# Clinical trial results:
# An Open-Label, Multicenter Study Evaluating the Safety and Tolerability of Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder.

## Summary

| | |
|---|---|
| EudraCT number | 2012-003489-42 |
| Trial protocol | HU GB ES IT DE SE NL BG |
| Global end of trial date | 22 September 2014 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 02 March 2016 |
| First version publication date | 12 August 2015 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 31-12-294 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01727713 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Otsuka Pharmaceutical Development & Commercialization, Inc. |
| Sponsor organisation address | 2440 Research Boulevard, Rockville, Maryland, United States, 20850 |
| Public contact | Eva Kohegyi, Otsuka Pharmaceutical Development & Commercialization, Inc., 001 6095246790, Eva.Kohegyi@otsuka-us.com |
| Scientific contact | Eva Kohegyi, Otsuka Pharmaceutical Development & Commercialization, Inc., 001 6095246790, Eva.Kohegyi@otsuka-us.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 26 January 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 September 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 September 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the long-term safety and tolerability of aripiprazole once-daily treatment with oral tablets in children and adolescents (7 -17 years of age) with a diagnosis of Tourette's Disorder (TD). The secondary objective was to evaluate the efficacy of once-daily aripiprazole in the suppression of tics in children and adolescents with a diagnosis of TD, as measured by change from baseline to endpoint on the total tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS).

Protection of trial subjects:

In accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline and the applicable local laws and regulatory requirements of the countries in which the trial was conducted, copies of the protocol, amendments, informed consent form (ICF), informed assent form, and subject recruitment materials were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 January 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Canada: 23 |
| Country: Number of subjects enrolled | Hungary: 9 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | United States: 74 |
| Worldwide total number of subjects | 110 |
| EEA total number of subjects | 13 |

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) | 52 |
| Adolescents (12-17 years) | 56 |
| Adults (18-64 years) | 2 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A Phase 3 open-label, multicenter study evaluating the safety and tolerability of once-daily oral Aripiprazole in children and adolescents with TD. Participants who reached 18 years of age during their participation in Trial 31-12-293 (NCT01727700) were enrolled in this trial.

### Pre-assignment

Screening details:

Participants who successfully completed the randomized, double-blind, placebo-controlled trial of once-daily Aripiprazole (protocol 31-12-293-NCT01727700) were eligible to enter this extension trial.

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | Open-label Aripiprazole |

Arm description:

All participants in this open-label extension trial were assigned to once-daily aripiprazole, which was flexibly dosed at the discretion of the investigator on the basis of treatment response and medication tolerability.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Aripiprazole |
| Investigational medicinal product code | |
| Other name | OPC-14597 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

The once-daily aripiprazole was flexibly dosed at the discretion of the investigator on the basis of treatment response and medication tolerability. Aripiprazole was formulated into tablets containing 2, 5, 10, and 15 mg (milligram) of aripiprazole per tablet.

| **Number of subjects in period 1** | Open-label Aripiprazole |
|---|---|
| Started | 110 |
| Completed | 75 |
| Not completed | 35 |
| Consent withdrawn by subject | 13 |
| Adverse event, non-fatal | 10 |
| Lost to follow-up | 5 |
| Participant met withdrawal criteria | 5 |
| Protocol deviation | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall trial |

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 110 | 110 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 0 | |
| Newborns (0-27 days) | | 0 | |
| Infants and toddlers (28 days-23 months) | | 0 | |
| Children (2-11 years) | | 0 | |
| Adolescents (12-17 years) | | 0 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 11.7 | | |
| standard deviation | ± 2.9 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 24 | 24 | |
| Male | 86 | 86 | |

## End points

### End points reporting groups

| Reporting group title | Open-label Aripiprazole |
|---|---|

Reporting group description:

All participants in this open-label extension trial were assigned to once-daily aripiprazole, which was flexibly dosed at the discretion of the investigator on the basis of treatment response and medication tolerability.

### Primary: Percentage of participants with adverse events.

| End point title | Percentage of participants with adverse events.[1] |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a patient or participant enrolled in the clinical trial and which does not necessarily have to have a causal relationship with the study drug. A treatment emergent adverse event (TEAE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not considered related to have a causal relationship with the study drug. Serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires in-patient hospitalization or prolonged hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

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

End point timeframe:

Baseline to Follow-up period (30±3 days after the last trial visit)

Notes:

[1] - No statistical analyses have been specifiN

whether the value was clinically significant based on the pre-defined criteria for identifying laboratory values of potential clinical relevance. Percentage of participants noted with abnormal laboratory values are reported below.

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

End point timeframe:

Baseline to Week 52

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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Hematology-Eosinophils (high) | 3.7 | | | |
| Hematology-Hemoglobin A1C (high) | 0.9 | | | |
| Hematology-Absolute neutrophils (low) | 13 | | | |
| Hematology-White blood count (low) | 4.6 | | | |
| Chemistry-Total bilirubin (high) | 1.9 | | | |
| Chemistry-Creatine phosphokinase (high) | 0.9 | | | |
| Chemistry-Fasting glucose (high) | 3.2 | | | |
| Chemistry-LDL cholesterol (high) | 3.3 | | | |
| Chemistry-Triglycerides (high) | 17.4 | | | |
| Chemistry-Uric acid (high) | 0.9 | | | |
| Chemistry-Potassium (high) | 0.9 | | | |
| Urinalysis-Urine glucose (high) | 1 | | | |
| Urinalysis-Urine protein (high) | 1.9 | | | |
| Prolactin (high) | 3.8 | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of participants with clinically significant abnormal vital signs.

| End point title | Percentage of participants with clinically significant abnormal vital signs.[3] |
|---|---|

End point description:

Vital sign measurements included systolic and diastolic blood pressure (BP) and heart rate, which were performed at all clinic visits. Criteria for identifying vital signs of potential clinical relevance included: Heart rate: ≥ 15 beats per minute (bpm) increase/decrease from Baseline (final visit of study 31-12-293); Systolic BP: ≥ 20 mmHg increase/decrease from Baseline; Diastolic BP: ≥ 15mmHg increase/decrease from Baseline; Orthostatic hypotension: ≥ 20 mmHg decrease in systolic BP and a ≥ 25 bpm increase in heart rate from supine to sitting/standing. Percentage of participants noted with abnormal vital sign measurements are reported below.

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

End point timeframe:

Baseline to Week 52

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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Heart rate-Supine (increase) | 0.9 | | | |
| Heart rate-Supine (decrease) | 0.9 | | | |
| Heart rate-Standing (increase) | 9.3 | | | |
| Systolic Supine BP (decrease) | 6.5 | | | |
| Systolic Standing BP (decrease) | 3.7 | | | |
| Diastolic Supine BP (decrease) | 0.9 | | | |
| Diastolic Standing BP (decrease) | 5.6 | | | |
| Orthostatic hypotension | 2.7 | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of participants with clinically significant abnormal electrocardiogram (ECG).

| End point title | Percentage of participants with clinically significant abnormal electrocardiogram (ECG).[4] |
|---|---|

End point description:

Three 12-lead ECGs (scheduled 5 minutes apart) were recorded. Some of the pre-defined criteria for identifying ECG measurements of potential clinical relevance included: Tachycardia/sinus tachycardia: increase of ≥15 bpm from Baseline; increase in QTc of ≥10% from Baseline. The other abnormalities not present at Baseline and were present during the time of measurement were recorded. Percentage of participants noted with abnormal ECG findings are reported below.

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

End point timeframe:

Baseline to Week 52

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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 106 | | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Tachycardia | 0.9 | | | |
| Sinus Tachycardia | 0.9 | | | |
| Supraventricular premature beat | 1.9 | | | |
| Ventricular premature beat | 0.9 | | | |

| | | | | |
|---|---|---|---|---|
| Right bundle branch block | 1.9 | | | |
| QTcB | 0.9 | | | |
| QTcN | 0.9 | | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Mean change from Baseline in body weight.

| End point title | Mean change from Baseline in body weight.[5] |
|---|---|

End point description:

Criteria for identifying weight of potential clinical relevance was: ≥ 7% kilogram increase/decrease from Baseline (Final visit of Trial 31-12-293 [NCT01727700]).

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

End point timeframe:

Baseline to Weeks 12, 28, 36, 44, 52/Last visit.

Notes:

[5] - 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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 108 | | | |
| Units: Kilogram | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 (N=102) | 1.8 (± 2.3) | | | |
| Week 28 (N=90) | 4.8 (± 3.8) | | | |
| Week 36 (N=88) | 5.8 (± 4.4) | | | |
| Week 44 (N=81) | 6.8 (± 5.3) | | | |
| Week 52 (N=77) | 8 (± 5.4) | | | |
| Last visit (N=106) | 7.2 (± 5.8) | | | |

### Statistical analyses

No statistical analyses for this end point

### Primary: Mean change from Baseline in Body Mass Index (BMI).

| End point title | Mean change from Baseline in Body Mass Index (BMI).[6] |
|---|---|

End point description:

BMI was calculated at the Baseline visit (using the Baseline height from study 31-12-293 [NCT01727700]) and at Weeks 28 and 52/ET where height measured at baseline in the current trial was used to calculate BMI.

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

End point timeframe:

Baseline to Weeks 28, 52 and Last visit.

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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 108 | | | |
| Units: Kg/M^2 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 28 (N=90) | 3.3 (± 16.2) | | | |
| Week 52 (N=77) | 1.9 (± 2.3) | | | |
| Last visit (N=106) | 1.8 (± 2.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Mean change from Baseline in Waist circumference.

| End point title | Mean change from Baseline in Waist circumference.[7] |
|---|---|

End point description:

Waist circumference was measured at Baseline, Weeks 12, 28, 36, 44, and the Week 52/last visit in centimeters.

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

End point timeframe:

Baseline to Weeks 12, 28, 36, 44, and 52/last visit.

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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 108 | | | |
| Units: Centimeter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 (N=102) | 2.2 (± 8.3) | | | |
| Week 28 (N=90) | 3.7 (± 9.7) | | | |
| Week 36 (N=87) | 3.5 (± 6.5) | | | |
| Week 44 (N=80) | 4.5 (± 6.7) | | | |
| Week 52 (N=75) | 5.5 (± 6.5) | | | |
| Last visit (N=106) | 4.6 (± 6.4) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Abnormal Involuntary Movement Scale (AIMS) total score.

| End point title | Change from Baseline in Abnormal Involuntary Movement Scale (AIMS) total score.[8] |
|---|---|

End point description:

The AIMS assessment consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) were observed unobtrusively while the participant was at rest, and the investigator also made global judgments on the participant's dyskinesias (items 8 through 10). Each item was rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness/severe distress). In addition, the AIMS included 2 yes/no questions that addressed the subject's dental status (since an edentulous state can cause lingual dyskinesias). The AIMS movement rating score (range 0 to 28) was the sum of the rating scores for facial and oral moments (ie, items 1 to 4), extremity movements (ie, items 5 and 6), and trunk movements (ie, item 7).

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, and Last visit

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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (N=107) | -1 (± 3) | | | |
| Week 8 (N=105) | -1.3 (± 3.4) | | | |
| Week 12 (N=104) | -1.7 (± 3.7) | | | |
| Week 20 (N=100) | -1.8 (± 3.9) | | | |
| Week 28 (N=92) | -2 (± 4.3) | | | |
| Week 36 (N=88) | -2.2 (± 4.5) | | | |
| Week 44 (N=82) | -2.3 (± 4.6) | | | |
| Week 52 (N=77) | -2.3 (± 4.7) | | | |
| Last vist (N=109) | -1.8 (± 4.3) | | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Simpson-Angus Scale (SAS) total score.

| End point title | Change from Baseline in Simpson-Angus Scale (SAS) total score.[9] |
|---|---|

End point description:

The SAS consists of a list of 10 symptoms of Parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item was rated on a 5-point scale, with a score of 1 representing absence of symptoms, and a score of 5 representing a severe condition. The SAS total score (range 10 to 50) was the sum of the rating scores for 10 items from the SAS panel.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, and Last visit

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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (N=107) | 0 (± 0.9) | | | |
| Week 8 (N=104) | 0 (± 0.9) | | | |
| Week 12 (N=104) | 0 (± 0.9) | | | |
| Week 20 (N=100) | -0.1 (± 0.7) | | | |
| Week 28 (N=92) | -0.2 (± 0.8) | | | |
| Week 36 (N=88) | -0.2 (± 0.8) | | | |
| Week 44 (N=82) | -0.2 (± 0.8) | | | |
| Week 52 (N=77) | -0.1 (± 0.8) | | | |
| Last vist (N=109) | -0.1 (± 0.7) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Barnes Akathisia Rating Scale (BARS) total score.

| End point title | Change from Baseline in Barnes Akathisia Rating Scale (BARS) total score.[10] |
|---|---|

End point description:

The BARS consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the participant, participant distress due to akathisia, and global evaluation of akathisia. The first 3 items were rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation was made on a 6-point scale, with 0 representing absence of symptoms and a score of 5 representing severe akathisia. To complete this scale, participants were observed while they were seated and then standing for a minimum of 2 minutes in each position. The BARS global score (range 0 to 5) was derived from the global clinical assessment of akathisia from the BARS panel.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, and Last visit

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: Not performed

| End point values | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (N=107) | 0 (± 0.4) | | | |
| Week 8 (N=105) | 0 (± 0.4) | | | |
| Week 12 (N=104) | 0 (± 0.3) | | | |
| Week 20 (N=100) | -0.1 (± 0.3) | | | |
| Week 28 (N=92) | -0.1 (± 0.3) | | | |
| Week 36 (N=88) | -0.1 (± 0.3) | | | |
| Week 44 (N=82) | -0.1 (± 0.3) | | | |
| Week 52 (N=77) | -0.1 (± 0.3) | | | |
| Last vist (N=109) | 0 (± 0.3) | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Suicidal Ideation Intensity Total Score based on Columbia-Suicide Severity Rating Scale (C-SSRS).

| End point title | Change from Baseline in Suicidal Ideation Intensity Total Score based on Columbia-Suicide Severity Rating Scale (C-SSRS).[11] |
|---|---|

End point description:

The C-SSRS consists of a baseline evaluation that assesses the lifetime experience of the participant with suicide events and suicidal ideation and a post baseline/"since last visit" evaluation that focuses on suicidality since the last trial visit. The C-SSRS data at Baseline and post baseline were summarized for incidence of reporting: Suicidality, Suicidal behavior (and its 4 types), Suicidal ideation (and its 5 types). The intensity score of each item ranges from 1 (least severe) to 5 (most severe), which leads to the range of the total score from 0 to 25.

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

End point timeframe:

Baseline, Weeks 1, 2, 4, 8, 12, 20, 28, 36, 44, 52, and Last visit

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: Not performed

| End point values | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 1 (N=108) | -0.1 (± 0.7) | | | |
| Week 2 (N=106) | 0 (± 0.5) | | | |
| Week 4 (N=107) | 0 (± 0.8) | | | |
| Week 8 (N=105) | -0.1 (± 0.8) | | | |
| Week 12 (N=104) | 0 (± 0.5) | | | |
| Week 20 (N=100) | -0.1 (± 0.5) | | | |
| Week 28 (N=92) | 0.1 (± 1) | | | |

| | | | | |
|---|---|---|---|---|
| Week 36 (N=88) | 0.1 (± 1.3) | | | |
| Week 44 (N=82) | 0 (± 0) | | | |
| Week 52 (N=77) | 0.2 (± 1.3) | | | |
| Last vist (N=110) | 0 (± 1.3) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Change from Baseline in average score of attention deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD) of Swanson, Nolan, and Pelham-IV Rating Scale (SNAP-IV).**

| End point title | Change from Baseline in average score of attention deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD) of Swanson, Nolan, and Pelham-IV Rating Scale (SNAP-IV).[12] |
|---|---|

End point description:

The SNAP-IV Rating Scale is a revision of the SNAP Questionnaire. The SNAP-IV assesses inattention and hyperactivity/impulsivity, as well as oppositional defiant disorder that are often present in children with ADD/ADHD. The SNAP-IV was administered as a semi-structured interview with the participant and caregiver. The SNAP-IV is based on a 0 to 3 rating scale: not at all = 0, just a little = 1, quite a bit = 2, and very much = 3. The ADD/ADHD subscale includes items 1 through 19 (items 1–9 measure inattention, items 11–19 measure hyperactivity/ impulsivity, and item 10 for inattention domain), items 4, 8, 11, 31, and 32 measure inattention/overactivity, and items 21, 23, 29, 34, and 35 measure aggression/defiance. Items 4, 8, 11, 21, 32, 33, 36, 37, 38, and 39 form the Conners Index.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, and Last visit

Notes:

[12] - 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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (N=107) | -0.2 (± 0.4) | | | |
| Week 8 (N=105) | -0.2 (± 0.4) | | | |
| Week 12 (N=104) | -0.3 (± 0.4) | | | |
| Week 20 (N=100) | -0.2 (± 0.4) | | | |
| Week 28 (N=92) | -0.2 (± 0.4) | | | |
| Week 36 (N=88) | -0.2 (± 0.4) | | | |
| Week 44 (N=82) | -0.2 (± 0.4) | | | |
| Week 52 (N=77) | -0.2 (± 0.4) | | | |
| Last vist (N=109) | -0.2 (± 0.5) | | | |

**Statistical analyses**

No statistical analyses for this end point

## Primary: Change from Baseline in Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

| End point title | Change from Baseline in Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).[13] |
|---|---|

End point description:

The CY-BOCS is a semi-structured interview used with children and adolescents aged 6 to 17 years to rate the severity and type of symptoms in participants with obsessive compulsive disorder. In general, the items depend on the participant's report; however, the final rating is based on the clinical judgment of the interviewer and should include additional information supplied by others. Nineteen items are rated in the CY-BOCS, but only items 1 through 10 (excluding items 1b and 6b) are used to determine the total score. The total CY-BOCS score is the sum of items 1 through 10 (excluding lb and 6b), whereas the obsession and compulsion subtotals are the sums of items 1 through 5 (excluding lb) and 6 through 10 (excluding 6b), respectively.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, and Last visit

Notes:

[13] - 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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (N=107) | -0.2 (± 2.6) | | | |
| Week 8 (N=105) | -0.1 (± 3) | | | |
| Week 12 (N=104) | -0.5 (± 2.7) | | | |
| Week 20 (N=100) | -0.6 (± 3) | | | |
| Week 28 (N=92) | -0.5 (± 3.3) | | | |
| Week 36 (N=88) | -0.7 (± 3.4) | | | |
| Week 44 (N=82) | -0.8 (± 3.7) | | | |
| Week 52 (N=77) | -0.9 (± 3.9) | | | |
| Last vist (N=109) | -0.7 (± 3.4) | | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Children's Depression Rating Scale - Revised (CDRS-R).

| End point title | Change from Baseline in Children's Depression Rating Scale - Revised (CDRS-R).[14] |
|---|---|

End point description:

Modeled after the Hamilton Rating Scale for Depression, the CDRS-R has long been used to diagnose depression and determine its severity. The CDRS-R is a brief rating scale based on a semi-structured interview with the child and an adult informant who knows the child well. Designed for 6- to 12-year-old children, and successfully used with adolescents, it can be administered in 15 to 20 minutes. The interviewer rates 17 symptom areas (including those that serve as Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision criteria for a diagnosis of depression): impaired

schoolwork, difficulty having fun, social withdrawal, appetite disturbance, sleep disturbance, excessive fatigue, physical complaints, irritability, excessive guilt, low self-esteem, depressed feelings, morbid ideas, suicidal ideas, excessive weeping, depressed facial affect, listless speech, and hypoactivity.

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

End point timeframe:

Baseline, Weeks 4, 8, 12, 20, 28, 36, 44, 52, and Last visit

Notes:

[14] - 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: Not performed

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 109 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (N=104) | -0.4 (± 4.4) | | | |
| Week 8 (N=100) | -0.4 (± 3.8) | | | |
| Week 12 (N=100) | -0.3 (± 3.2) | | | |
| Week 20 (N=97) | -0.1 (± 4.2) | | | |
| Week 28 (N=91) | 0.2 (± 5) | | | |
| Week 36 (N=87) | 0.4 (± 4.4) | | | |
| Week 44 (N=82) | -0.3 (± 3.3) | | | |
| Week 52 (N=77) | 0.6 (± 3.8) | | | |
| Last vist (N=107) | 0.7 (± 4.5) | | | |

**Statistical analyses**

No statistical analyses for this end point

**Primary: Change from Baseline in Pediatric Anxiety Rating Scale (PARS).**

| End point title | Change from Baseline in Pediatric Anxiety Rating Scale |
|---|---|

| End point values | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (N=107) | -0.3 (± 3) | | | |
| Week 8 (N=105) | -0.3 (± 3.6) | | | |
| Week 12 (N=104) | -0.5 (± 2.6) | | | |
| Week 20 (N=100) | -0.4 (± 2.9) | | | |
| Week 28 (N=91) | -0.2 (± 3.1) | | | |
| Week 36 (N=88) | -0.7 (± 3) | | | |
| Week 44 (N=82) | -0.5 (± 2.7) | | | |
| Week 52 (N=77) | -0.4 (± 3.5) | | | |
| Last vist (N=109) | -0.4 (± 3.5) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to endpoint on the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS).

| End point title | Change from Baseline to endpoint on the Total Tic Score (TTS) of the Yale Global Tic Severity Scale (YGTSS). |
|---|---|

End point description:

The YGTSS is a semi-structured clinical interview designed to measure current tic severity. This scale consists of a tic inventory, with 5 separate ratings to assess the number, intensity, frequency, complexity and interference of tics, plus an overall impairment/disability score. The YGTSS is a validated measurement that has been widely used in clinical trials, has been demonstrated to be sensitive to treatment effects, and represents the “reference standard” in paediatric tic assessment. Ratings are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each, including number, frequency, intensity, complexity, and interference. Summation of these 10 scores (ie, 0-50) provides a TTS that was the secondary outcome measure in this trial. The YGTSS ranking of impairment, with a maximum of 50 points, is based on the impact of the tic disorder on areas of self-esteem, family life, social acceptance, and school scores.

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

End point timeframe:

Baseline to Week 52

| End point values | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 52 (N=77) | -8.6 (± 10.2) | | | |
| Last visit (N=109) | -6.6 (± 10.9) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Clinical Global Impressions for Tourette's Syndrome (CGI-TS) change score at endpoint.

| | |
|---|---|
| End point title | Mean Clinical Global Impressions for Tourette's Syndrome (CGI-TS) change score at endpoint. |

End point description:

The CGI is a 7-point Likert scale used in a multitude of clinical trials as a clinical global measure to assess the severity and change in disease symptomatology (ie, tics). The CGI was included as a secondary scale to provide a more complete assessment of clinical efficacy. The CGI-TS change score obtained from CGI-TS improvement scale assessment. The CGI-TS improvement scale was rated in reference to the participant's baseline condition at the time of entry into the open-label study rather than the CGI-TS baseline condition at the time the participant enrolled into the parent trial. Response choices were 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

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

End point timeframe:

Baseline to Week 52

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 52 (N=77) | 2.5 (± 1.6) | | | |
| Last visit (N=109) | 2.5 (± 1.6) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline to endpoint in CGI-TS severity of illness score.

| | |
|---|---|
| End point title | Change from Baseline to endpoint in CGI-TS severity of illness score. |

End point description:

The CGI is a 7-point Likert scale used in a multitude of clinical trials as a clinical global measure to assess the severity and change in disease symptomatology (ie, tics). The CGI was included as a secondary scale to provide a more complete assessment of clinical efficacy.

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

| End point timeframe: |
|---|
| Baseline to Week 52 |

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 52 (N=77)<br>Last visit (N=109) | -0.9 (± 1.2)<br>-0.7 (± 1.3) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change from Baseline to endpoint in Total YGTSS score.

| End point title | Mean change from Baseline to endpoint in Total YGTSS score. |
|---|---|

End point description:

The YGTSS consists of a tic inventory, with 5 separate rating scales to rate the severity of symptoms (on a scale of 0 to 5 for 5 different dimensions, including number, frequency, intensity, complexity, and interference) for motor and vocal tics, and an impairment ranking. The YGTSS TTS is the summation of the severity scores of motor and vocal tics (range of 0 to 50). The total YGTSS score is the summation of the severity scores of motor and vocal tics and the ranking of impairment (total score range of 0 to 100).

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

| End point timeframe: |
|---|
| Baseline to Week 52 |

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 52 (N=77)<br>Last visit (N=109) | -18 (± 23.7)<br>-14 (± 24.3) | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with response (response rate).

| End point title | Percentage of participants with response (response rate). |
|---|---|
| End point description: | |
| Clinical response was defined as > 25% improvement from Baseline to endpoint in YGTSS TTS or a CGI-TS change score of 1 (very much improved) or 2 (much improved) at endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| Weeks 4, 8, 12, 20, 28, 36, 44 and 52 | |

| **End point values** | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Percentage of participants with response | | | | |
| number (not applicable) | | | | |
| Week 4 (N=107) | 80.4 | | | |
| Week 8 (N=105) | 81.9 | | | |
| Week 12 (N=104) | 82.7 | | | |
| Week 20 (N=100) | 75 | | | |
| Week 28 (N=92) | 77.2 | | | |
| Week 36 (N=88) | 75 | | | |
| Week 44 (N=81) | 75.3 | | | |
| Week 52 (N=77) | 67.5 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with treatment discontinuation (treatment discontinuation rate).

| End point title | Percentage of participants with treatment discontinuation (treatment discontinuation rate). |
|---|---|
| End point description: | |
| The treatment discontinuation rate was calculated as the number of discontinued participants (ie, those withdrawn from the study without completing the Week 52 visit) divided by the number of all enrolled participants. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 52 | |

| End point values | Open-label Aripiprazole | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 | | | |
| Units: Percentage of discontinued participants | | | | |
| number (not applicable) | 31.8 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Day 0 (Baseline) until Follow-up 30 Days (±3 days) after the last trial visit. | |
| Assessment type | Non-systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |
| **Reporting groups** | |
| Reporting group title | Open-label Aripiprazole |
| Reporting group description: | |
| All participants in this open-label extension trial were assigned to once-daily aripiprazole, which was flexibly dosed at the discretion of the investigator on the basis of treatment response and medication tolerability. | |

| Serious adverse events | Open-label Aripiprazole | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 110 (3.64%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intentional overdose | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Tourette's disorder | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious mononucleosis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | Open-label Aripiprazole | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 84 / 110 (76.36%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 11 / 110 (10.00%) | | |
| occurrences (all) | 12 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Irritability | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 3 | | |
| Malaise | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 110 (6.36%) | | |
| occurrences (all) | 8 | | |
| Immune system disorders | | | |

| | | | |
|---|---|---|---|
| House dust allergy | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Multiple allergies | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 3 | | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 3 | | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 4 | | |
| Hiccups | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 2 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 3 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 4 | | |
| Sleep apnoea syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Vocal cord disorder | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Aggression | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 4 | | |
| Agitation | | | |
| subjects affected / exposed | 4 / 110 (3.64%) | | |
| occurrences (all) | 6 | | |
| Anger | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Anxiety | | | |
| subjects affected / exposed | 6 / 110 (5.45%) | | |
| occurrences (all) | 6 | | |
| Attention deficit/hyperactivity disorder | | | |
| subjects affected / exposed | 5 / 110 (4.55%) | | |
| occurrences (all) | 6 | | |
| Blunted affect | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Bruxism | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Depression | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 3 | | |
| Depressed mood | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Emotional disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Emotional poverty | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Flat affect | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Head banging | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Initial insomnia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 3 | | |
| Mood altered | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Obsessive-compulsive disorder | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Restlessness | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Somnambulism | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 3 | | |
| TIC | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 110 (5.45%) | | |
| occurrences (all) | 9 | | |
| Investigations | | | |
| Bilirubin conjugated increased | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Protein urine present | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Weight increased | | | |
| subjects affected / exposed | 26 / 110 (23.64%) | | |
| occurrences (all) | 27 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Animal bite | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Hand fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Patella fracture | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Akathisia | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 3 | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 110 (4.55%) | | |
| occurrences (all) | 6 | | |
| Dyskinesia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Dystonia | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Headache | | | |
| subjects affected / exposed | 11 / 110 (10.00%) | | |
| occurrences (all) | 12 | | |
| Migraine | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Migraine with aura | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Excessive eye blinking | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Eye inflammation | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Strabismus | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Vision blurred | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 2 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 2 | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 4 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 3 | | |
| Dry mouth | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Eructation | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 2 | | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 8 / 110 (7.27%) | | |
| occurrences (all) | 9 | | |
| Retching | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 110 (9.09%) | | |
| occurrences (all) | 12 | | |
| Hepatobiliary disorders | | | |
| Hepatitis acute | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Urinary hesitation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |
| Ear infection | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 5 / 110 (4.55%) | | |
| occurrences (all) | 5 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 4 / 110 (3.64%) | | |
| occurrences (all) | 5 | | |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 4 | | |
| Localised infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 11 / 110 (10.00%) | | |
| occurrences (all) | 12 | | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis streptococcal | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 2 | | |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 110 (4.55%) | | |
| occurrences (all) | 5 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 110 (3.64%) | | |
| occurrences (all) | 4 | | |
| Viral infection | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |
| Viral rash | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Hyperinsulinaemia | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | | |
| occurrences (all) | 2 | | |

| | | | |
|---|---|---|---|
| Increased appetite | | | |
| subjects affected / exposed | 6 / 110 (5.45%) | | |
| occurrences (all) | 6 | | |
| Insulin resistance | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | | |
| occurrences (all) | 1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 26 October 2012 | A summary of the single amendment to the protocol is provided below:<br>Added dose groups to match Trial 31-12-293; Removed Gilles de la Tourette Syndrome Quality of Life Scale assessments; Specified the entire SNAP-IV Rating Scale was to be used, rather than only the ADHD subscales; Changed the titration schedule; Clarified guidelines on the concomitant use of benzodiazepines; Added an inclusion criterion that only subjects who completed Trial 31-12-293 could be enrolled. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported