



## Clinical trial results:

### F1J-MC-HMFN (a) An Open-Label Study of Tolerability, Safety, and Pharmacokinetics of Duloxetine in the Treatment of Children and Adolescents with Major Depressive Disorder

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2017-000211-16    |
| Trial protocol           | Outside EU/EEA    |
| Global end of trial date | 22 September 2008 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 16 April 2017 |
| First version publication date | 16 April 2017 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | F1J-MC-HMFN |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT00529789     |
| WHO universal trial number (UTN)   | -               |
| Other trial identifiers            | Trial ID: 11664 |

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, 1 877-CTLILLY,  |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559, |

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                       | 22 September 2008 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 22 September 2008 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 22 September 2008 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary purpose of your participation in this study is to help answer the following research question, and not to provide you treatment for your condition. Whether duloxetine once daily orally is tolerated and safe, in children (aged 7 through 11 years) and adolescents (aged 12 through 17 years) with Major Depressive Disorder.

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                          | 31 August 2007 |
| 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: 72 |
| Worldwide total number of subjects   | 72                |
| 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)                     | 31 |
| Adolescents (12-17 years)                 | 41 |
| Adults (18-64 years)                      | 0  |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Period I was a 2-week Screening/Washout Phase. Period II was a 10-week Dose-Titrating with Pharmacokinetic Sampling Phase. Period III was an 8-week Safety and Tolerability Phase. Period IV was a 3-month Extended Safety and Tolerability Phase. Period V was a 2-week Taper Phase. Results presented are for combined Periods II/III and Period IV.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Study Period II/III         |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|           |            |
|-----------|------------|
| Arm title | Duloxetine |
|-----------|------------|

Arm description:

20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks;  
If patient is  $\leq 40$  kilograms (kg), initial dose is 20 mg, then titrated up.  
If patient is  $>40$  kg, initial dose is 30 mg, then titrated up.

|                                        |              |
|----------------------------------------|--------------|
| 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:

A dose range of 20 - 120 milligrams (mg) Duloxetine every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is  $\leq 40$  kilograms (kg), initial dose is 20 mg, then titrated up. If patient is  $>40$  kg, initial dose is 30 mg, then titrated up.

| Number of subjects in period 1 | Duloxetine |
|--------------------------------|------------|
| Started                        | 72         |
| Completed                      | 48         |
| Not completed                  | 24         |
| Parent/Caregiver Decision      | 9          |
| Consent withdrawn by subject   | 1          |
| Physician decision             | 3          |
| Adverse event, non-fatal       | 3          |
| Lost to follow-up              | 3          |
| Lack of efficacy               | 2          |
| Protocol deviation             | 3          |

**Period 2**

|                              |                             |
|------------------------------|-----------------------------|
| Period 2 title               | Study Period IV             |
| Is this the baseline period? | No                          |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

**Arms**

|                  |            |
|------------------|------------|
| <b>Arm title</b> | Duloxetine |
|------------------|------------|

Arm description:

20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is  $\leq 40$  kilograms (kg), initial dose is 20 mg, then titrated up. If patient is  $>40$  kg, initial dose is 30 mg, then titrated up.

|                                        |              |
|----------------------------------------|--------------|
| 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:

A dose range of 20 - 120 milligrams (mg) Duloxetine every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is  $\leq 40$  kilograms (kg), initial dose is 20 mg, then titrated up. If patient is  $>40$  kg, initial dose is 30 mg, then titrated up.

| <b>Number of subjects in period 2</b> | Duloxetine |
|---------------------------------------|------------|
| Started                               | 48         |
| Completed                             | 42         |
| Not completed                         | 6          |
| Parent/Caregiver Decision             | 1          |
| Adverse event, non-fatal              | 1          |
| Lost to follow-up                     | 3          |
| Lack of efficacy                      | 1          |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks;

If patient is ≤40 kilograms (kg), initial dose is 20 mg, then titrated up.

If patient is >40 kg, initial dose is 30 mg, then titrated up.

| Reporting group values                                | Duloxetine | Total |  |
|-------------------------------------------------------|------------|-------|--|
| Number of subjects                                    | 72         | 72    |  |
| Age categorical                                       |            |       |  |
| Units: Subjects                                       |            |       |  |
| In utero                                              | 0          | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0          | 0     |  |
| Newborns (0-27 days)                                  | 0          | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0          | 0     |  |
| Children (2-11 years)                                 | 31         | 31    |  |
| Adolescents (12-17 years)                             | 41         | 41    |  |
| Adults (18-64 years)                                  | 0          | 0     |  |
| From 65-84 years                                      | 0          | 0     |  |
| 85 years and over                                     | 0          | 0     |  |
| Age continuous                                        |            |       |  |
| Units: years                                          |            |       |  |
| arithmetic mean                                       | 12.5       |       |  |
| standard deviation                                    | ± 2.9      | -     |  |
| Gender categorical                                    |            |       |  |
| Units: Subjects                                       |            |       |  |
| Female                                                | 35         | 35    |  |
| Male                                                  | 37         | 37    |  |
| Region of Enrollment                                  |            |       |  |
| Units: Subjects                                       |            |       |  |
| United States                                         | 72         | 72    |  |
| Race/Ethnicity                                        |            |       |  |
| Units: Subjects                                       |            |       |  |
| African                                               | 17         | 17    |  |
| Caucasian                                             | 42         | 42    |  |
| East Asian                                            | 1          | 1     |  |
| Hispanic                                              | 11         | 11    |  |
| Native American                                       | 1          | 1     |  |
| Tobacco Use                                           |            |       |  |
| Tobacco use was based on cotinine level.              |            |       |  |
| Units: Subjects                                       |            |       |  |
| No                                                    | 70         | 70    |  |
| Yes                                                   | 1          | 1     |  |
| Not Available                                         | 1          | 1     |  |

|                                                                                            |       |   |  |
|--------------------------------------------------------------------------------------------|-------|---|--|
| Body Mass Index (BMI)                                                                      |       |   |  |
| Body mass index is an estimate of body fat based on body weight divided by height squared. |       |   |  |
| Units: Subjects                                                                            |       |   |  |
| arithmetic mean                                                                            | 23.7  |   |  |
| standard deviation                                                                         | ± 6.4 | - |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                  |                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Reporting group title                                                                                                                                                                                                                                            | Duloxetine            |
| Reporting group description:<br>20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks;<br>If patient is ≤40 kilograms (kg), initial dose is 20 mg, then titrated up.<br>If patient is >40 kg, initial dose is 30 mg, then titrated up. |                       |
| Reporting group title                                                                                                                                                                                                                                            | Duloxetine            |
| Reporting group description:<br>20 - 120 milligrams (mg) every day, once-daily (QD), by mouth (PO) for 30 weeks; If patient is ≤40 kilograms (kg), initial dose is 20 mg, then titrated up. If patient is >40 kg, initial dose is 30 mg, then titrated up.       |                       |
| Subject analysis set title                                                                                                                                                                                                                                       | Duloxetine Dose 20mg  |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis    |
| Subject analysis set description:<br>Summary of observed plasma concentrations of duloxetine 20 mg.                                                                                                                                                              |                       |
| Subject analysis set title                                                                                                                                                                                                                                       | Duloxetine Dose 30mg  |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis    |
| Subject analysis set description:<br>Summary of observed plasma concentrations of duloxetine 30 mg.                                                                                                                                                              |                       |
| Subject analysis set title                                                                                                                                                                                                                                       | Duloxetine Dose 60mg  |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis    |
| Subject analysis set description:<br>Summary of observed plasma concentrations of duloxetine 60 mg.                                                                                                                                                              |                       |
| Subject analysis set title                                                                                                                                                                                                                                       | Duloxetine Dose 90mg  |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis    |
| Subject analysis set description:<br>Summary of observed plasma concentrations of duloxetine 90 mg.                                                                                                                                                              |                       |
| Subject analysis set title                                                                                                                                                                                                                                       | Duloxetine Dose 120mg |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis    |
| Subject analysis set description:<br>Summary of observed plasma concentrations of duloxetine 120 mg.                                                                                                                                                             |                       |

### Primary: Number of Participants with Emergence of Suicidal Ideation During Period II/III

|                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                        | Number of Participants with Emergence of Suicidal Ideation During Period II/III <sup>[1]</sup> |
| End point description:<br>Emergence of Any Suicidal Ideation: Item 13 of Children's Depression Rating Scale-Revised (CDRS-R) has possible scores of 1 (no thoughts of suicide) to 7 (contemplation of suicide). Emergence of suicidal ideation was defined as an increase in severity of suicidal ideation for those patients who did not have suicidal ideation at baseline (Week 0). |                                                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                         | Primary                                                                                        |
| End point timeframe:<br>Baseline to 18 weeks                                                                                                                                                                                                                                                                                                                                           |                                                                                                |

#### Notes:

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

| End point values            | Duloxetine      |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 72              |  |  |  |
| Units: participants         |                 |  |  |  |
| number (not applicable)     | 2               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Emergence of Suicidal Ideation During Period IV

|                 |                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Emergence of Suicidal Ideation During Period IV <sup>[2]</sup> |
|-----------------|--------------------------------------------------------------------------------------------|

End point description:

Emergence of Any Suicidal Ideation: Item 13 of Children's Depression Rating Scale-Revised (CDRS-R) has possible scores of 1 (no thoughts of suicide) to 7 (contemplation of suicide). Emergence of suicidal ideation was defined as an increase in severity of suicidal ideation for those patients who did not have suicidal ideation at baseline (Week 0).

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

End point timeframe:

Week 0 and Between 18 and 30 Weeks

Notes:

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

| End point values            | Duloxetine      |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 48              |  |  |  |
| Units: participants         |                 |  |  |  |
| number (not applicable)     | 0               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period II/III

|                 |                                                                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period II/III <sup>[3]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. Some questions are yes/no and some are on a scale of 1 (low severity) to 5 (high severity). Completed suicide and non-fatal suicide events are yes/no questions and results presented are the number of participants with these events. Worsening of suicidal ideation was an increase in severity of suicidal ideation from baseline.



|                                                                                                                                                                                                                                                         |                 |  |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|--|--|--|
| End point type                                                                                                                                                                                                                                          | Primary         |  |  |  |
| End point timeframe:                                                                                                                                                                                                                                    |                 |  |  |  |
| Baseline to 18 Weeks                                                                                                                                                                                                                                    |                 |  |  |  |
| Notes:                                                                                                                                                                                                                                                  |                 |  |  |  |
| [3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.                                                                                     |                 |  |  |  |
| Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted. |                 |  |  |  |
| <b>End point values</b>                                                                                                                                                                                                                                 | Duloxetine      |  |  |  |
| Subject group type                                                                                                                                                                                                                                      | Reporting group |  |  |  |
| Number of subjects analysed                                                                                                                                                                                                                             | 72              |  |  |  |
| Units: participants                                                                                                                                                                                                                                     |                 |  |  |  |
| number (not applicable)                                                                                                                                                                                                                                 |                 |  |  |  |
| Completed Suicide                                                                                                                                                                                                                                       | 0               |  |  |  |
| Non-fatal Suicide Event                                                                                                                                                                                                                                 | 1               |  |  |  |
| Worsening of Suicidal Ideation                                                                                                                                                                                                                          | 1               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period IV

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                     |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Number of Participants Experiencing Suicidal Ideation or Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) During Period IV <sup>[4]</sup> |  |  |  |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                     |  |  |  |
| The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. Some questions are yes/no and some are on a scale of 1 (low severity) to 5 (high severity). Completed suicide and non-fatal suicide events are yes/no questions and results presented are the number of participants with these events. Worsening of suicidal ideation was an increase in severity of suicidal ideation from baseline. |                                                                                                                                                                     |  |  |  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Primary                                                                                                                                                             |  |  |  |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                     |  |  |  |
| Between 18 and 30 Weeks                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                     |  |  |  |
| Notes:                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                     |  |  |  |
| [4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                     |  |  |  |
| Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.                                                                                                                                                                                                                    |                                                                                                                                                                     |  |  |  |
| End point values                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Duloxetine                                                                                                                                                          |  |  |  |
| Subject group type                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Reporting group                                                                                                                                                     |  |  |  |
| Number of subjects analysed                                                                                                                                                                                                                                                                                                                                                                                                                                                | 45 <sup>[5]</sup>                                                                                                                                                   |  |  |  |
| Units: participants                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                     |  |  |  |
| number (not applicable)                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                     |  |  |  |
| Completed suicide                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0                                                                                                                                                                   |  |  |  |
| Non-fatal suicide event                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0                                                                                                                                                                   |  |  |  |
| Worsening of Suicidal Ideation                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1                                                                                                                                                                   |  |  |  |

Notes:

[5] - Number of enrolled patients with baseline and post-baseline values in Period IV.

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period II/III

|                 |                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period II/III <sup>[6]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Total number of patients with any abnormal post-baseline value, based on all values at scheduled and unscheduled visits. Criteria: High Diastolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Systolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Pulse = increase of at least 25 to a value of at least 110.

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

End point timeframe:

Baseline to 18 Weeks

Notes:

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | Duloxetine      |  |  |  |
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 72              |  |  |  |
| Units: participants           |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| High Diastolic Blood Pressure | 22              |  |  |  |
| High Systolic Blood Pressure  | 25              |  |  |  |
| High Pulse                    | 2               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period IV

|                 |                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Meeting Criteria for Potentially Clinically Significant Vital Sign Values at Any Time During Period IV <sup>[7]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Total number of patients with any abnormal post-baseline value, based on all values at scheduled and unscheduled visits. Criteria: High Diastolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Systolic Blood Pressure = increase of at least 5 mmHg to a value above the 95th percentile; High Pulse = increase of at least 25 to a value of at least 110.

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

End point timeframe:

Between 18 and 30 Weeks

Notes:

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

| End point values              | Duloxetine      |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 45              |  |  |  |
| Units: participants           |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| High Diastolic Blood Pressure | 3               |  |  |  |
| High Systolic Blood Pressure  | 1               |  |  |  |
| High Pulse                    | 0               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period II/III

|                 |                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period II/III <sup>[8]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The results shown are for all laboratory analytes where PCS criteria were met, based on criteria used for adult studies. Criteria: High Alanine transaminase (>165 Units/Liter [U/L]); High Creatine Phosphokinase (females: >507 U/L; males: >594 U/L); Low Glucose (<2.498 millimoles/L); Low Hematocrit (females: <0.32; males <0.37); Low Hemoglobin (females <5.896 millimoles/L [mmol/L] iron; males <7.137 mmol/L iron); High Inorganic Phosphorus (>1.776 millimoles/L); Low Leukocyte Count (<2.8 X10<sup>9</sup>/L).

Number of patients with baseline (and none abnormal) and post-baseline values, based on all values at scheduled and unscheduled visits

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

End point timeframe:

Baseline to 18 Weeks

Notes:

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

| End point values                   | Duloxetine      |  |  |  |
|------------------------------------|-----------------|--|--|--|
| Subject group type                 | Reporting group |  |  |  |
| Number of subjects analysed        | 72              |  |  |  |
| Units: participants                |                 |  |  |  |
| number (not applicable)            |                 |  |  |  |
| High Alanine Transaminase (N=69)   | 1               |  |  |  |
| High Creatine Phosphokinase (N=69) | 6               |  |  |  |

|                                  |    |  |  |  |
|----------------------------------|----|--|--|--|
| Low Glucose (N=69)               | 1  |  |  |  |
| Low Hematocrit (N=60)            | 8  |  |  |  |
| Low Hemoglobin (N=67)            | 1  |  |  |  |
| High Inorganic Phosphorus (N=62) | 16 |  |  |  |
| Low Leukocyte Count (N=68)       | 1  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period IV

|                 |                                                                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Meeting Criteria for Potentially Clinically Significant (PCS) Laboratory Analyte Values at Any Time During Period IV <sup>[9]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The results shown are for all laboratory analytes where PCS criteria were met, based on criteria used for adult studies. Criteria: High Alkaline Phosphatase (>420 Units/Liter [U/L]); Low Hematocrit (females <0.32; males <0.37); High Inorganic Phosphorus (>1.776 millimoles/L).

Total number of patients with baseline (and none abnormal) and post-baseline values in Period IV, based on all values at scheduled and unscheduled visits.

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

End point timeframe:

Between 18 and 30 Weeks

Notes:

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

|                                  |                 |  |  |  |
|----------------------------------|-----------------|--|--|--|
| <b>End point values</b>          | Duloxetine      |  |  |  |
| Subject group type               | Reporting group |  |  |  |
| Number of subjects analysed      | 48              |  |  |  |
| Units: participants              |                 |  |  |  |
| number (not applicable)          |                 |  |  |  |
| High Alkaline Phosphatase (N=42) | 1               |  |  |  |
| Low Hematocrit (N=39)            | 1               |  |  |  |
| High Inorganic Phosphorus (N=39) | 3               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Meeting Criteria for Potentially Clinically Significant Electrocardiograms at Any Time in Period II/III

|                 |                                                                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Meeting Criteria for Potentially Clinically Significant Electrocardiograms at Any Time in Period II/III <sup>[10]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|

---

**End point description:**

Total number of patients with any abnormal post-baseline values, based on all values at scheduled and unscheduled visits. Criteria: High QRS Interval =  $\geq 100$  milliseconds (msec); High QTc Bazette's or Fredericia's correction - Female =  $\geq 470$  msec; High QTc Bazette's or Fredericia's correction - Male =  $\geq 450$  msec.

Number of patients with baseline (and none abnormal) and post-baseline values, based on all values at scheduled and unscheduled visits

---

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

---

End point timeframe:

Baseline to 18 Weeks

---

**Notes:**

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

| End point values                        | Duloxetine      |  |  |  |
|-----------------------------------------|-----------------|--|--|--|
| Subject group type                      | Reporting group |  |  |  |
| Number of subjects analysed             | 72              |  |  |  |
| Units: participants                     |                 |  |  |  |
| number (not applicable)                 |                 |  |  |  |
| High QRS Interval (N=63)                | 1               |  |  |  |
| High QTc Bazette's Correction (N=64)    | 2               |  |  |  |
| High QTc Fredericia's Correction (N=65) | 0               |  |  |  |

---

**Statistical analyses**

No statistical analyses for this end point

---

---

**Primary: Number of Participants with Potentially Clinically Significant Electrocardiograms at Any Time in Period IV**

---

---

|                 |                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Potentially Clinically Significant Electrocardiograms at Any Time in Period IV <sup>[11]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|

---

**End point description:**

Total number of patients with any abnormal post-baseline values, based on all values at scheduled and unscheduled visits. Criteria: High QRS Interval =  $\geq 100$  milliseconds (msec); High QTc Bazette's or Fredericia's correction - Female =  $\geq 470$  msec; High QTc Bazette's or Fredericia's correction - Male =  $\geq 450$  msec.

Number of patients with baseline (and none abnormal) and post-baseline values, based on all values at scheduled and unscheduled visits.

---

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

---

End point timeframe:

Between 18 and 30 Weeks

---

**Notes:**

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

Justification: The primary objective of this study was to assess the safety and tolerability of duloxetine in children and adolescents. This was an open-label, single arm study with no comparison groups and statistical analyses were not conducted.

| End point values                        | Duloxetine      |  |  |  |
|-----------------------------------------|-----------------|--|--|--|
| Subject group type                      | Reporting group |  |  |  |
| Number of subjects analysed             | 48              |  |  |  |
| Units: participants                     |                 |  |  |  |
| number (not applicable)                 |                 |  |  |  |
| High QRS Interval (N=39)                | 1               |  |  |  |
| High QTc Bazette's Correction (N=41)    | 1               |  |  |  |
| High QTc Fredericia's Correction (N=41) | 0               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics: Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose

|                        |                                                                                                                                           |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Pharmacokinetics: Summary of Observed Duloxetine Plasma Concentrations Stratified by Duloxetine Dose                                      |
| End point description: | Plasma samples were obtained at steady state, and approximately 95% of duloxetine concentrations were within the 24 hour dosing interval. |
| End point type         | Secondary                                                                                                                                 |
| End point timeframe:   | Weeks 2, 4, 6, 8, 10, 14, 18                                                                                                              |

| End point values                        | Duloxetine Dose 20mg | Duloxetine Dose 30mg | Duloxetine Dose 60mg | Duloxetine Dose 90mg |
|-----------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                      | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed             | 14                   | 53                   | 41                   | 33                   |
| Units: nanograms per milliliter (ng/mL) |                      |                      |                      |                      |
| arithmetic mean (standard deviation)    | 15.2 (± 12)          | 20.8 (± 21.2)        | 41.1 (± 34.7)        | 57.6 (± 43.2)        |

| End point values                        | Duloxetine Dose 120mg |  |  |  |
|-----------------------------------------|-----------------------|--|--|--|
| Subject group type                      | Subject analysis set  |  |  |  |
| Number of subjects analysed             | 19                    |  |  |  |
| Units: nanograms per milliliter (ng/mL) |                       |  |  |  |
| arithmetic mean (standard deviation)    | 77.6 (± 54.6)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to 18 Weeks and 30 Weeks in Clinical Global Impressions of Severity Scale (CGI-S)

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline to 18 Weeks and 30 Weeks in Clinical Global Impressions of Severity Scale (CGI-S) |
|-----------------|--------------------------------------------------------------------------------------------------------|

### End point description:

Measures severity of illness at the time of assessment compared with start of treatment. Scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). Baseline is the same timepoint (Week 0) for both comparisons, but due to differences in number of patients in both periods (II/III vs IV), the baseline values may be slightly different.

18 Week results are for all enrolled patients with a baseline and at least one non-missing post-baseline value; 30 Week results are for the enrolled patients with a baseline and at least one non-missing post-baseline value in Period IV. Last observation carried forward.

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

### End point timeframe:

Week 0 (Baseline), 18 Weeks, 30 Weeks

| End point values                     | Duloxetine         | Duloxetine         |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 72 <sup>[12]</sup> | 45 <sup>[13]</sup> |  |  |
| Units: units on a scale              |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| 18 Week Baseline                     | 4.5 (± 0.58)       | 0 (± 0)            |  |  |
| 18 Week Change from Baseline         | -2.11 (± 1.17)     | 0 (± 0)            |  |  |
| 30 Week Baseline                     | 0 (± 0)            | 4.5 (± 0.59)       |  |  |
| 30 Week Change from Baseline         | 0 (± 0)            | -2.7 (± 1.07)      |  |  |

### Notes:

[12] - All enrolled patients with a baseline and at least 1 non-missing post-baseline value at 18 Weeks.

[13] - All enrolled patients with a baseline and at least 1 non-missing post-baseline value at 30 Weeks.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to 18 Weeks and 30 Weeks in Children's Depression Rating Scale-Revised (CDRS-R) Total Score

|                 |                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline to 18 Weeks and 30 Weeks in Children's Depression Rating Scale-Revised (CDRS-R) Total Score |
|-----------------|------------------------------------------------------------------------------------------------------------------|

### End point description:

Measures presence and severity of depression. Consists of 17 items scored on a 1-5 or 1-7 scale. A rating of 1 indicates normal, thus the minimum score is 17. The maximum score is 113. In general, scores below 20 indicate an absence of depression; scores of 20 or 30 indicate borderline depression; scores of 40 to 60 indicate moderate depression. Baseline is the same timepoint (Week 0) for both comparisons, but due to differences in number of patients in both periods (II/III vs IV), the baseline values may be slightly different.

18 Week results are for all enrolled patients with a baseline and at least one non-missing post-baseline value; 30 Week results are for the enrolled patients with a baseline and at least one non-missing post-baseline value in Period IV. Last observation carried forward.

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

### End point timeframe:

Week 0 (Baseline), 18 Weeks, 30 Weeks

| End point values                     | Duloxetine         | Duloxetine         |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 72 <sup>[14]</sup> | 45 <sup>[15]</sup> |  |  |
| Units: units on a scale              |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| 18 Week Baseline                     | 61.69 (± 8.98)     | 0 (± 0)            |  |  |
| 18 Week Change from Baseline         | -32.11 (± 12.92)   | 0 (± 0)            |  |  |
| 30 Week Baseline                     | 0 (± 0)            | 61.8 (± 9.28)      |  |  |
| 30 Week Change from Baseline         | 0 (± 0)            | -38.8 (± 11.14)    |  |  |

Notes:

[14] - All enrolled patients with a baseline and at least one post-baseline value at 18 Weeks.

[15] - All enrolled patients with a baseline and at least one post-baseline value at 30 Weeks.

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Adverse Events Leading to Discontinuation

|                 |                                           |
|-----------------|-------------------------------------------|
| End point title | Adverse Events Leading to Discontinuation |
|-----------------|-------------------------------------------|

End point description:

A listing of adverse events leading to discontinuation from the study. Abbreviation in data table: ADHD = Attention-Deficit/Hyperactivity Disorder.

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

End point timeframe:

Week 0 (Baseline) to 30 Weeks

| End point values            | Duloxetine      | Duloxetine      |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 72              | 48              |  |  |
| Units: participants         |                 |                 |  |  |
| number (not applicable)     |                 |                 |  |  |
| Nausea                      | 1               | 0               |  |  |
| Worsening of ADHD           | 1               | 0               |  |  |
| Rash                        | 1               | 0               |  |  |
| Irritability                | 0               | 1               |  |  |

### 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-HMFN

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Duloxetine-SPII-III |
|-----------------------|---------------------|

Reporting group description: -

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Duloxetine-SPIV |
|-----------------------|-----------------|

Reporting group description: -

| Serious adverse events                            | Duloxetine-SPII-III | Duloxetine-SPIV |  |
|---------------------------------------------------|---------------------|-----------------|--|
| Total subjects affected by serious adverse events |                     |                 |  |
| subjects affected / exposed                       | 5 / 72 (6.94%)      | 0 / 48 (0.00%)  |  |
| number of deaths (all causes)                     | 0                   | 0               |  |
| number of deaths resulting from adverse events    | 0                   | 0               |  |
| Psychiatric disorders                             |                     |                 |  |
| depression                                        |                     |                 |  |
| alternative dictionary used: MedDRA 11.0          |                     |                 |  |
| subjects affected / exposed                       | 1 / 72 (1.39%)      | 0 / 48 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1               | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0           |  |
| oppositional defiant disorder                     |                     |                 |  |
| alternative dictionary used: MedDRA 11.0          |                     |                 |  |
| subjects affected / exposed                       | 1 / 72 (1.39%)      | 0 / 48 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 1               | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0           |  |
| self injurious behaviour                          |                     |                 |  |
| alternative dictionary used: MedDRA 11.0          |                     |                 |  |
| subjects affected / exposed                       | 2 / 72 (2.78%)      | 0 / 48 (0.00%)  |  |
| occurrences causally related to treatment / all   | 0 / 2               | 0 / 0           |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0           |  |

|                                                                                                                                                                                                                                           |                                  |                                  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|--|
| suicidal ideation<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                    | 1 / 72 (1.39%)<br>0 / 1<br>0 / 0 | 0 / 48 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Infections and infestations<br>gastroenteritis viral<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 1 / 72 (1.39%)<br>0 / 1<br>0 / 0 | 0 / 48 (0.00%)<br>0 / 0<br>0 / 0 |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                                                                                                                                                                                                                                                         | Duloxetine-SPII-III                            | Duloxetine-SPIV                                |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|------------------------------------------------|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                                                                                                                                                                                      | 57 / 72 (79.17%)                               | 21 / 48 (43.75%)                               |  |
| General disorders and administration site conditions<br>fatigue<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)<br><br>irritability<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all) | 5 / 72 (6.94%)<br>5<br><br>2 / 72 (2.78%)<br>2 | 2 / 48 (4.17%)<br>2<br><br>1 / 48 (2.08%)<br>1 |  |
| Reproductive system and breast disorders<br>menstruation delayed<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)<br><br>ovarian cyst<br>alternative dictionary used:<br>MedDRA 11.0                                                    | 0 / 72 (0.00%)<br>0                            | 1 / 48 (2.08%)<br>1                            |  |

|                                                                                                                                 |                     |                     |  |
|---------------------------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                | 1 / 72 (1.39%)<br>1 | 1 / 48 (2.08%)<br>1 |  |
| Respiratory, thoracic and mediastinal disorders                                                                                 |                     |                     |  |
| asthma exercise induced<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)      | 1 / 72 (1.39%)<br>1 | 1 / 48 (2.08%)<br>1 |  |
| cough<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 72 (4.17%)<br>3 | 1 / 48 (2.08%)<br>1 |  |
| pharyngolaryngeal pain<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)       | 3 / 72 (4.17%)<br>3 | 1 / 48 (2.08%)<br>1 |  |
| respiratory tract congestion<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all) | 2 / 72 (2.78%)<br>2 | 0 / 48 (0.00%)<br>0 |  |
| rhinorrhoea<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 72 (5.56%)<br>5 | 1 / 48 (2.08%)<br>1 |  |
| Psychiatric disorders                                                                                                           |                     |                     |  |
| aggression<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 72 (0.00%)<br>0 | 1 / 48 (2.08%)<br>1 |  |
| anxiety<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)                      | 2 / 72 (2.78%)<br>2 | 0 / 48 (0.00%)<br>0 |  |
| bruxism<br>alternative dictionary used:<br>MedDRA 11.0                                                                          |                     |                     |  |

|                                                                                                                                                                                                                                                                                                    |                                |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 72 (4.17%)</p> <p>3</p>                                                                                                                                                                                                         | <p>1 / 48 (2.08%)</p> <p>1</p> |  |
| <p>insomnia</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>3 / 72 (4.17%)</p> <p>3</p>                                                                                                                                     | <p>1 / 48 (2.08%)</p> <p>1</p> |  |
| <p>libido increased</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>0 / 72 (0.00%)</p> <p>0</p>                                                                                                                             | <p>1 / 48 (2.08%)</p> <p>1</p> |  |
| <p>oppositional defiant disorder</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 72 (2.78%)</p> <p>2</p>                                                                                                                | <p>0 / 48 (0.00%)</p> <p>0</p> |  |
| <p>restlessness</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 72 (2.78%)</p> <p>2</p>                                                                                                                                 | <p>1 / 48 (2.08%)</p> <p>1</p> |  |
| <p>suicidal ideation</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 72 (1.39%)</p> <p>1</p>                                                                                                                            | <p>1 / 48 (2.08%)</p> <p>1</p> |  |
| <p>Investigations</p> <p>white blood cell count decreased</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>1 / 72 (1.39%)</p> <p>1</p>                                                                                       | <p>1 / 48 (2.08%)</p> <p>1</p> |  |
| <p>Injury, poisoning and procedural complications</p> <p>excoriation</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>2 / 72 (2.78%)</p> <p>2</p> <p>skin laceration</p> <p>alternative dictionary used:<br/>MedDRA 11.0</p> | <p>1 / 48 (2.08%)</p> <p>1</p> |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                               |                                                                                                                                                            |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 3 / 72 (4.17%)<br>3                                                                                                                                           | 1 / 48 (2.08%)<br>1                                                                                                                                        |  |
| Cardiac disorders<br>palpitations<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1 / 72 (1.39%)<br>1                                                                                                                                           | 1 / 48 (2.08%)<br>1                                                                                                                                        |  |
| Nervous system disorders<br>dizziness<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)<br><br>headache<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)<br><br>migraine<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)<br><br>sedation<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)<br><br>somnolence<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all)<br><br>tremor<br>alternative dictionary used:<br>MedDRA 11.0<br>subjects affected / exposed<br>occurrences (all) | 7 / 72 (9.72%)<br>7<br><br>10 / 72 (13.89%)<br>13<br><br>1 / 72 (1.39%)<br>1<br><br>7 / 72 (9.72%)<br>7<br><br>7 / 72 (9.72%)<br>8<br><br>0 / 72 (0.00%)<br>0 | 0 / 48 (0.00%)<br>0<br><br>0 / 48 (0.00%)<br>0<br><br>1 / 48 (2.08%)<br>1<br><br>1 / 48 (2.08%)<br>1<br><br>2 / 48 (4.17%)<br>2<br><br>1 / 48 (2.08%)<br>1 |  |
| Eye disorders<br>myopia<br>alternative dictionary used:<br>MedDRA 11.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                               |                                                                                                                                                            |  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 72 (1.39%)<br>1 | 1 / 48 (2.08%)<br>1 |  |
| Gastrointestinal disorders                       |                     |                     |  |
| abdominal pain upper                             |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 6 / 72 (8.33%)      | 0 / 48 (0.00%)      |  |
| occurrences (all)                                | 8                   | 0                   |  |
| constipation                                     |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 0 / 72 (0.00%)      | 1 / 48 (2.08%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| diarrhoea                                        |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 2 / 72 (2.78%)      | 0 / 48 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| dry mouth                                        |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 4 / 72 (5.56%)      | 2 / 48 (4.17%)      |  |
| occurrences (all)                                | 4                   | 2                   |  |
| flatulence                                       |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 2 / 72 (2.78%)      | 0 / 48 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| nausea                                           |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 18 / 72 (25.00%)    | 1 / 48 (2.08%)      |  |
| occurrences (all)                                | 20                  | 1                   |  |
| vomiting                                         |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 10 / 72 (13.89%)    | 1 / 48 (2.08%)      |  |
| occurrences (all)                                | 13                  | 1                   |  |
| Skin and subcutaneous tissue disorders           |                     |                     |  |
| hyperhidrosis                                    |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 72 (0.00%)<br>0 | 1 / 48 (2.08%)<br>1 |  |
| Infections and infestations                      |                     |                     |  |
| ear infection                                    |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 2 / 72 (2.78%)      | 0 / 48 (0.00%)      |  |
| occurrences (all)                                | 2                   | 0                   |  |
| gastroenteritis viral                            |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 3 / 72 (4.17%)      | 1 / 48 (2.08%)      |  |
| occurrences (all)                                | 3                   | 1                   |  |
| influenza                                        |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 3 / 72 (4.17%)      | 0 / 48 (0.00%)      |  |
| occurrences (all)                                | 3                   | 0                   |  |
| nasopharyngitis                                  |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 9 / 72 (12.50%)     | 0 / 48 (0.00%)      |  |
| occurrences (all)                                | 9                   | 0                   |  |
| pharyngitis streptococcal                        |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 1 / 72 (1.39%)      | 1 / 48 (2.08%)      |  |
| occurrences (all)                                | 1                   | 1                   |  |
| sinusitis                                        |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 2 / 72 (2.78%)      | 1 / 48 (2.08%)      |  |
| occurrences (all)                                | 2                   | 1                   |  |
| upper respiratory tract infection                |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |
| subjects affected / exposed                      | 2 / 72 (2.78%)      | 0 / 48 (0.00%)      |  |
| occurrences (all)                                | 3                   | 0                   |  |
| Metabolism and nutrition disorders               |                     |                     |  |
| decreased appetite                               |                     |                     |  |
| alternative dictionary used:<br>MedDRA 11.0      |                     |                     |  |

|                                             |                |                |  |
|---------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                 | 4 / 72 (5.56%) | 1 / 48 (2.08%) |  |
| occurrences (all)                           | 4              | 1              |  |
| obesity                                     |                |                |  |
| alternative dictionary used:<br>MedDRA 11.0 |                |                |  |
| subjects affected / exposed                 | 1 / 72 (1.39%) | 1 / 48 (2.08%) |  |
| occurrences (all)                           | 1              | 1              |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

---

### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported