score was expressed as an impairment percentage (0-100) where higher numbers indicated greater impairment and less productivity. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline

| End point values | All Subjects | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 193 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Percent Absenteeism (N= 86) | 15.22 (± 25.36) | | | |
| Percent Presenteeism (N= 83) | 53.98 (± 21.52) | | | |

| | | | | |
|---|---|---|---|---|
| Percent Overall Work Impairment (N= 82) | 57.96 (± 23.42) | | | |
| Percent Activity Impairment (N=193) | 64.97 (± 18.77) | | | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Health Utilization Assessment (Total Office Visits, Number of Hospitalizations and Number of Emergency Room Visits) at Baseline

| End point title | Health Utilization Assessment (Total Office Visits, Number of Hospitalizations and Number of Emergency Room Visits) at Baseline |
|---|---|

End point description:

The healthcare utilization assessment was used to capture healthcare utilization data at Baseline. This assessment contained 10 questions related to aspects of healthcare services. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation. Here "99999" in the mean and standard deviation of number of hospitalizations, signifies not available (NA). Mean and standard deviation were not calculated as no subject was evaluated for this time point.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline

| **End point values** | All Subjects | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 193 | | | |
| Units: Visits | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total office visits (N= 193) | 5.01 (± 6.6) | | | |
| Number of hospitalizations (N= 0) | 99999 (± 99999) | | | |
| Number of emergency room visits (N= 12) | 1.83 (± 1) | | | |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Health Utilization Assessment (Time for Help No Payment) at Baseline

| End point title | Health Utilization Assessment (Time for Help No Payment) at Baseline |
|---|---|

End point description:

The healthcare utilization assessment was used to capture healthcare utilization data at Baseline. This assessment contained 10 questions related to aspects of healthcare services. 'Time for help no payment' refers to time other people spent without receiving payment to help with activities the patient cannot

perform due to fibromyalgia. ITT population, defined as all subjects who were randomized, treated (i.e, received at least one dose of study medication) and had at least one post-randomization efficacy evaluation.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

Baseline

| **End point values** | All Subjects | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 193 | | | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | 50.37 (± 98.1) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 16

Adverse event reporting additional description:

The same event may appear as both an adverse event (AE) and a serious adverse event (SAE). However, what is presented are distinct events. An event may be categorized as serious in one subject and as nonserious in another subject, or one subject may have experienced both a serious and nonserious event during the study.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Pregabalin |

Reporting group description:

The below table included subjects who received pregabalin in either treatment period pooled together due to the crossover study design. This crossover study consisted of two double blind 6-week treatment periods where subjects were randomized to pregabalin or placebo for the first period, and were then switched to the other treatment for the second period (3 weeks dose optimization and 3 weeks fixed dose for each treatment period). Pregabalin was administered as immediate release (IR) capsule with a starting dose of 150 mg/day and increased up to 300 - 450 mg/day during the dose optimization process. There was a 2-week single-blind taper or washout period between treatment periods.

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

Reporting group description:

The below table included subjects who received placebo in either treatment period pooled together due to the crossover study design. This crossover study consisted of two double blind 6-week treatment periods where subjects were randomized to pregabalin or placebo for the first period, and were then switched to the other treatment for the second period (3 weeks dose optimization and 3 weeks fixed dose for each treatment period). There was a 2-week single-blind taper or washout period between treatment periods.

| Serious adverse events | Pregabalin | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 1 / 177 (0.56%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Brain neoplasm malignant | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Detoxification | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Pregabalin | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 139 / 181 (76.80%) | 106 / 177 (59.89%) | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 2 / 177 (1.13%) | |
| occurrences (all) | 2 | 2 | |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 177 (1.13%) | |
| occurrences (all) | 1 | 2 | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 177 (1.13%) | |
| occurrences (all) | 1 | 2 | |
| Crying | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cyst | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Energy increased | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 12 / 181 (6.63%) | 8 / 177 (4.52%) | |
| occurrences (all) | 13 | 9 | |
| Feeling abnormal | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 0 / 177 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Feeling drunk | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Feeling jittery | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 177 (0.00%) | |
| occurrences (all) | 3 | 0 | |

| | | | |
|---|---|---|---|
| Hunger | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 1 / 177 (0.56%) | |
| occurrences (all) | 3 | 1 | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Irritability | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 1 / 177 (0.56%) | |
| occurrences (all) | 3 | 1 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mucosal dryness | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 7 / 181 (3.87%) | 3 / 177 (1.69%) | |
| occurrences (all) | 8 | 3 | |
| Pain | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 4 / 177 (2.26%) | |
| occurrences (all) | 0 | 4 | |
| Swelling | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|---|---|---|
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal dryness | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 1 / 177 (0.56%) | |
| occurrences (all) | 2 | 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Nasal dryness | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 5 / 177 (2.82%) | |
| occurrences (all) | 3 | 5 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper-airway cough syndrome | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Abnormal dreams | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anxiety | | | |
| subjects affected / exposed | 8 / 181 (4.42%) | 7 / 177 (3.95%) | |
| occurrences (all) | 8 | 10 | |
| Apathy | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Bradyphrenia | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 177 (1.13%) | |
| occurrences (all) | 1 | 2 | |
| Depression | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 4 / 177 (2.26%) | |
| occurrences (all) | 5 | 4 | |
| Disorientation | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 0 / 177 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Euphoric mood | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Initial insomnia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 13 / 181 (7.18%) | 1 / 177 (0.56%) | |
| occurrences (all) | 14 | 1 | |
| Nervousness | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 2 / 177 (1.13%) | |
| occurrences (all) | 3 | 2 | |

| | | | |
|---|---|---|---|
| Nightmare | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 4 / 177 (2.26%) | |
| occurrences (all) | 1 | 4 | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Restlessness | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Suicidal ideation | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Thinking abnormal | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood glucose increased | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood pressure increased | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 3 / 177 (1.69%) | |
| occurrences (all) | 0 | 3 | |
| Eosinophil count increased | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Urine output decreased | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 16 / 181 (8.84%) | 3 / 177 (1.69%) | |
| occurrences (all) | 16 | 3 | |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Fall | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 1 / 177 (0.56%) | |
| occurrences (all) | 4 | 1 | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Laceration | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 177 (1.13%) | |
| occurrences (all) | 0 | 2 | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle strain | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 177 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Post concussion syndrome | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Skeletal injury | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tendon rupture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Areflexia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 0 / 177 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Burning sensation | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Clumsiness | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Disturbance in attention | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 4 / 177 (2.26%) | |
| occurrences (all) | 5 | 4 | |
| Dizziness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 51 / 181 (28.18%) | 12 / 177 (6.78%) | |
| occurrences (all) | 67 | 14 | |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Headache | | | |
| subjects affected / exposed | 14 / 181 (7.73%) | 17 / 177 (9.60%) | |
| occurrences (all) | 4 | 20 | |
| Hypersomnia | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 177 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hyporeflexia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Memory impairment | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 1 / 177 (0.56%) | |
| occurrences (all) | 5 | 1 | |
| Mental impairment | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 3 / 177 (1.69%) | |
| occurrences (all) | 1 | 3 | |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 1 / 177 (0.56%) | |
| occurrences (all) | 2 | 1 | |
| Presyncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychomotor hyperactivity | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Repetitive speech | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sedation | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 2 / 177 (1.13%) | |
| occurrences (all) | 4 | 2 | |
| Somnolence | | | |
| subjects affected / exposed | 36 / 181 (19.89%) | 8 / 177 (4.52%) | |
| occurrences (all) | 48 | 8 | |
| Stupor | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tension headache | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood and lymphatic system disorders | | | |
| Neutrophilia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Vertigo | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Eye disorders | | | |

| | | | |
|---|---|---|---|
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Dry eye | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 177 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Eye disorder | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Vision blurred | | | |
| subjects affected / exposed | 7 / 181 (3.87%) | 3 / 177 (1.69%) | |
| occurrences (all) | 7 | 3 | |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 1 / 177 (0.56%) | |
| occurrences (all) | 2 | 1 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 3 / 177 (1.69%) | |
| occurrences (all) | 3 | 3 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 4 / 177 (2.26%) | |
| occurrences (all) | 1 | 4 | |
| Constipation | | | |
| subjects affected / exposed | 19 / 181 (10.50%) | 4 / 177 (2.26%) | |
| occurrences (all) | 20 | 4 | |
| Dental caries | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 181 (8.84%) | 7 / 177 (3.95%) | |
| occurrences (all) | 16 | 7 | |
| Dry mouth | | | |
| subjects affected / exposed | 12 / 181 (6.63%) | 1 / 177 (0.56%) | |
| occurrences (all) | 12 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Flatulence | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 2 / 177 (1.13%) | |
| occurrences (all) | 4 | 2 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Irritable bowel syndrome | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Lip swelling | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 17 / 181 (9.39%) | 12 / 177 (6.78%) | |
| occurrences (all) | 19 | 15 | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia oral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 177 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Salivary gland pain | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Toothache | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 5 / 177 (2.82%) | |
| occurrences (all) | 1 | 5 | |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Night sweats | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 4 / 177 (2.26%) | |
| occurrences (all) | 4 | 4 | |
| Pruritus generalised | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 181 (0.55%) | 3 / 177 (1.69%) | |
| occurrences (all) | 1 | 3 | |
| Rash generalised | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin lesion | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Incontinence | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oliguria | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 2 / 177 (1.13%) | |
| occurrences (all) | 3 | 2 | |
| Back pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 181 (1.66%) | 4 / 177 (2.26%) | |
| occurrences (all) | 3 | 4 | |
| Fibromyalgia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Flank pain | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Medial tibial stress syndrome | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 1 / 177 (0.56%) | |
| occurrences (all) | 4 | 1 | |
| Muscle twitching | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 177 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 181 (1.66%) | 3 / 177 (1.69%) | |
| occurrences (all) | 3 | 3 | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 177 (1.13%) | |
| occurrences (all) | 1 | 2 | |
| Bronchitis viral | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Ear infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 177 (1.13%) | |
| occurrences (all) | 1 | 2 | |
| Folliculitis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 3 / 177 (1.69%) | |
| occurrences (all) | 0 | 3 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 2 / 177 (1.13%) | |
| occurrences (all) | 4 | 2 | |
| Influenza | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 2 / 177 (1.13%) | |
| occurrences (all) | 3 | 2 | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 181 (2.76%) | 10 / 177 (5.65%) | |
| occurrences (all) | 5 | 10 | |

| | | | |
|---|---|---|---|
| Oral herpes | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 177 (1.13%) | |
| occurrences (all) | 1 | 2 | |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 2 / 177 (1.13%) | |
| occurrences (all) | 4 | 2 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 1 / 177 (0.56%) | |
| occurrences (all) | 2 | 1 | |
| Vaginal infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 177 (1.13%) | |
| occurrences (all) | 1 | 2 | |
| Metabolism and nutrition disorders | | | |
| Fluid retention | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 177 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Folate deficiency | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 177 (0.56%) | |
| occurrences (all) | 0 | 1 | |
| Food craving | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 177 (0.56%) | |
| occurrences (all) | 1 | 1 | |
| Increased appetite | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 0 / 177 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Polydipsia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 177 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 December 2012 | Benefit and risk summary was added. Subject withdrawal and adverse event reporting were updated. Pregnancy testing requirements were expanded. Clarifications regarding prohibited and allowable medications were added. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported