



Clinical trial results:

A Double-Blind, Efficacy and Safety Study of Duloxetine versus Placebo in the Treatment of Children and Adolescents with Generalized Anxiety Disorder

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-001599-46 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 03 June 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 24 December 2017 |
| First version publication date | 24 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | F1J-MC-HMGI |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01226511 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Eli Lilly and Company: 12929 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eli Lilly and Company |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285 |
| Public contact | Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact | Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559, |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 June 2013 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 June 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to find out if duloxetine [30-120 milligrams (mg)] given once a day by mouth for 10 weeks to children and adolescents, is better than placebo when treating Generalized Anxiety Disorder (GAD).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 21 June 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 | United States: 206 |
| Country: Number of subjects enrolled | Mexico: 52 |
| Country: Number of subjects enrolled | South Africa: 23 |
| Worldwide total number of subjects | 281 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 128 |
| Adolescents (12-17 years) | 144 |
| Adults (18-64 years) | 9 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

All Randomized participants from one site were excluded from this results record. All randomized participants from this site were not considered as part of the ITT population & were excluded from Subject Disposition, Baseline characteristics, efficacy and safety analyses due to major quality issues at that site.

Pre-assignment

Screening details:

This study had 4 periods: Screening period (1-week), acute treatment period (10-week, double-blind period with flexible duloxetine dosing), extension treatment (18-week period, of which 16 weeks were open-label treatment with flexible duloxetine dosing), and a taper period (2 weeks recommended at discontinuation from study any point after Week 2).

Period 1

| | |
|------------------------------|--|
| Period 1 title | Acute Treatment period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject, Carer, Assessor |

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Duloxetine/Duloxetine |

Arm description:

Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Duloxetine |
| Investigational medicinal product code | |
| Other name | LY248686, Cymbalta |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

30 to 120 Duloxetine mg administered orally.

| | |
|------------------|--------------------|
| Arm title | Placebo/Duloxetine |
|------------------|--------------------|

Arm description:

Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

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

Dosage and administration details:

Placebo administered orally.

| Number of subjects in period 1^[1] | Duloxetine/Duloxetine | Placebo/Duloxetine |
|---|-----------------------|--------------------|
| Started | 135 | 137 |
| Completed | 104 | 106 |
| Not completed | 31 | 31 |
| Parent/Caregiver Decision | 4 | 7 |
| Consent withdrawn by subject | 10 | 6 |
| Adverse event, non-fatal | 7 | 6 |
| Lost to follow-up | 3 | 6 |
| Lack of efficacy | 2 | 1 |
| Protocol deviation | 5 | 5 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 39 in Duloxetine/Duloxetine group & 35 Participants in Placebo/Duloxetine group who completed extension treatment period did not enter the taper period.

Period 2

| | |
|------------------------------|----------------------------|
| Period 2 title | Extension Treatment Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

18-week treatment period of which 16 weeks were open-label.

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Duloxetine/Duloxetine |

Arm description:

Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

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

| | |
|---|--------------------|
| Investigational medicinal product name | Duloxetine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: 30 to 120 mg administered orally. | |
| Arm title | Placebo/Duloxetine |

Arm description:

Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

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

Dosage and administration details:

30 to 120 mg administered orally.

| Number of subjects in period 2 | Duloxetine/Duloxetine | Placebo/Duloxetine |
|---------------------------------------|-----------------------|--------------------|
| Started | 104 | 106 |
| Completed | 79 | 81 |
| Not completed | 25 | 25 |
| Parent/Caregiver Decision | 7 | 8 |
| Consent withdrawn by subject | 1 | 3 |
| Adverse event, non-fatal | 8 | 7 |
| Lost to follow-up | 4 | 3 |
| Lack of efficacy | 3 | 2 |
| Protocol deviation | 2 | 2 |

Period 3

| | |
|------------------------------|-------------------------|
| Period 3 title | Taper Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Duloxetine/Duloxetine |

Arm description:

Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

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

Dosage and administration details:

30 to 120 mg administered orally.

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

Dosage and administration details:

Placebo administered orally.

| | |
|------------------|--------------------|
| Arm title | Placebo/Duloxetine |
|------------------|--------------------|

Arm description:

Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

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

Dosage and administration details:

30 to 120 mg administered orally.

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

Dosage and administration details:

Placebo administered orally.

| Number of subjects in period 3^[2] | Duloxetine/Duloxetine | Placebo/Duloxetine |
|---|-----------------------|--------------------|
| Started | 49 | 55 |
| Completed | 44 | 52 |
| Not completed | 5 | 3 |
| Parent/Caregiver Decision | 1 | 1 |
| Adverse event, non-fatal | 1 | - |
| Lost to follow-up | 2 | 2 |
| Protocol deviation | 1 | - |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 39 in Duloxetine/Duloxetine group & 35 Participants in Placebo/Duloxetine group who completed extension treatment period did not enter the taper period.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Duloxetine/Duloxetine |
|-----------------------|-----------------------|

Reporting group description:

Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|-----------------------|--------------------|
| Reporting group title | Placebo/Duloxetine |
|-----------------------|--------------------|

Reporting group description:

Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| Reporting group values | Duloxetine/Duloxetine | Placebo/Duloxetine | Total |
|---|-----------------------|--------------------|-------|
| Number of subjects | 135 | 137 | 272 |
| Age, Customized Units: participants | | | |
| 7 - 11 Years | 62 | 66 | 128 |
| 12 - 17 Years | 73 | 71 | 144 |
| Age continuous Units: | 12.55 ± 2.596 | 12.2 ± 2.904 | - |
| Gender, Male/Female Units: | | | |
| Male | 65 | 62 | 127 |
| Female | 70 | 75 | 145 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaska Native | 7 | 6 | 13 |
| Asian | 1 | 1 | 2 |
| Black or African American | 9 | 10 | 19 |
| White | 112 | 111 | 223 |
| More than one race | 6 | 9 | 15 |
| Region of Enrollment Units: Subjects | | | |
| United States | 98 | 99 | 197 |
| Mexico | 26 | 26 | 52 |
| South Africa | 11 | 12 | 23 |

End points

End points reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Duloxetine/Duloxetine |
|-----------------------|-----------------------|

Reporting group description:

Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|-----------------------|--------------------|
| Reporting group title | Placebo/Duloxetine |
|-----------------------|--------------------|

Reporting group description:

Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|-----------------------|-----------------------|
| Reporting group title | Duloxetine/Duloxetine |
|-----------------------|-----------------------|

Reporting group description:

Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|-----------------------|--------------------|
| Reporting group title | Placebo/Duloxetine |
|-----------------------|--------------------|

Reporting group description:

Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|-----------------------|-----------------------|
| Reporting group title | Duloxetine/Duloxetine |
|-----------------------|-----------------------|

Reporting group description:

Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| | |
|-----------------------|--------------------|
| Reporting group title | Placebo/Duloxetine |
|-----------------------|--------------------|

Reporting group description:

Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. Duloxetine was provided in 30-mg capsules.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period, and participants who received the lowest dose of duloxetine or placebo at the end of treatment period

participation received placebo over the 2-week recommended tapering period.

| | |
|--|---|
| Subject analysis set title | Duloxetine (Acute Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period. | |
| Subject analysis set title | Placebo (Acute Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period. | |
| Subject analysis set title | Duloxetine (Acute Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period. | |
| Subject analysis set title | Placebo (Acute Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received placebo capsules orally, QD for 10 weeks during the acute treatment period. | |
| Subject analysis set title | Placebo (Acute Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. | |
| Subject analysis set title | Placebo/Duloxetine (Extension Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. | |
| Subject analysis set title | Duloxetine/Duloxetine (Extension Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. | |
| Subject analysis set title | Duloxetine/Duloxetine (Extension Treatment) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Participants received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks during the acute treatment period and flexible doses of duloxetine 30 to 120 mg orally, QD for 18 weeks during the optional extension treatment period. | |

Primary: Change from Baseline to 10-Week Endpoint in the Pediatric Anxiety Rating Scale (PARS) Severity Score Evaluated for Symptoms Identified on the Generalized Anxiety Subsection of the PARS Symptom Checklist

| | |
|-----------------|--|
| End point title | Change from Baseline to 10-Week Endpoint in the Pediatric Anxiety Rating Scale (PARS) Severity Score Evaluated for Symptoms Identified on the Generalized Anxiety Subsection of the PARS Symptom Checklist |
|-----------------|--|

End point description:

PARS severity score for GAD was assessed for all symptoms identified in the generalized anxiety section of the PARS symptom checklist. PARS severity score for GAD was derived by summing 5 of 7 severity/impairment/interference items (2, 3, 5, 6, 7); each item ranged from 0 (none) to 5 (extreme severity/impairment/interference). PARS severity scores for GAD ranged from 0 (none) to 25 (extreme severity), with a score of 15 indicating moderate illness severity. Least squares (LS) mean was calculated using a mixed-effects model repeated measures (MMRM) approach adjusted for baseline,

pooled investigator, age category, visit, treatment, treatment*visit, age category*visit, and baseline*visit.

Analysis Population Description: Randomized participants with a baseline and at least 1 post-baseline PARS severity score for GAD during the acute treatment period, excluding 9 participants from 1 site with major quality issues.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline, 10 weeks | |

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-------------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 135 | 133 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -9.7 (\pm 0.502) | -7.05 (\pm 0.5) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis |
|---|--|
| Comparison groups | Duloxetine (Acute Treatment) v Placebo (Acute Treatment) |
| Number of subjects included in analysis | 268 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares (LS) mean difference |
| Point estimate | -2.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.03 |
| upper limit | -1.27 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

Secondary: Response Rate at Endpoint for Generalized Anxiety Disorder (GAD) Using Pediatric Anxiety Rating Scale (PARS) Severity Score for GAD

| | |
|-----------------|---|
| End point title | Response Rate at Endpoint for Generalized Anxiety Disorder (GAD) Using Pediatric Anxiety Rating Scale (PARS) Severity Score for GAD |
|-----------------|---|

End point description:

Response rate was defined as the percentage of participants having a 50% improvement from baseline to endpoint on the PARS severity score for GAD. PARS severity score for GAD was assessed for all symptoms identified in the generalized anxiety section of the PARS symptom checklist. PARS severity score for GAD was derived by summing 5 of 7 severity/impairment/interference items (2, 3, 5, 6, 7); each item ranged from 0 (none) to 5 (extreme severity/impairment/interference). PARS severity scores

for GAD ranged from 0 (none) to 25 (extreme severity), with a score of 15 indicating moderate illness severity.

Analysis Population Description: Randomized participants with a baseline and at least 1 post-baseline PARS severity score for GAD [last observation carried forward (LOCF)] during the acute treatment period, excluding 9 participants from 1 site with major quality issues.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 10 weeks | |

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-----------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 135 | 133 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 51 | 37 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to 10-Week Endpoint on the Pediatric Anxiety Rating Scale (PARS) Severity Total Score Evaluated for All Symptoms Identified on the PARS Symptom Checklist

| | |
|-----------------|--|
| End point title | Change from Baseline to 10-Week Endpoint on the Pediatric Anxiety Rating Scale (PARS) Severity Total Score Evaluated for All Symptoms Identified on the PARS Symptom Checklist |
|-----------------|--|

End point description:

PARS severity total score was assessed for all symptoms identified on the PARS symptom checklist. PARS severity total score was derived by summing 5 of 7 severity/impairment/interference items (2, 3, 5, 6, 7); each item ranged from 0 (none) to 5 (extreme severity/impairment/interference). PARS severity total scores ranged from 0 (none) to 25 (extreme severity), with a score of 15 indicating moderate illness severity. Least squares (LS) mean was calculated using a mixed-effects model repeated measures (MMRM) approach adjusted for treatment, pooled investigator, visit, baseline, age category, treatment*visit, baseline*visit, and age category*visit.

Analysis Population Description: Randomized participants with a baseline and at least 1 post-baseline PARS severity total score during the acute treatment period, excluding 9 participants from 1 site with major quality issues.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 10 weeks | |

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-------------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 135 | 133 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -9.15 (\pm 0.479) | -6.36 (\pm 0.477) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to 10-Week Endpoint on the Clinical Global Impression of Severity (CGI-S) Scale

| | |
|-----------------|--|
| End point title | Change from Baseline to 10-Week Endpoint on the Clinical Global Impression of Severity (CGI-S) Scale |
|-----------------|--|

End point description:

The CGI-S scale evaluated the severity of illness at the time of assessment. Scores ranged from 1 (normal, not at all ill) to 7 (among the most extremely ill). Higher scores indicated a greater severity of illness. Least squares (LS) mean was calculated using a mixed-effects model repeated measures (MMRM) approach adjusted for treatment, pooled investigator, visit, baseline, age category, treatment*visit, baseline*visit, and age category*visit.

Analysis Population Description: Randomized participants with a baseline and at least 1 post-baseline CGI-S score during the acute treatment period, excluding 9 participants from 1 site with major quality issues.

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

End point timeframe:

Baseline, 10 weeks

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-------------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 135 | 133 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -1.93 (\pm 0.114) | -1.38 (\pm 0.113) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Remission Rate at Endpoint for generalized anxiety disorder (GAD) Using Clinical Global Impressions of Severity (CGI-S) Scale

| | |
|-----------------|---|
| End point title | Remission Rate at Endpoint for generalized anxiety disorder (GAD) Using Clinical Global Impressions of Severity (CGI-S) Scale |
|-----------------|---|

End point description:

Remission rate was defined as the percentage of participants having a CGI-S score ≤ 2 at endpoint. The CGI-S scale evaluated the severity of illness at the time of assessment. Scores ranged from 1 (normal, not at all ill) to 7 (among the most extremely ill). Higher scores indicated a greater severity of illness.

Analysis Population Description: Randomized participants with at least 1 post-baseline CGI-S score [last observation carried forward (LOCF)] during the acute treatment period, excluding 9 participants from 1 site with major quality issues.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 10 weeks | |

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-----------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 135 | 133 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 45 | 30 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to 10-Week Endpoint in the Children's Global Assessment Scale (CGAS)

| | |
|-----------------|---|
| End point title | Change from Baseline to 10-Week Endpoint in the Children's Global Assessment Scale (CGAS) |
|-----------------|---|

End point description:

The CGAS was a clinician-rated assessment of general functioning. CGAS raw scores ranged from 1 (greatest impairment) to 100 (superior functioning). Lower scores indicated a lower level of functioning and greater impairment. Least squares (LS) mean from an analysis of covariance (ANCOVA) was adjusted for treatment, pooled investigator, baseline, and age category.

Analysis Population Description: Randomized participants with a baseline and at least 1 post-baseline [last observation carried forward (LOCF)] CGAS score during the acute treatment period, excluding 9 participants from 1 site with major quality issues.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, 10 weeks | |

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-------------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 123 | 124 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 17.14 (\pm 1.232) | 12.16 (\pm 1.219) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants During the 10-Week Period with Treatment-Emergent (New or Worsening) Suicidal Ideation as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

| | |
|-----------------|--|
| End point title | Percentage of Participants During the 10-Week Period with Treatment-Emergent (New or Worsening) Suicidal Ideation as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) |
|-----------------|--|

End point description:

The C-SSRS captured occurrence, severity, and frequency of suicide-related thoughts and behaviors. Suicidal ideation: a "yes" answer to any 1 of 5 suicidal ideation questions: wish to be dead, and 4 different categories of active suicidal ideation. Results reported as percentage of participants with treatment-emergent (new or worsening) suicidal ideation from baseline=(number of participants with changes compared to baseline/total number of participants at risk)*100.

Analysis Population Description: Randomized participants with a baseline and at least 1 post-baseline C-SSRS suicidal ideation score during the acute treatment period, whose baseline maximum C-SSRS suicidal ideation score was <5. Nine (9) participants from 1 site with major quality issues were excluded.

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

End point timeframe:

Baseline up to 10 weeks

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-----------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 135 | 134 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 5.9 | 5.2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants During the 10-Week Period with Treatment-Emergent (New or Worsening) Suicidal Behavior as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

| | |
|-----------------|--|
| End point title | Percentage of Participants During the 10-Week Period with Treatment-Emergent (New or Worsening) Suicidal Behavior as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) |
|-----------------|--|

End point description:

The C-SSRS captured occurrence, severity, and frequency of suicide-related thoughts and behaviors. Suicidal behavior: a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Reported as percentage of participants with treatment-emergent (new or worsening) suicidal behavior from baseline=(number of participants with changes compared to baseline/total number of participants at risk)*100.

Analysis Population Description: Randomized participants with a baseline and at least 1 post-baseline C-SSRS suicidal behavior score during the acute treatment period, excluding 9 participants from 1 site with major quality issues.

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

End point timeframe:

Baseline up to 10 weeks

| End point values | Duloxetine (Acute Treatment) | Placebo (Acute Treatment) | | |
|-----------------------------------|------------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 135 | 134 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from 10-Week to 28-Week Endpoint in the Pediatric Anxiety Rating Scale (PARS) Severity Score Evaluated for Symptoms Identified on the Generalized Anxiety Subsection of the PARS Symptom Checklist

| | |
|-----------------|---|
| End point title | Change from 10-Week to 28-Week Endpoint in the Pediatric Anxiety Rating Scale (PARS) Severity Score Evaluated for Symptoms Identified on the Generalized Anxiety Subsection of the PARS Symptom Checklist |
|-----------------|---|

End point description:

PARS severity score for GAD was assessed for all symptoms identified in the generalized anxiety section of the PARS symptom checklist. PARS severity score for GAD was derived by summing 5 of 7 severity/impairment/interference items (2, 3, 5, 6, 7); each item ranged from 0 (none) to 5 (extreme severity/impairment/interference). PARS severity scores for GAD ranged from 0 (none) to 25 (extreme severity), with a score of 15 indicating moderate illness severity. Least squares (LS) mean was calculated using a mixed-effects model repeated measures (MMRM) approach adjusted for pooled investigator, visit, baseline, age category, baseline*visit, and age category*visit within reporting groups.

Analysis Population Description: Randomized participants with a PARS severity score for GAD during the acute treatment period and at least 1 PARS severity score for GAD during the extension treatment period, excluding 9 participants from 1 site with major quality issues.

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

End point timeframe:

10 weeks, 28 weeks

| End point values | Duloxetine/Duloxetine | Placebo/Duloxetine | | |
|-------------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 104 | 105 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -3.33 (\pm 0.352) | -5.15 (\pm 0.452) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from 10-Week to 28-Week Endpoint on the Pediatric Anxiety Rating Scale (PARS) Severity Total Score Evaluated for All Symptoms Identified on the PARS Symptom ChecklistSymptoms

| | |
|-----------------|---|
| End point title | Change from 10-Week to 28-Week Endpoint on the Pediatric Anxiety Rating Scale (PARS) Severity Total Score Evaluated for All Symptoms Identified on the PARS Symptom ChecklistSymptoms |
|-----------------|---|

End point description:

PARS severity total score was assessed for all symptoms identified on the PARS symptom checklist. PARS severity total score was derived by summing 5 of 7 severity/impairment/interference items (2, 3, 5, 6, 7); each item ranged from 0 (none) to 5 (extreme severity/impairment/interference). PARS severity total scores ranged from 0 (none) to 25 (extreme severity), with a score of 15 indicating moderate illness severity. Least squares (LS) mean was calculated using a mixed-effects model repeated measures (MMRM) approach adjusted for pooled investigator, visit, baseline, age category, baseline*visit, and age category*visit within reporting groups.

Analysis Population Description: Randomized participants with a PARS severity total score during the acute treatment period and at least 1 PARS severity total score during the extension treatment period, excluding 9 participants from 1 site with major quality issues.

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

End point timeframe:

10 weeks, 28 weeks

| End point values | Duloxetine/Duloxetine | Placebo/Duloxetine | | |
|-------------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 104 | 105 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -3.32 (\pm 0.357) | -5.26 (\pm 0.432) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from 10-Week to 28-Week Endpoint on the Clinical Global Impression of Severity (CGI-S) Scale

| | |
|---|---|
| End point title | Change from 10-Week to 28-Week Endpoint on the Clinical Global Impression of Severity (CGI-S) Scale |
| End point description: | |
| The CGI-S scale evaluated the severity of mental illness at the time of assessment. Scores ranged from 1 (normal, not at all ill) to 7 (among the most extremely ill). Higher scores indicated a greater severity of illness. Least squares (LS) mean was calculated using a mixed-effects model repeated measures (MMRM) approach adjusted for pooled investigator, visit, baseline, age category, baseline*visit, and age category*visit within reporting groups. | |
| Analysis Population Description: Randomized participants with a CGI-S score during the acute treatment period and at least 1 CGI-S score during the extension treatment period, excluding 9 participants from 1 site with major quality issues. | |
| End point type | Secondary |
| End point timeframe: | |
| 10 weeks, 28 weeks | |

| End point values | Duloxetine/Duloxetine | Placebo/Duloxetine | | |
|-------------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 104 | 105 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -0.76 (± 0.093) | -1.17 (± 0.088) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from 10-Week to 28-Week Endpoint in the Children's Global Assessment Scale (CGAS)

| | |
|--|--|
| End point title | Change from 10-Week to 28-Week Endpoint in the Children's Global Assessment Scale (CGAS) |
| End point description: | |
| The CGAS was a clinician-rated assessment of general functioning. CGAS raw scores ranged from 1 (greatest impairment) to 100 (superior functioning). Lower scores indicated a lower level of functioning and greater impairment. Least squares (LS) mean from an analysis of covariance (ANCOVA) was adjusted for pooled investigator, baseline, and age category within reporting groups. | |
| Analysis Population Description: Randomized participants with a CGAS score during the acute treatment period and at least 1 CGAS score during the extension treatment period [last observation carried forward (LOCF)], excluding 9 participants from 1 site with major quality issues. | |
| End point type | Secondary |
| End point timeframe: | |
| 10 weeks, 28 weeks | |

| End point values | Duloxetine/Duloxetine | Placebo/Duloxetine | | |
|-------------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 | 105 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 7.32 (± 1.19) | 10.48 (± 1.03) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants During the 18-Week Extension Period with Treatment-Emergent (New or Worsening) Suicidal Ideation as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

| | |
|-----------------|--|
| End point title | Percentage of Participants During the 18-Week Extension Period with Treatment-Emergent (New or Worsening) Suicidal Ideation as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) |
|-----------------|--|

End point description:

The C-SSRS captured occurrence, severity, and frequency of suicide-related thoughts and behaviors. Suicidal ideation: a "yes" answer to any 1 of 5 suicidal ideation questions: wish to be dead, and 4 different categories of active suicidal ideation. Results reported as percentage of participants with treatment-emergent (new or worsening) suicidal ideation from baseline=(number of participants with changes compared to baseline/total number of participants at risk)*100.

Analysis Population Description: Randomized participants with a C-SSRS suicidal ideation score <5 at the last 2 visits in the acute treatment period and at least 1 C-SSRS suicidal ideation score during the extension treatment period. Nine (9) participants from 1 site with major quality issues were excluded.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 10 weeks up to 28 weeks | |

| End point values | Duloxetine/Duloxetine | Placebo/Duloxetine | | |
|-----------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 104 | 105 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 3 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants During the 18-Week Extension Period with Treatment-Emergent (New or Worsening) Suicidal Behavior as Assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS)

| | |
|-----------------|--|
| End point title | Percentage of Participants During the 18-Week Extension Period with Treatment-Emergent (New or Worsening) Suicidal |
|-----------------|--|

End point description:

The C-SSRS captured occurrence, severity, and frequency of suicide-related thoughts and behaviors. Suicidal behavior: a "yes" answer to any of 5 suicidal behavior questions: preparatory acts or behavior, aborted attempt, interrupted attempt, actual attempt, and completed suicide. Reported as percentage of participants with treatment-emergent (new or worsening) suicidal behavior from baseline=(number of participants with changes compared to baseline/total number of participants at risk)*100.

Analysis Population Description: Randomized participants with a C-SSRS suicidal behavior score at the last 2 visits in the acute treatment period and at least 1 C-SSRS suicidal behavior score during the extension treatment period, excluding 9 participants from 1 site with major quality issues.

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

End point timeframe:

10 weeks up to 28 weeks

| End point values | Duloxetine/Duloxetine | Placebo/Duloxetine | | |
|-----------------------------------|-----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 104 | 105 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

F1J-MC-HMGI

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Duloxetine-Acute |
|-----------------------|------------------|

Reporting group description:

Adverse events (AEs) during the acute treatment period for participants who received flexible doses of duloxetine 30 to 120 milligrams (mg) orally, once daily (QD) for 10 weeks.

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

Reporting group description:

AEs during the acute treatment period for participants who received placebo capsules orally, QD for 10 weeks.

| | |
|-----------------------|----------------------|
| Reporting group title | Duloxetine-Extension |
|-----------------------|----------------------|

Reporting group description:

AEs during the extension treatment period for participants who received flexible doses of duloxetine 30 to 120 mg orally, QD during both the acute and extension treatment periods (up to 28 weeks).

| | |
|-----------------------|------------------------------|
| Reporting group title | Placebo/Duloxetine-Extension |
|-----------------------|------------------------------|

Reporting group description:

AEs during the extension treatment period for participants who received placebo capsules orally, QD during the acute treatment period (10 weeks) and flexible doses of duloxetine 30 to 120 mg orally, QD during the extension treatment period (up to 18 weeks).

| | |
|-----------------------|------------------|
| Reporting group title | Duloxetine-Taper |
|-----------------------|------------------|

Reporting group description:

AEs during the taper period for participants who were dispensed duloxetine prior to entering the taper phase.

Participants who received higher doses of duloxetine at the end of treatment period participation received gradually lower doses of duloxetine over the 2-week recommended tapering period.

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

Reporting group description:

AEs during the taper period for participants who were dispensed placebo prior to entering the taper phase.

Participants who received the lowest dose of duloxetine or placebo at the end of treatment period participation received placebo over the 2-week recommended tapering period.

| Serious adverse events | Duloxetine-Acute | Placebo-Acute | Duloxetine-Extension |
|---|------------------|-----------------|----------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 2 / 104 (1.92%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------------------------|-----------------------------------|-----------------------------------|
| acute psychosis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 135 (0.00%) 0 / 0 0 / 0 | 0 / 137 (0.00%) 0 / 0 0 / 0 | 0 / 104 (0.00%) 0 / 0 0 / 0 |
| bipolar disorder alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 135 (0.00%) 0 / 0 0 / 0 | 0 / 137 (0.00%) 0 / 0 0 / 0 | 0 / 104 (0.00%) 0 / 0 0 / 0 |
| self-injurious ideation alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 135 (0.74%) 1 / 1 0 / 0 | 0 / 137 (0.00%) 0 / 0 0 / 0 | 0 / 104 (0.00%) 0 / 0 0 / 0 |
| suicidal ideation alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 135 (0.74%) 1 / 1 0 / 0 | 0 / 137 (0.00%) 0 / 0 0 / 0 | 1 / 104 (0.96%) 1 / 1 0 / 0 |
| Infections and infestations adenoiditis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 135 (0.00%) 0 / 0 0 / 0 | 0 / 137 (0.00%) 0 / 0 0 / 0 | 1 / 104 (0.96%) 0 / 1 0 / 0 |
| tonsillitis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 135 (0.00%) 0 / 0 0 / 0 | 0 / 137 (0.00%) 0 / 0 0 / 0 | 1 / 104 (0.96%) 0 / 1 0 / 0 |

| Serious adverse events | Placebo/Duloxetine- Extension | Duloxetine-Taper | Placebo-Taper |
|------------------------------------|----------------------------------|------------------|---------------|
| Total subjects affected by serious | | | |

| | | | |
|---|-----------------|----------------|----------------|
| adverse events | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 1 / 97 (1.03%) | 1 / 7 (14.29%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| acute psychosis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| bipolar disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| self-injurious ideation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| suicidal ideation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 97 (1.03%) | 1 / 7 (14.29%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| adenoiditis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| tonsillitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Duloxetine-Acute | Placebo-Acute | Duloxetine-Extension |
|---|--------------------|-------------------|----------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 106 / 135 (78.52%) | 90 / 137 (65.69%) | 73 / 104 (70.19%) |
| Vascular disorders | | | |
| hot flush | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| hypotension | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 2 |
| pallor | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| Surgical and medical procedures | | | |
| tooth extraction | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| asthenia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| chest discomfort | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 1 | 1 |
| chest pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 3 | 0 | 1 |
| crying | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| fatigue | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 11 / 135 (8.15%) | 6 / 137 (4.38%) | 4 / 104 (3.85%) |
| occurrences (all) | 11 | 6 | 4 |
| feeling abnormal | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| feeling cold | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| inflammation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| inflammatory pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| influenza like illness | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| irritability | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 6 / 137 (4.38%) | 4 / 104 (3.85%) |
| occurrences (all) | 4 | 6 | 4 |
| malaise | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| medical device pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| non-cardiac chest pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| oedema peripheral | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 1 | 1 |
| pyrexia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 4 / 137 (2.92%) | 2 / 104 (1.92%) |
| occurrences (all) | 2 | 5 | 2 |
| temperature intolerance | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| thirst | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 1 / 137 (0.73%) 1 | 0 / 104 (0.00%) 0 |
| Immune system disorders multiple allergies alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 1 / 104 (0.96%) 1 |
| seasonal allergy alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 137 (0.00%) 0 | 2 / 104 (1.92%) 2 |
| Social circumstances educational problem alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 1 / 137 (0.73%) 1 | 0 / 104 (0.00%) 0 |
| Reproductive system and breast disorders breast mass alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| dysmenorrhoea alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[1] occurrences (all) | 2 / 70 (2.86%) 3 | 2 / 75 (2.67%) 2 | 0 / 104 (0.00%) 0 |
| orchitis noninfective alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[2] occurrences (all) | 0 / 135 (0.00%) 0 | 1 / 62 (1.61%) 1 | 0 / 104 (0.00%) 0 |
| ovarian cyst alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[3] occurrences (all) | 1 / 70 (1.43%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| vaginal haemorrhage alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed ^[4] | 1 / 70 (1.43%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| asthma | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| cough | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 6 / 135 (4.44%) | 0 / 137 (0.00%) | 4 / 104 (3.85%) |
| occurrences (all) | 6 | 0 | 4 |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| epistaxis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 2 / 104 (1.92%) |
| occurrences (all) | 4 | 1 | 2 |
| nasal congestion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 1 | 1 |
| oropharyngeal pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 10 / 135 (7.41%) | 3 / 137 (2.19%) | 1 / 104 (0.96%) |
| occurrences (all) | 10 | 3 | 1 |
| pharyngeal inflammation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| productive cough | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| respiratory tract congestion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| rhinitis allergic | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| rhinorrhoea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| sinus congestion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| yawning | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| abnormal behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| abnormal dreams | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| activation syndrome | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| affect liability | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| aggression | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 137 (1.46%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 2 | 1 |
| agitation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| anger | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| anxiety | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| apathy | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| attention deficit/hyperactivity disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| bruxism | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|------------------|-----------------|-----------------|
| compulsive handwashing | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| depression | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| distractibility | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| fear | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| flat affect | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| impulsive behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 2 / 104 (1.92%) |
| occurrences (all) | 0 | 0 | 2 |
| initial insomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| insomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 12 / 135 (8.89%) | 7 / 137 (5.11%) | 1 / 104 (0.96%) |
| occurrences (all) | 13 | 8 | 1 |
| intentional self-injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 3 / 104 (2.88%) |
| occurrences (all) | 1 | 1 | 3 |
| Major depression | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| middle insomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| negativism | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| nervousness | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| nightmare | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| obsessive thoughts | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| onychophagia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| oppositional defiant disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| panic attack | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| phobia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| psychotic disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| self injurious behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| sexually inappropriate behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sleep disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 137 (1.46%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| sleep terror | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| suicidal ideation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 2 / 104 (1.92%) |
| occurrences (all) | 1 | 1 | 3 |
| tic | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| withdrawal syndrome | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| blood pressure increased | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| blood triglycerides increased | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| electrocardiogram qt prolonged | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| heart rate increased | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| neutrophil count increased | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| weight decreased | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 5 / 135 (3.70%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| weight increased | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 135 (1.48%) | 3 / 137 (2.19%) | 2 / 104 (1.92%) |
| occurrences (all) | 2 | 3 | 2 |
| white blood cell count increased | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| animal bite | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| ankle fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| arthropod bite | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| arthropod sting | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| bone contusion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| burns first degree | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| concussion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| fall | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| fibula fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| head injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| human bite | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| humerus fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| joint dislocation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| laceration | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| ligament sprain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 2 / 104 (1.92%) |
| occurrences (all) | 0 | 0 | 2 |

| | | | |
|---|-----------------|-----------------|-----------------|
| limb injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 2 | 1 | 1 |
| lip injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| muscle rupture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| muscle strain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 1 | 1 |
| post procedural swelling | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| procedural pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| road traffic accident | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| scratch | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| sunburn | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| tendon injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| thermal burn | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| upper limb fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |
| bundle branch block right | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| palpitations | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 6 / 135 (4.44%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| sinus arrhythmia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sinus tachycardia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| tachycardia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 1 / 104 (0.96%) 1 |
| Nervous system disorders | | | |
| disturbance in attention | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 2 | 1 | 1 |
| dizziness | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 10 / 135 (7.41%) | 2 / 137 (1.46%) | 5 / 104 (4.81%) |
| occurrences (all) | 10 | 2 | 5 |
| dizziness postural | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| dysgeusia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| dyskinesia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| headache | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 27 / 135 (20.00%) | 23 / 137 (16.79%) | 13 / 104 (12.50%) |
| occurrences (all) | 37 | 29 | 17 |
| hypersomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 1 | 1 |
| hypoesthesia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 2 / 104 (1.92%) |
| occurrences (all) | 0 | 0 | 2 |
| migraine | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 2 / 137 (1.46%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 2 | 1 |
| myoclonus | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| paraesthesia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 3 / 137 (2.19%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| poor quality sleep | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| post-traumatic headache | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| psychomotor hyperactivity | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 2 / 137 (1.46%) | 1 / 104 (0.96%) |
| occurrences (all) | 3 | 2 | 1 |
| sedation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| somnolence | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 16 / 135 (11.85%) | 9 / 137 (6.57%) | 3 / 104 (2.88%) |
| occurrences (all) | 16 | 9 | 4 |

| | | | |
|---|--|--|--|
| tremor alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 4 / 135 (2.96%) 4 | 1 / 137 (0.73%) 1 | 2 / 104 (1.92%) 2 |
| Ear and labyrinth disorders ear pain alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) motion sickness alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) tinnitus alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) vertigo alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 1 / 135 (0.74%) 1 0 / 135 (0.00%) 0 0 / 135 (0.00%) 0 | 2 / 137 (1.46%) 2 0 / 137 (0.00%) 0 1 / 137 (0.73%) 1 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 0 / 104 (0.00%) 0 0 / 104 (0.00%) 0 0 / 104 (0.00%) 0 |
| Eye disorders blepharospasm alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) blindness alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) conjunctival haemorrhage alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) eye pain | 1 / 135 (0.74%) 1 1 / 135 (0.74%) 1 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 0 / 137 (0.00%) 0 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 0 / 104 (0.00%) 0 0 / 104 (0.00%) 0 |

| | | | |
|---|---------------------------------|---------------------------------|---------------------------------|
| <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 135 (0.00%)</p> <p>0</p> | <p>0 / 137 (0.00%)</p> <p>0</p> | <p>0 / 104 (0.00%)</p> <p>0</p> |
| <p>mydriasis</p> <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 135 (1.48%)</p> <p>2</p> | <p>0 / 137 (0.00%)</p> <p>0</p> | <p>0 / 104 (0.00%)</p> <p>0</p> |
| <p>strabismus</p> <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 135 (0.74%)</p> <p>1</p> | <p>0 / 137 (0.00%)</p> <p>0</p> | <p>0 / 104 (0.00%)</p> <p>0</p> |
| <p>vision blurred</p> <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 135 (0.00%)</p> <p>0</p> | <p>0 / 137 (0.00%)</p> <p>0</p> | <p>0 / 104 (0.00%)</p> <p>0</p> |
| <p>Gastrointestinal disorders</p> <p>abdominal discomfort</p> <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 135 (2.22%)</p> <p>3</p> | <p>4 / 137 (2.92%)</p> <p>4</p> | <p>0 / 104 (0.00%)</p> <p>0</p> |
| <p>abdominal distension</p> <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 135 (0.74%)</p> <p>1</p> | <p>1 / 137 (0.73%)</p> <p>2</p> | <p>1 / 104 (0.96%)</p> <p>1</p> |
| <p>abdominal pain</p> <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 135 (1.48%)</p> <p>2</p> | <p>0 / 137 (0.00%)</p> <p>0</p> | <p>2 / 104 (1.92%)</p> <p>2</p> |
| <p>abdominal pain lower</p> <p>alternative dictionary used: MedDRA 16.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 135 (0.00%)</p> <p>0</p> | <p>2 / 137 (1.46%)</p> <p>2</p> | <p>0 / 104 (0.00%)</p> <p>0</p> |
| <p>abdominal pain upper</p> <p>alternative dictionary used: MedDRA 16.0</p> | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 13 / 135 (9.63%) | 9 / 137 (6.57%) | 5 / 104 (4.81%) |
| occurrences (all) | 15 | 10 | 6 |
| aphthous stomatitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| chapped lips | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| colitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| constipation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 5 / 135 (3.70%) | 4 / 137 (2.92%) | 0 / 104 (0.00%) |
| occurrences (all) | 6 | 4 | 0 |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 9 / 135 (6.67%) | 6 / 137 (4.38%) | 1 / 104 (0.96%) |
| occurrences (all) | 10 | 6 | 3 |
| dry mouth | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 2 | 2 | 1 |
| dyspepsia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 2 / 104 (1.92%) |
| occurrences (all) | 0 | 0 | 2 |
| eructation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 1 | 1 |

| | | | |
|---|-----------------|-----------------|-----------------|
| flatulence | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| food poisoning | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| frequent bowel movements | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| gastritis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| gastroesophageal reflux disease | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| gingival pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| lip dry | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| mouth ulceration | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| nausea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-------------------|------------------|------------------|
| subjects affected / exposed | 28 / 135 (20.74%) | 8 / 137 (5.84%) | 10 / 104 (9.62%) |
| occurrences (all) | 35 | 8 | 10 |
| odynophagia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| oral mucosal blistering | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| toothache | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 2 / 104 (1.92%) |
| occurrences (all) | 0 | 0 | 2 |
| vomiting | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 22 / 135 (16.30%) | 10 / 137 (7.30%) | 5 / 104 (4.81%) |
| occurrences (all) | 23 | 10 | 7 |
| Skin and subcutaneous tissue disorders | | | |
| acne | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 2 | 0 | 1 |
| alopecia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| dermatitis allergic | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| dermatitis contact | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 137 (0.00%) | 2 / 104 (1.92%) |
| occurrences (all) | 2 | 0 | 2 |
| dry skin | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| erythema | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| hyperhidrosis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 4 | 2 | 1 |
| night sweats | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| petechiae | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| pruritus | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 4 | 1 |
| rash | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 137 (1.46%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 2 | 1 |
| rash maculo-papular | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|----------------------|----------------------|----------------------|
| rash papular alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 137 (0.00%) 0 | 1 / 104 (0.96%) 1 |
| rash pruritic alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| urticaria alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 1 / 137 (0.73%) 1 | 0 / 104 (0.00%) 0 |
| Renal and urinary disorders enuresis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| hypertonic bladder alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 1 / 137 (0.73%) 1 | 0 / 104 (0.00%) 0 |
| pollakiuria alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| urinary hesitation alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| Endocrine disorders hypothyroidism alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| arthralgia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| back pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| bone pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| flank pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| muscle spasms | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| muscle twitching | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| musculoskeletal pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| myalgia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| neck pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| pain in extremity | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 2 / 104 (1.92%) |
| occurrences (all) | 1 | 2 | 2 |
| synovial cyst | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| temporomandibular joint syndrome | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| bronchitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 4 / 137 (2.92%) | 2 / 104 (1.92%) |
| occurrences (all) | 4 | 4 | 2 |
| conjunctivitis infective | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| ear infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 137 (1.46%) | 3 / 104 (2.88%) |
| occurrences (all) | 1 | 2 | 3 |
| fungus infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 1 | 1 |
| gastroenteritis viral | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 2 / 137 (1.46%) | 1 / 104 (0.96%) |
| occurrences (all) | 4 | 2 | 1 |
| gastrointestinal infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| gastrointestinal viral infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| genital candidiasis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| hand-foot-and-mouth disease | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| herpes simplex | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| hordeolum | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| influenza | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 3 / 137 (2.19%) | 6 / 104 (5.77%) |
| occurrences (all) | 4 | 3 | 6 |

| | | | |
|---|-----------------|------------------|-----------------|
| labyrinthitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| lower respiratory tract infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 4 / 135 (2.96%) | 12 / 137 (8.76%) | 4 / 104 (3.85%) |
| occurrences (all) | 4 | 13 | 4 |
| oral herpes | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| otitis externa | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| otitis media | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| pharyngitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 135 (2.22%) | 1 / 137 (0.73%) | 2 / 104 (1.92%) |
| occurrences (all) | 3 | 1 | 2 |
| pharyngitis streptococcal | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 137 (1.46%) | 3 / 104 (2.88%) |
| occurrences (all) | 1 | 2 | 3 |
| pharyngotonsillitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 135 (0.74%) | 2 / 137 (1.46%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 2 | 1 |
| pneumonia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 1 | 1 |
| rhinitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 1 / 137 (0.73%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 1 | 1 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 4 / 137 (2.92%) | 6 / 104 (5.77%) |
| occurrences (all) | 1 | 4 | 6 |
| skin infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| staphylococcal infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 0 / 104 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| tonsillitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 135 (0.74%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 1 | 0 | 1 |
| tooth infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 135 (0.00%) | 0 / 137 (0.00%) | 1 / 104 (0.96%) |
| occurrences (all) | 0 | 0 | 1 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 135 (1.48%) | 4 / 137 (2.92%) | 3 / 104 (2.88%) |
| occurrences (all) | 2 | 4 | 4 |

| | | | |
|---|-------------------------|----------------------|----------------------|
| urinary tract infection alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 2 / 137 (1.46%) 2 | 3 / 104 (2.88%) 3 |
| vaginitis bacterial alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[5] occurrences (all) | 1 / 70 (1.43%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| viral infection alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 2 / 137 (1.46%) 2 | 0 / 104 (0.00%) 0 |
| viral upper respiratory tract infection alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 135 (0.74%) 1 | 0 / 137 (0.00%) 0 | 0 / 104 (0.00%) 0 |
| Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 20 / 135 (14.81%) 21 | 7 / 137 (5.11%) 7 | 1 / 104 (0.96%) 1 |
| dehydration alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 135 (0.00%) 0 | 0 / 137 (0.00%) 0 | 1 / 104 (0.96%) 1 |
| increased appetite alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 135 (1.48%) 2 | 4 / 137 (2.92%) 4 | 0 / 104 (0.00%) 0 |

| Non-serious adverse events | Placebo/Duloxetine- Extension | Duloxetine-Taper | Placebo-Taper |
|--|----------------------------------|------------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 73 / 106 (68.87%) | 12 / 97 (12.37%) | 1 / 7 (14.29%) |
| Vascular disorders | | | |

| | | | |
|--|----------------------|---------------------|--------------------|
| hot flush alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 3 / 106 (2.83%) 3 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| hypotension alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| pallor alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Surgical and medical procedures tooth extraction alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| General disorders and administration site conditions asthenia alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 7 (0.00%) 0 |
| chest discomfort alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| chest pain alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| crying alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 1 / 97 (1.03%) 1 | 0 / 7 (0.00%) 0 |
| fatigue | | | |

| | | | |
|---|-----------------|----------------|---------------|
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 9 / 106 (8.49%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 9 | 0 | 0 |
| feeling abnormal | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| feeling cold | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| inflammation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| inflammatory pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| influenza like illness | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| irritability | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 106 (2.83%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| malaise | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| medical device pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| non-cardiac chest pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| oedema peripheral | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| pyrexia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| temperature intolerance | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| thirst | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| multiple allergies | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| seasonal allergy | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Social circumstances educational problem alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Reproductive system and breast disorders breast mass alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) dysmenorrhoea alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[1] occurrences (all) orchitis noninfective alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[2] occurrences (all) ovarian cyst alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[3] occurrences (all) vaginal haemorrhage alternative dictionary used: MedDRA 16.0 subjects affected / exposed ^[4] occurrences (all) | 0 / 106 (0.00%) 0 2 / 59 (3.39%) 2 0 / 106 (0.00%) 0 0 / 106 (0.00%) 0 0 / 106 (0.00%) 0 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 0 / 97 (0.00%) 0 0 / 97 (0.00%) 0 0 / 97 (0.00%) 0 0 / 97 (0.00%) 0 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders asthma alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) cough alternative dictionary used: | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |

| | | | |
|---|-----------------|----------------|---------------|
| MedDRA 16.0 | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| dyspnoea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| epistaxis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| nasal congestion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| oropharyngeal pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 7 / 106 (6.60%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| pharyngeal inflammation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| productive cough | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| respiratory tract congestion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| rhinitis allergic | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| rhinorrhoea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sinus congestion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| yawning | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Psychiatric disorders | | | |
| abnormal behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| abnormal dreams | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| activation syndrome | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| affect lability | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| aggression | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| agitation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| anger | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| anxiety | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| apathy | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| attention deficit/hyperactivity disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| bruxism | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| compulsive handwashing | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| depression | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|-----------------|----------------|---------------|
| distractibility | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| fear | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| flat affect | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| impulsive behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| initial insomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| insomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 106 (2.83%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| intentional self-injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Major depression | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| middle insomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| negativism | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| nervousness | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| nightmare | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| obsessive thoughts | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| onychophagia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| oppositional defiant disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| panic attack | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| phobia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-----------------|----------------|---------------|
| psychotic disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| self injurious behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sexually inappropriate behaviour | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| sleep disorder | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sleep terror | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| suicidal ideation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| tic | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| withdrawal syndrome | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |

| | | | |
|---|----------------------|---------------------|--------------------|
| blood pressure increased alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| blood triglycerides increased alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| electrocardiogram qt prolonged alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| heart rate increased alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| neutrophil count increased alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| weight decreased alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 106 (1.89%) 2 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| weight increased alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| white blood cell count increased alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-----------------|----------------|---------------|
| animal bite | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| ankle fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| arthropod bite | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| arthropod sting | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| bone contusion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| burns first degree | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| concussion | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| fall | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| fibula fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| head injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| human bite | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| humerus fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| joint dislocation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| laceration | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| ligament sprain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| limb injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| lip injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-----------------|----------------|---------------|
| muscle rupture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| muscle strain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| post procedural swelling | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| procedural pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| road traffic accident | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| scratch | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sunburn | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| tendon injury | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| thermal burn | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| upper limb fracture | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| bundle branch block right | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| palpitations | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sinus arrhythmia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| sinus tachycardia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| tachycardia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| disturbance in attention | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| dizziness | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-------------------|----------------|---------------|
| subjects affected / exposed | 7 / 106 (6.60%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 9 | 1 | 0 |
| dizziness postural | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| dysgeusia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| dyskinesia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| headache | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 11 / 106 (10.38%) | 3 / 97 (3.09%) | 0 / 7 (0.00%) |
| occurrences (all) | 13 | 3 | 0 |
| hypersomnia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| hypoesthesia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| migraine | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| myoclonus | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|-----------------------|---------------------|--------------------|
| paraesthesia alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 106 (1.89%) 2 | 1 / 97 (1.03%) 1 | 0 / 7 (0.00%) 0 |
| poor quality sleep alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| post-traumatic headache alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| psychomotor hyperactivity alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| sedation alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 106 (1.89%) 2 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| somnolence alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 8 / 106 (7.55%) 11 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| tremor alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 106 (1.89%) 2 | 1 / 97 (1.03%) 1 | 0 / 7 (0.00%) 0 |
| Ear and labyrinth disorders ear pain alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) motion sickness alternative dictionary used: MedDRA 16.0 | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| tinnitus | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| vertigo | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Eye disorders | | | |
| blepharospasm | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| blindness | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| conjunctival haemorrhage | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| eye pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| mydriasis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| strabismus | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| vision blurred | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| abdominal discomfort | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| abdominal distension | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| abdominal pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| abdominal pain lower | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| abdominal pain upper | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 7 / 106 (6.60%) | 2 / 97 (2.06%) | 0 / 7 (0.00%) |
| occurrences (all) | 7 | 2 | 0 |
| aphthous stomatitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| chapped lips | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| colitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| constipation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| diarrhoea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| dry mouth | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| dyspepsia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| eructation | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| flatulence | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 0 | 1 |
| food poisoning | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-------------------|----------------|---------------|
| frequent bowel movements | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| gastritis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| gastrooesophageal reflux disease | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| gingival pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| lip dry | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| mouth ulceration | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| nausea | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 13 / 106 (12.26%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 16 | 1 | 0 |
| odynophagia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| oral mucosal blistering | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| toothache | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| vomiting | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| acne | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| alopecia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| dermatitis allergic | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| dermatitis contact | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| dry skin | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| erythema | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| hyperhidrosis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| night sweats | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| petechiae | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| pruritus | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| rash | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| rash maculo-papular | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| rash papular | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| rash pruritic | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|----------------------|---------------------|--------------------|
| urticaria alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 106 (1.89%) 2 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Renal and urinary disorders enuresis alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 5 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| hypertonic bladder alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| pollakiuria alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| urinary hesitation alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Endocrine disorders hypothyroidism alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders arthralgia alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 106 (1.89%) 2 | 1 / 97 (1.03%) 2 | 0 / 7 (0.00%) 0 |
| back pain alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 2 / 106 (1.89%) 2 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |

| | | | |
|---|-----------------|----------------|---------------|
| bone pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| flank pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| muscle spasms | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| muscle twitching | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| musculoskeletal pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| myalgia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| neck pain | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| pain in extremity | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| synovial cyst | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| temporomandibular joint syndrome | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| bronchitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| conjunctivitis infective | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| ear infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| fungus infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| gastroenteritis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 3 / 106 (2.83%) | 1 / 97 (1.03%) | 0 / 7 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| gastroenteritis viral | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| gastrointestinal infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| gastrointestinal viral infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| genital candidiasis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| hand-foot-and-mouth disease | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| herpes simplex | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| hordeolum | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| influenza | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| labyrinthitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| lower respiratory tract infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-----------------|----------------|---------------|
| nasopharyngitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| oral herpes | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| otitis externa | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| otitis media | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| pharyngitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| pharyngitis streptococcal | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| pharyngotonsillitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| pneumonia | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| rhinitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |

| | | | |
|---|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| sinusitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| skin infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| staphylococcal infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| tonsillitis | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| tooth infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| upper respiratory tract infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| urinary tract infection | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| vaginitis bacterial | | | |
| alternative dictionary used: MedDRA 16.0 | | | |
| subjects affected / exposed ^[5] | 0 / 106 (0.00%) | 0 / 97 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|-----------------------|---------------------|--------------------|
| viral infection alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| viral upper respiratory tract infection alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 1 / 106 (0.94%) 1 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 9 / 106 (8.49%) 10 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| dehydration alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |
| increased appetite alternative dictionary used: MedDRA 16.0 subjects affected / exposed occurrences (all) | 0 / 106 (0.00%) 0 | 0 / 97 (0.00%) 0 | 0 / 7 (0.00%) 0 |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific event, total number exposed corresponds to only female subjects.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific event, total number exposed corresponds to only male subjects.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific event, total number exposed corresponds to only female subjects.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific event, total number exposed corresponds to only female subjects.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific event, total number exposed corresponds to only female subjects.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 25 February 2011 | Dose range was changed based on health authority recommendation. |
| 31 July 2012 | Statistical analysis sample size was changed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

All Randomized participants from one site were excluded due to major quality issues at site; they were not considered part of ITT population and were excluded from the subject disposition, baseline characteristics, efficacy and safety analyses.

Notes: