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
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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 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 Units: years			
arithmetic mean	11.7		
standard deviation	± 2.9	-	
Gender categorical 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 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)				
Participants with TEAEs	84			
Participants with severe TEAEs	5			
Participants with serious TEAEs	4			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with clinically significant abnormal laboratory test results.

End point title	Percentage of participants with clinically significant abnormal laboratory test results.[2]

End point description:

Laboratory tests including hematology, serum chemistry, and urinalysis were performed for all the participants. The central laboratory was used for all laboratory testing whenever possible. Any value outside the normal range was flagged for the attention of the study physician who was to indicate

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 description:

The PARS is used to rate the severity of anxiety in children and adolescents, aged 6 to 17 years. The PARS has 2 sections: the symptom checklist and the severity items. The symptom checklist is used to determine the child’s repertoire of symptoms during the past week. The 7-item severity list is used to determine severity of symptoms and the PARS total score. The time frame for the PARS is the past week. Only those symptoms endorsed for the past week are included in the symptom checklist and rated on the severity items. The PARS total severity score was the sum of items 2, 3, 5, 6, and 7. Codes “8” (Not applicable) and “9” (Does not know) are equivalent to 0 in the summation. The total severity score ranged from 0 to 25.

End point type	Primary

End point timeframe:

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

Notes:

[15] - 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)	-0.3 (± 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)	-0.9 (± 1.2)			
Last visit (N=109)	-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)	-18 (± 23.7)			
Last visit (N=109)	-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%)		
occurrences (all)	1		
Paresthesia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Sedation			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	6		
Somnolence			
subjects affected / exposed	13 / 110 (11.82%)		
occurrences (all)	14		
Syncope			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Middle ear effusion			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences (all)	1		
Tympanic membrane perforation			

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 occurrences (all)	1 / 110 (0.91%) 1		
Eructation subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 2		
Flatulence subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Nausea subjects affected / exposed occurrences (all)	8 / 110 (7.27%) 9		
Retching subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Salivary hypersecretion subjects affected / exposed occurrences (all)	2 / 110 (1.82%) 3		
Vomiting subjects affected / exposed occurrences (all)	10 / 110 (9.09%) 12		
Hepatobiliary disorders Hepatitis acute subjects affected / exposed occurrences (all)	 1 / 110 (0.91%) 1		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 1 / 110 (0.91%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 1 / 110 (0.91%) 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 occurrences (all)	6 / 110 (5.45%) 6		
Insulin resistance subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Iron deficiency subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 1		
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 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: 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