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

Summary

EudraCT number	2011-000469-11
Trial protocol	DE BG RO HU
Global end of trial date	13 March 2014

Results information

Result version number	v2 (current)
This version publication date	18 March 2016
First version publication date	16 August 2015
Version creation reason	• Correction of full data set Minor corrections to units

Trial information

Trial identification

Sponsor protocol code	31-10-274

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01416441
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., +1 609 524 6790, Eva.Kohegyi@otsuka-us.com
Scientific contact	Eva Kohegyi, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524 6790, 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	02 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2014
Global end of trial reached?	Yes
Global end of trial date	13 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the long-term safety and tolerability of aripiprazole once-weekly treatment with oral tablets in children and adolescents (7 to 17 years) with a diagnosis of Tourette's Disorder.

Protection of trial subjects:

The trial was conducted 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), and informed assent form (IAF) 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	19 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 15
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	Ukraine: 21
Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Romania: 8
Worldwide total number of subjects	170
EEA total number of subjects	30

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)	66
Adolescents (12-17 years)	99
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 170 participants at 79 trial sites in 10 countries.

Pre-assignment

Screening details:

Participants who had successfully completed either of the randomized, double-blind, placebo-controlled studies of once-weekly aripiprazole (studies 2011-000467-27 and 2011-000468-83) were eligible to enter this 52-week open-label extension trial as judged by the study physician and there had been no significant protocol violations or adverse events

Period 1

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

Blinding implementation details:

Not applicable as this was an open-label trial.

Arms

Arm title	Aripiprazole

Arm description:

All participants were administered oral aripiprazole tablets once weekly (QW) with a titrated dose starting from 52.5 milligram (mg), on Day 1 and increasing to 77.5 mg and 110 mg for the remainder of the trial, the dose could be adjusted between these 3 dose levels as determined by investigator discretion.

Arm type	Experimental
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	
Other name	Aripiprazole enteric-coated extended-release (ECER) Tablets, Abilify, OPC-14597
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Once-weekly formulation of aripiprazole as a flexible-dose regimen

Number of subjects in period 1	Aripiprazole
Started	170
Completed	89
Not completed	81
Physician decision	2
Consent withdrawn by subject	12
Adverse events	6
Sponsor discontinued trial	43
Met withdrawal criteria	10
Lost to follow-up	5

Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Aripiprazole
Reporting group description:	
All participants were administered oral aripiprazole tablets once weekly (QW) with a titrated dose starting from 52.5 milligram (mg), on Day 1 and increasing to 77.5 mg and 110 mg for the remainder of the trial, the dose could be adjusted between these 3 dose levels as determined by investigator discretion.	

Reporting group values	Aripiprazole	Total	
Number of subjects	170	170	
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	12.2		
standard deviation	± 2.9	-	
Gender categorical Units: Subjects			
Female	45	45	
Male	125	125	

End points

End points reporting groups

Reporting group title	Aripiprazole

Reporting group description:

All participants were administered oral aripiprazole tablets once weekly (QW) with a titrated dose starting from 52.5 milligram (mg), on Day 1 and increasing to 77.5 mg and 110 mg for the remainder of the trial, the dose could be adjusted between these 3 dose levels as determined by investigator discretion.

Primary: Number of participants with clinically significant abnormal laboratory test results

End point title	Number of participants with clinically significant abnormal laboratory test results[1]

End point description:

The laboratory values were one of the parameters to measure the safety and tolerability of individual participants. Participants with potentially clinically significant lab values in serum chemistry, hematology, urinalyses and prolactin tests that were identified based on pre-defined criteria. Any value outside the normal range was flagged for the attention of the investigator who must indicate whether or not a flagged value is of clinical significance.

End point type	Primary

End point timeframe:

Baseline to Last 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Number of participants				
number (not applicable)				
Chemistry-Alkaline phosphatase (N= 164)	0			
Chemistry-Alanine aminotransferase (N= 164)	1			
Chemistry-Aspartate aminotransferase (N= 164)	1			
Chemistry-Bilirubin, total (N= 164)	4			
Chemistry-Calcium (N= 164)	0			
Chemistry-Chloride (N= 164)	0			
Chemistry-Creatine phosphokinase (N= 164)	4			
Chemistry-Creatinine (N= 164)	0			
Chemistry-Glucose (N= 58)	1			
Chemistry-Glucose, fasting (N= 146)	1			
Chemistry-HDL cholesterol, fasting (N= 145)	3			
Chemistry-Lactic dehydrogenase (N= 164)	1			
Chemistry-LDL-Cholesterol, fasting (N= 145)	2			

Chemistry-potassium (N= 164)	0			
Chemistry-sodium (N= 164)	0			
Chemistry- Triglycerides, fasting (N= 145)	19			
Chemistry- Urea nitrogen (N= 164)	0			
Chemistry-Uric acid (N= 164)	0			
Urinalysis-Glucose, urine (N= 156)	3			
Urinalysis-Protein, urine (N= 156)	1			
Other-Prolactin (N= 159)	3			
Haematology-Eosinophils (N= 163)	3			
Haematology-Hematocrit (N= 142)	0			
Haematology-Hemoglobin (N= 163)	3			
Haematology-Neutrophils (N= 163)	0			
Haematology-Platelet count (N= 163)	0			
Haematology-White blood count (N= 163)	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with clinically significant vital signs

End point title	Number of participants with clinically significant vital signs[2]

End point description:

Vital signs assessments included orthostatic (supine and standing) blood pressure (BP) measured as millimeter of mercury [mmHg]), heart rate, (measured in beats per minute [bpm]), boy weight (measured in kilograms [kg]) and body temperature. Incidence of clinically relevant abnormal values in heart rate, systolic and diastolic blood pressure and weight were identified based on pre-defined criteria. Orthostatic assessments of blood pressure and heart rate were made after the participant has been supine for at least 5 minutes and again after the participant has been standing for approximately 2 minutes, but not more than 3 minutes.

End point type	Primary

End point timeframe:

Baseline to Last Visit

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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Number of participants				
number (not applicable)				
Heart rate supine-increase ≥15 bpm (N= 168)	1			
Heart rate supine-decrease ≥15 bpm (N= 168)	0			
Heart rate standing-increase ≥15 bpm (N= 167)	4			
Heart rate standing-decrease ≥15 bpm (N= 167)	0			

Systolic supine BP-increase ≥20 mmHg (N= 168)	0			
Systolic supine BP-decrease ≥20 mmHg (N= 168)	1			
Systolic standing BP-increase ≥20 mmHg (N= 167)	0			
Systolic standing BP-decrease ≥20 mmHg (N= 167)	1			
Diastolic supine BP-increase ≥15 mmHg (N= 168)	0			
Diastolic supine BP-decrease ≥15 mmHg (N= 168)	0			
Diastolic standing BP-increase ≥15 mmHg (N= 167)	1			
Diastolic standing BP-decrease ≥15 mmHg (N= 167)	0			
Orthostatic hypotension (N= 169)	2			
Weight-gain ≥ 7% (N= 166)	82			
Weight-loss ≥ 7% (N= 166)	6			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with clinically significant electrocardiogram (ECG)

End point title	Number of participants with clinically significant electrocardiogram (ECG)[3]

End point description:

The ECG was one of the parameters to measure the safety and tolerability of individual participants. Incidence of clinically relevant abnormal ECG values in were identified based on pre-defined criteria. Twelve (12)-lead ECGs were recorded at Baseline Visit, Weeks 4, 12, 24, and 52. At each required visit, 3 ECG recordings were performed. Each ECG was obtained approximately 5 minutes apart and the average of all assessments.

End point type	Primary

End point timeframe:

Baseline to Last Visit

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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Number of participants				
number (not applicable)				
Tachycardia (N= 154)	1			
Bradycardia (N= 154)	0			
Sinus tachycardia (N= 154)	1			
Sinus bradycardia (N= 154)	0			
Supraventricular premature beat (N= 154)	4			
Ventricular premature beat (N= 154)	3			
Supraventricular tachycardia (N= 154)	0			

Ventricular tachycardia (N= 154)	0			
Atrial fibrillation (N= 154)	0			
Atrial flutter (N= 154)	0			
Primary atrioventricular block (N= 154)	0			
Secondary atrioventricular block (N= 154)	0			
Tertiary atrioventricular block (N= 154)	0			
Left bundle branch block (N= 154)	0			
Right bundle branch block (N= 154)	2			
Pre-excitation syndrome (N= 154)	0			
Other intraventricular conduction block (N= 154)	0			
Acute or sub-acute infarction (N= 154)	0			
Old infarction (N= 154)	0			
Myocardial ischemia (N= 154)	0			
Symmetrical T-wave inversion (N= 154)	1			
QTcB (N= 154)	3			
QTcF (N= 154)	0			
QTcN (N= 154)	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with suicidality and suicidal ideation as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)

End point title	Number of participants with suicidality and suicidal ideation as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)[4]

End point description:

Suicidality was defined as reporting at least one occurrence of any suicidal behavior or suicidal ideation. Suicidal behavior was defined as reporting any type of suicidal behaviors (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior). Suicidal ideation was defined as reporting any type of suicidal ideation. The suicidal ideation intensity total score is the sum of intensity scores of 5 items (frequency, duration, controllability, deterrents, and reasons for ideation). The score of each intensity item ranges from 0 (none) to 5 (worst) which leads to the range of the total score from 0 to 25. A missing score of any item resulted in a missing total score. If no suicidal ideation was reported, a score of 0 was given to the intensity scale.

End point type	Primary

End point timeframe:

Baseline to Last Visit

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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Number of participants				
number (not applicable)				
Emergence of suicidal ideation (N= 167)	3			
TEAEs related to suicide (N= 170)	3			

Suicidality and suicidal ideation (N= 169)	4			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from Baseline in Abnormal Involuntary Movement Scale (AIMS)

End point title	Mean change from Baseline in Abnormal Involuntary Movement Scale (AIMS)[5]

End point description:

The AIMS Scale is an extrapyramidal symptoms (EPS) rating scale. The AIMS is a 12 item scale. The first 10 items e.g. facial and oral movements (items 1-4), extremity movements (items 5 and 6), trunk movements (item 7), investigators global assessment of dyskinesia (items 8 to 10) are rated from 0 to 4 (0=best, 4=worst). Items 11 and 12, related to dental status, have dichotomous responses, 0=no and 1=yes. The AIMS Total Score is the sum of the ratings for the first seven items. The possible total scores are from 0 to 28.

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	-0.1 (± 1.3)			
Week 8 (N= 158)	-0.1 (± 1.6)			
Week 12 (N= 152)	-0.4 (± 1.7)			
Week 16 (N= 147)	-0.5 (± 2)			
Week 20 (N= 134)	-0.5 (± 2)			
Week 24 (N= 123)	-0.6 (± 2.5)			
Week 32 (N= 114)	-0.8 (± 2.3)			
Week 40 (N= 104)	-0.8 (± 2.4)			
Week 52 (N= 90)	-0.9 (± 2.4)			
Last Visit (N= 168)	-0.8 (± 2.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from Baseline in Simpson Angus Scale (SAS)

End point title	Mean change from Baseline in Simpson Angus Scale (SAS)[6]

End point description:

The SAS is a rating scale used to measure EPS. The SAS scale 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), with each item rated from 0 to 4, with 0 being normal and 4 being the worst. The SAS Total score is sum of ratings for all 10 items, with possible Total scores from 0 to 40.

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	0 (± 0.3)			
Week 8 (N= 158)	0 (± 0.4)			
Week 12 (N= 152)	0 (± 0.3)			
Week 16 (N= 147)	0 (± 0.4)			
Week 20 (N= 134)	0 (± 0.2)			
Week 24 (N= 123)	0 (± 0.5)			
Week 32 (N= 114)	0 (± 0.4)			
Week 40 (N= 104)	0 (± 0.5)			
Week 52 (N= 89)	0 (± 0.5)			
Last Visit (N= 168)	0 (± 0.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from Baseline in Barnes Akathisia Rating Scale (BARS)

End point title	Mean change from Baseline in Barnes Akathisia Rating Scale (BARS)[7]

End point description:

The BARS was an EPS rating scale. The BARS was used to assess the presence and severity of akathisia. This scale consists of 4 items. Only the 4th item, the Global Clinical Assessment of Akathisia, was evaluated in this trial. This item is rated on a 6 point scale, with 0 being best (absent) and 5 being worst (severe akathisia).

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	0 (± 0.3)			
Week 8 (N= 158)	0 (± 0.2)			
Week 12 (N= 152)	0 (± 0.2)			
Week 16 (N= 147)	0 (± 0.2)			
Week 20 (N= 134)	0 (± 0.2)			
Week 24 (N= 123)	0 (± 0.1)			
Week 32 (N= 114)	0 (± 0.2)			
Week 40 (N= 104)	0 (± 0.2)			
Week 52 (N= 90)	0 (± 0.3)			
Last Visit (N= 168)	0 (± 0.3)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from Baseline in average score of Attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD) sub-scale of the Swanson, Nolan and Pelham-IV (SNAP-IV)

End point title	Mean change from Baseline in average score of Attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD) sub-scale of the Swanson, Nolan and Pelham-IV (SNAP-IV)[8]

End point description:

The SNAP-IV Rating Scale includes items to assess inattention and hyperactivity/impulsivity of ADD/ADHD and also items to assess Oppositional Defiant disorder. Each SNAP-IV item is rated on a 0 to 3 scale: Not at All = 0, Just A Little = 1, Quite A Bit = 2, and Very Much = 3. Subscale average scores on the SNAP-IV are calculated by summing the scores on the items in the subset and dividing by the number of items in the subset. The ADD/ADHD subscale includes items 1 to 19 (items 1 to 9 measure inattention, items 11 to 19 measure hyperactivity/impulsivity, and item 10 for inattention domain), items 4, 8, 11, 31, and 32 measuring inattention/overactivity, and items 21, 23, 29, 34, and 35 measuring aggression/defiance. Items 4, 8, 11, 21, 32, 33, 36, 37, 38, and 39 form the Conners Index. If there are missing values for the item scales, the average score will be computed using the rest of the non-missing item scales in the subset.

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	-0.1 (± 0.3)			
Week 8 (N= 158)	0 (± 0.3)			

Week 12 (N= 152)	-0.1 (± 0.3)			
Week 16 (N= 147)	-0.1 (± 0.4)			
Week 20 (N= 134)	-0.1 (± 0.3)			
Week 24 (N= 123)	-0.2 (± 0.4)			
Week 32 (N= 114)	-0.2 (± 0.4)			
Week 40 (N= 104)	-0.2 (± 0.4)			
Week 52 (N= 90)	-0.1 (± 0.4)			
Last Visit (N= 168)	-0.1 (± 0.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from Baseline in Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) total score

End point title	Mean change from Baseline in Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) total score[9]

End point description:

The CY-BOCS is used to assess characteristics of obsession and compulsion for the week prior to the interview. Nineteen items are rated in the CY-BOCS, but the total score is the sum of only items 1 to 10 (excluding items 1b and 6b). The obsession and compulsion subtotals are the sums of items 1 to 5 (excluding 1b) and 6 to 10 (excluding 6b), respectively. A missing value for any CY-BOCS item scale could result in a missing total score or obsession and compulsion subtotals of which the item scale is a component. At baseline, the full CY-BOCS interview is conducted. At all post-baseline time points, the "Questions on Obsessions" (items 1 to 5) and "Questions on Compulsions" (items 6 to 10) are reviewed and the target symptoms identified at baseline are the primary focus for rating severity.

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	-0.2 (± 1.6)			
Week 8 (N= 158)	-0.2 (± 1.9)			
Week 12 (N= 152)	-0.3 (± 1.8)			
Week 16 (N= 147)	-0.4 (± 1.9)			
Week 20 (N= 134)	-0.4 (± 2)			
Week 24 (N= 123)	-0.5 (± 2.2)			
Week 32 (N= 114)	-0.6 (± 2.5)			
Week 40 (N= 104)	-0.6 (± 2.4)			
Week 52 (N= 90)	-0.3 (± 2.4)			
Last Visit (N= 168)	-0.3 (± 2.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from Baseline in Children's Depression Rating Scale Revised (CDRS-R)

End point title	Mean change from Baseline in Children's Depression Rating Scale Revised (CDRS-R)[10]

End point description:

The CDRS-R is composed of 17 interviewer-rated symptom areas: 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. The CDRS-R total score is the sum of scores for the 17 symptom areas. A missing value for any CDRS-R item scale or a not rated item scale (indicated by the value of 0) could result in a missing total score.

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	0 (± 2.3)			
Week 8 (N= 158)	0 (± 2.6)			
Week 12 (N= 152)	-0.2 (± 3.1)			
Week 16 (N= 147)	-0.4 (± 2.9)			
Week 20 (N= 134)	-0.3 (± 3.1)			
Week 24 (N= 123)	-0.2 (± 2.5)			
Week 32 (N= 114)	-0.1 (± 2.8)			
Week 40 (N= 104)	-0.4 (± 2.7)			
Week 52 (N= 90)	-0.2 (± 3.3)			
Last Visit (N= 168)	0.3 (± 4.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from Baseline in Pediatric Anxiety Rating Scale (PARS) total severity score

End point title	Mean change from Baseline in Pediatric Anxiety Rating Scale (PARS) total severity score[11]

End point description:

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. Information is elicited from the child and parent(s) and the rater then combines information from all informants using his/her best judgment. The 7-item severity list is used to determine severity of symptoms and the PARS total score. The time frame for the PARS rating 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 is the sum of items 2, 3, 5, 6, and 7. The total severity score ranges from 0 to 25. Codes "8" (Not applicable) and "9" (Does not know) are not included in the summation (ie, equivalent to a score of 0 in the summation).

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 165)	-0.1 (± 2.6)			
Week 8 (N= 158)	-0.2 (± 2.4)			
Week 12 (N= 152)	-0.3 (± 1.8)			
Week 16 (N= 151)	-0.3 (± 2)			
Week 20 (N= 134)	-0.3 (± 2.1)			
Week 24 (N= 125)	-0.3 (± 2.3)			
Week 32 (N= 116)	-0.3 (± 2.4)			
Week 40 (N= 111)	-0.6 (± 2.3)			
Week 52 (N= 90)	-0.7 (± 2.4)			
Last Visit (N= 168)	-0.3 (± 2.6)			

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[12]

End point description:

Body weight was measured at, Baseline, Weeks 12 and 24, and the end-of-treatment visit.

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: kilogram				
arithmetic mean (standard deviation)				
Week 12 (N= 151)	1.4 (± 2.3)			
Week 24 (N= 123)	2.5 (± 3.9)			
Week 52 (N= 90)	4.7 (± 6)			
Last Visit (N= 166)	3.8 (± 5.1)			

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)[13]

End point description:

The BMI (kg/m2) was calculated from the Baseline height and the weight at the current visit using one of the following formulae, as appropriate: Weight (kg) divided by [Height (meters)]2.

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: KG/M²				
arithmetic mean (standard deviation)				
Week 12 (N= 150)	0.6 (± 0.9)			
Week 24 (N= 122)	0.4 (± 1.5)			
Week 52 (N= 90)	0.7 (± 2)			
Last Visit (N= 166)	0.6 (± 1.8)			

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[14]

End point description:

Waist circumference was measured at Baseline, Visit 1, and the end-of-treatment visit. Waist circumference was recorded before a participant's meal and at approximately the same time at each visit. Measurement was accomplished by locating the upper hip bone and the top of the right iliac crest

and placing the measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor assured that the tape was snug, but did not compress the skin, and is parallel to the floor. The measurement was made at the end of a normal exhalation

End point type	Primary

End point timeframe:

Baseline to 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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: centimeter				
arithmetic mean (standard deviation)				
Week 12 (N= 150)	0.4 (± 3.9)			
Week 24 (N= 122)	1 (± 5.2)			
Week 52 (N= 90)	2.3 (± 6.8)			
Last Visit (N= 166)	1.9 (± 5.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with adverse events (AEs)

End point title	Percentage of participants with adverse events (AEs)[15]

End point description:

An AE was defined as any untoward medical occurrence in a participant enrolled in a clinical trial and which did not necessarily have a causal relationship with the study medication. A treatment emergent adverse event (TEAE) was any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study medication, whether or not considered to have a causal relationship with the study medication. A serious-AE or reaction was any untoward occurrence that, at any dose, was fatal, life-threatening, required inpatient hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was any other medically significant event that, based on appropriate medical judgment, may have jeopardized the participant and may have required medical or surgical intervention to prevent one of the outcomes listed above.

End point type	Primary

End point timeframe:

AEs were reported from the signing of the informed consent until 30 days after the end of treatment

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: Statistical analysis was not performed for this endpoint

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: Number of participants				
number (not applicable)				
Participants with serious TEAEs	5			

Participants with severe TEAEs	8			
Participants discontinued medication	6			
Participants with TEAEs	104			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Yale Global Tic Severity Scale (YGTSS) total tic score

End point title	Mean change from Baseline in Yale Global Tic Severity Scale (YGTSS) total tic score

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 rating scales to rate the severity of symptoms, and an impairment ranking. 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 scores (ie, 0 to 50) provides a TTS that will be the primary outcome measure. 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. This is a fully validated scale in adults and has become a standard instrument for the evaluation of the severity of Tourette's Disorder in children.

End point type	Secondary

End point timeframe:

Baseline to Last Visit

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	-2.6 (± 5.4)			
Week 8 (N= 158)	-3.8 (± 5.6)			
Week 12 (N= 152)	-4.5 (± 6.7)			
Week 16 (N= 147)	-4.6 (± 6.8)			
Week 20 (N= 134)	-5.5 (± 7.2)			
Week 24 (N= 123)	-5.8 (± 7.9)			
Week 32 (N= 114)	-6 (± 9.1)			
Week 40 (N= 104)	-6.4 (± 9.3)			
Week 52 (N= 90)	-5.8 (± 8.8)			
Last Visit (N= 168)	-5.9 (± 8.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Clinical Global Impression for Tourette's

Syndrome (CGI-TS) severity of illness score

End point title	Mean change from Baseline in Clinical Global Impression for Tourette's Syndrome (CGI-TS) severity of illness score

End point description:

The severity of illness and efficacy of study drug for each participant was rated using the CGI-TS scale. To assess CGI-TS severity, the rater or investigator will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" However, the evaluation of illness will be limited to manifestations of Tourette's Disorder only. Response choices include: 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

End point type	Secondary

End point timeframe:

Baseline to Last Visit

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	0.2 (± 0.7)			
Week 8 (N= 158)	-0.4 (± 0.8)			
Week 12 (N= 152)	-0.4 (± 0.8)			
Week 16 (N= 147)	-0.5 (± 0.8)			
Week 20 (N= 134)	-0.6 (± 0.8)			
Week 24 (N= 123)	-0.5 (± 0.9)			
Week 32 (N= 114)	-0.6 (± 1)			
Week 40 (N= 104)	-0.7 (± 1.1)			
Week 52 (N= 90)	-0.7 (± 1.1)			
Last Visit (n= 168)	-0.6 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Gilles de la Tourette Quality of Life (GTS-QOL) overall score

End point title	Mean change from Baseline in Gilles de la Tourette Quality of Life (GTS-QOL) overall score

End point description:

The GTS-QOL is a disease-specific patient-reported scale for the measurement of health-related quality of life in patients with Tourette's Disorder, taking into account the complexity of the clinical picture of the disease. The questionnaire consists of a 27-item Tourette's Disorder-specific scale with 4 subscales (psychological, physical, obsessional, and cognitive).

End point type	Secondary

End point timeframe:

Baseline to Last Visit

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	-2.9 (± 8.2)			
Week 24 (N= 123)	-3.6 (± 11.3)			
Week 52 (N= 89)	-4.3 (± 10.5)			
Last Visit (N= 168)	-3.8 (± 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in total YGTSS score

End point title	Mean change from Baseline 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) of motor and vocal tics, and an impairment ranking. The Total YGTSS score is the summation of the severity scores of motor and vocal tics and also the ranking of impairment (range of 0 to 100). A missing value of a YGTSS item scale could result in a missing Total YGTSS score. A reduction in Total YGTSS score from baseline represents an improvement in symptoms.

End point type	Secondary

End point timeframe:

Baseline to Last Visit

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 4 (N= 163)	-5.6 (± 10.4)			
Week 8 (N= 158)	-7.4 (± 11.8)			
Week 12 (N= 152)	-8.6 (± 12.9)			
Week 16 (N= 147)	-9.4 (± 13.9)			
Week 20 (N= 134)	-10.7 (± 14.9)			
Week 24 (N= 123)	-10.4 (± 16)			
Week 32 (N= 114)	-11.6 (± 17.5)			
Week 40 (N= 104)	-12.6 (± 17.5)			
Week 52 (N= 90)	-10.8 (± 17.4)			
Last Visit (N= 168)	-11.4 (± 16.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate

End point title	Response rate

End point description:

Response rates (clinical response was defined as number of participants >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:

Baseline to Last Visit

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	168			
Units: percentage of participants				
number (not applicable)				
Week 4 (N= 163)	66.2			
Week 8 (N= 158)	69.7			
Week 12 (N= 152)	72.6			
Week 16 (N= 147)	72.3			
Week 20 (N= 134)	74.2			
Week 24 (N= 123)	71.8			
Week 32 (N= 114)	77.8			
Week 40 (N= 104)	80.8			
Week 52 (N= 90)	76.5			
Last Visit (N= 170)	71.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment discontinuation rate

End point title	Treatment discontinuation rate

End point description:

Treatment discontinuation rate was calculated as the number of participants who discontinued (i.e., those who were withdrawn from the study without completing the Week 53 visit).

End point type	Secondary

End point timeframe:
Baseline to Last Visit

End point values	Aripiprazole			
Subject group type	Reporting group			
Number of subjects analysed	170			
Units: percentage of participants				
number (not applicable)				
All reasons	47.6			
Other than sponsor discontinued study	22.4			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported from the signing of the informed consent until the follow-up visit

Adverse event reporting additional description:

Participants with AEs in multiple system organ classes were counted only once towards the total.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Aripiprazole

Reporting group description:

All participants were administered oral aripiprazole tablets once weekly (QW) with a titrated dose starting from 52.5 milligram (mg), 77.5 mg and 110 mg for a duration of 52-weeks beginning on the first day of the extension trial.

Serious adverse events	Aripiprazole		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 170 (2.94%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine phosphokinase increased			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Tourette's disorder			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Tremor			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 170 (0.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Aripiprazole		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 170 (33.53%)		

Investigations Weight increased subjects affected / exposed occurrences (all)	 14 / 170 (8.24%) 14		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	 19 / 170 (11.18%) 37 11 / 170 (6.47%) 56		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 10 / 170 (5.88%) 11 12 / 170 (7.06%) 13		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 12 / 170 (7.06%) 14 12 / 170 (7.06%) 17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2011	The primary reason for Protocol Amendment 1 was to include a participant treatment duration of 52 weeks to allow for a one-year exposure requirement for the safety evaluation. One additional study visit was incorporated for this purpose, and study visits were translated from "months" to "weeks" to assist sites with scheduling of participants visits. A clarification statement was added to allow participants turning 18 during the pivotal trial to be permitted to enter this open-label extension protocol. Other minor changes were made, including the correction of formatting issues.
14 February 2013	The protocol was modified to remove the option to allow participants who discontinued due to lack of efficacy to enter this open-label extension trial. Because more participants than anticipated were projected to this trial, the number of anticipated participants and the duration of the conduct of the study were increased. To clarify the protocol, new text was added describing exclusion of participants for QTc values > 450 msec. Inconsistencies within the protocol, such as the specification that the duration of follow-up was 30 (±3) days, were corrected to eliminate confusion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 March 2014	The trial was discontinued early based on the review of the recent data from placebo-controlled trial 31-10-272 (aripiprazole QW) relative to the results of placebo-controlled trial 31-12-293 (aripiprazole QD) in participants with TD. The aripiprazole QW formulation was found to be statistically superior to placebo in Trial 31-10-272, but the demonstrated efficacy was not as robust as that observed with the QD formulation in Trial 31-12-293. Therefore, Otsuka discontinued Trial 31-10-274 because the aripiprazole QW formulation was not pursued for the treatment of TD. Importantly, the trial closure was unrelated to any safety issues (no signals or items of concern have been identified).	-

Notes:

Limitations and caveats

None reported