



Clinical trial results:

A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-Dose Once-weekly Oral Aripiprazole in Children and Adolescents with Tourette's Disorder Summary

EudraCT number	2011-000468-83
Trial protocol	DE BG
Global end of trial date	12 March 2014

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	31-10-273
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, MD, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 609 524 6790, Eva.Kohegyi@otsuka-us.com
Scientific contact	Eva Kohegyi, MD, 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	08 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2014
Global end of trial reached?	Yes
Global end of trial date	12 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to compare the efficacy of aripiprazole with placebo in the suppression of tics in children and adolescents (7-17 years) with a diagnosis of Tourette's Disorder. The primary efficacy measure is change from Baseline to endpoint (Week 8) on the Total Tic score (TTS) of the Yale Global Tic Severity Scale (YGTSS). Secondary efficacy measures included Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) and Gilles de la Tourette Syndrome - Quality of Life Scale (GTS-QOL). The secondary objective was to evaluate the safety and tolerability of aripiprazole once-weekly treatment with oral tablets in children and adolescents with Tourette's Disorder.

Protection of trial subjects:

This trial was conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable local laws and regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 August 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	Romania: 15
Country: Number of subjects enrolled	Ukraine: 27
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Germany: 6
Worldwide total number of subjects	83
EEA total number of subjects	26

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)	39
Adolescents (12-17 years)	44
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 83 participants at 38 trial sites in the following 5 countries: Bulgaria, Germany, Romania, Ukraine, and the United States.

Pre-assignment

Screening details:

This trial consisted of 2 distinct phases: a pre-treatment phase and a treatment phase. The pre-treatment phase consisted of a screening period, a washout period, and a Baseline visit. This was followed by an 8-week treatment phase. There was a follow-up period (30 ± 3 days) for those participants who did not roll-over into the open-label trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The blind was not broken for any participants before database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aripiprazole 52.5 mg

Arm description:

Participants were administered aripiprazole orally with a dose of 52.5 milligram (mg) weekly for the 8-week treatment phase.

Arm type	Experimental
Investigational medicinal product name	Aripiprazole enteric-coated extended-release (ECER) Tablets 52.5 mg
Investigational medicinal product code	
Other name	Aripiprazole, OPC-14597
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered a dosage of 52.5 mg aripiprazole tablets orally weekly

Arm title	Aripiprazole 77.5 mg
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Arm description:

Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

Arm type	Experimental
Investigational medicinal product name	Aripiprazole ECER Tablets 77.5 mg
Investigational medicinal product code	
Other name	Aripiprazole, OPC-14597
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered a dosage of 77.5 mg aripiprazole tablets orally weekly

Arm title	Aripiprazole 110 mg
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Arm description:

Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

Arm type	Experimental
Investigational medicinal product name	Aripiprazole ECER Tablets 110 mg
Investigational medicinal product code	
Other name	Aripiprazole, OPC-14597
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered a dosage of 110 mg aripiprazole tablets orally weekly

Arm title	Placebo
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Arm description:

Participants were administered matching placebo tablets weekly

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were administered matching placebo tablets in the same way as aripiprazole

Number of subjects in period 1	Aripiprazole 52.5 mg	Aripiprazole 77.5 mg	Aripiprazole 110 mg
Started	20	21	21
Completed	17	17	16
Not completed	3	4	5
Consent withdrawn by subject	-	1	2
Adverse Event	-	1	-
Lost to follow-up	2	-	-
Sponsor Discontinued Trial	-	2	2
Lack of efficacy	1	-	-
Protocol deviation	-	-	1

Number of subjects in period 1	Placebo
Started	21
Completed	18
Not completed	3
Consent withdrawn by subject	1
Adverse Event	-
Lost to follow-up	-
Sponsor Discontinued Trial	2
Lack of efficacy	-
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Aripiprazole 52.5 mg
Reporting group description: Participants were administered aripiprazole orally with a dose of 52.5 milligram (mg) weekly for the 8-week treatment phase.	
Reporting group title	Aripiprazole 77.5 mg
Reporting group description: Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.	
Reporting group title	Aripiprazole 110 mg
Reporting group description: Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.	
Reporting group title	Placebo
Reporting group description: Participants were administered matching placebo tablets weekly	

Reporting group values	Aripiprazole 52.5 mg	Aripiprazole 77.5 mg	Aripiprazole 110 mg
Number of subjects	20	21	21
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	11.5	11.7	12.5
standard deviation	± 3.4	± 2.8	± 2.7
Gender categorical Units: Subjects			
Female	3	8	3
Male	17	13	18

Reporting group values	Placebo	Total	
Number of subjects	21	83	
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	11.8		
standard deviation	± 2.7	-	
Gender categorical			
Units: Subjects			
Female	6	20	
Male	15	63	

End points

End points reporting groups

Reporting group title	Aripiprazole 52.5 mg
Reporting group description: Participants were administered aripiprazole orally with a dose of 52.5 milligram (mg) weekly for the 8-week treatment phase.	
Reporting group title	Aripiprazole 77.5 mg
Reporting group description: Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.	
Reporting group title	Aripiprazole 110 mg
Reporting group description: Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.	
Reporting group title	Placebo
Reporting group description: Participants were administered matching placebo tablets weekly	

Primary: Mean change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) total tic score

End point title	Mean change from Baseline to Week 8 in Yale Global Tic Severity Scale (YGTSS) total tic score ^[1]
End point description: The YGTSS is a semi-structured clinical interview designed to measure current tic severity. This scale consisted of a tic inventory, with 5 separate rating scales to rate the severity of symptoms, and an impairment ranking. Ratings were 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. The total tic score (TTS) ranged from 0 (none) to 50 (severe) with higher score for more severe symptoms (greater reduction from baseline for greater improvement). 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. In an Intent-to-Treat (ITT) population, participants were randomly assigned to the double-blind treatment.	
End point type	Primary
End point timeframe: Baseline to Week 8	

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: No statistical analyses were defined for this endpoint because the trial was discontinued by the sponsor with a much smaller sample size than originally planned.

End point values	Aripiprazole 52.5 mg	Aripiprazole 77.5 mg	Aripiprazole 110 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	16	18
Units: Units on a scale				
arithmetic mean (standard deviation)	-8.2 (± 4.8)	-9.9 (± 6.7)	-14.5 (± 7.7)	-9.6 (± 7.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) change score at Week 8

End point title	Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) change score at Week 8
End point description: The severity of illness and efficacy of study medication for each participant were rated using the CGI-TS scale. The study physician were to rate the participants total improvement whether or not it is due to study treatment. All responses were compared to the participants condition at Baseline (Day 0). Response choices include: 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: Week 8	

End point values	Aripiprazole 52.5 mg	Aripiprazole 77.5 mg	Aripiprazole 110 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	16	16	18
Units: Units on a scale				
arithmetic mean (standard deviation)	2.7 (± 1)	2.8 (± 0.8)	2.3 (± 1.1)	2.6 (± 0.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Gilles de la Tourette Quality of Life (GTS-QOL) at Week 8

End point title	Mean change from Baseline in Gilles de la Tourette Quality of Life (GTS-QOL) at Week 8
End point description: The GTS-QOL is a disease-specific patient-reported scale for the measurement of health-related quality of life in participants 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). The GTS-QOL total score ranged from 0 (extremely dissatisfied with life) and 100 (extremely satisfied with life).	
End point type	Secondary
End point timeframe: Baseline to Week 8	

End point values	Aripiprazole 52.5 mg	Aripiprazole 77.5 mg	Aripiprazole 110 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	17	16	18
Units: Units on a scale				
arithmetic mean (standard deviation)	8.8 (± 14.1)	3.8 (± 24.4)	13.1 (± 20.9)	13.4 (± 15.9)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signing of the informed consent until the follow-up visit 30 ($\pm$ 3) days.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Aripiprazole 52.5 mg
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Reporting group description:

Participants were administered aripiprazole orally with a dose of 52.5 mg weekly for the 8-week treatment phase.

Reporting group title	Aripiprazole 77.5 mg
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Reporting group description:

Participants were administered 77.5 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

Reporting group title	Aripiprazole 110 mg
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Reporting group description:

Participants were administered 110 mg of aripiprazole oral tablets weekly for the 8-week treatment phase.

Reporting group title	Placebo
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Reporting group description:

Participants were administered matching placebo tablets weekly

Serious adverse events	Aripiprazole 52.5 mg	Aripiprazole 77.5 mg	Aripiprazole 110 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Aripiprazole 52.5 mg	Aripiprazole 77.5 mg	Aripiprazole 110 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)	8 / 21 (38.10%)	17 / 21 (80.95%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	4 / 21 (19.05%)
occurrences (all)	0	1	5
Influenza like illness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Pharyngeal erythema			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Anxiety			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Apathy			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Hallucination, auditory			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Restlessness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Investigations			
Blood prolactin decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1

Palpitations			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Disturbance in attention			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	2 / 20 (10.00%)	0 / 21 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	3
Headache			
subjects affected / exposed	2 / 20 (10.00%)	2 / 21 (9.52%)	8 / 21 (38.10%)
occurrences (all)	2	3	10
Hypotonia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Sedation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Slow response to stimuli			
subjects affected / exposed	0 / 20 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)	3 / 21 (14.29%)	6 / 21 (28.57%)
occurrences (all)	1	11	9
Tremor			
subjects affected / exposed	1 / 20 (5.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1
Eye disorders			
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	0 / 21 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 21 (4.76%) 1	1 / 21 (4.76%) 2
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1
Abdominal pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 21 (4.76%) 1	0 / 21 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 21 (4.76%) 1	2 / 21 (9.52%) 2
Diarrhoea subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	2 / 21 (9.52%) 2
Lip dry subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1
Nausea subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2	0 / 21 (0.00%) 0	3 / 21 (14.29%) 3
Vomiting subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	1 / 21 (4.76%) 1	2 / 21 (9.52%) 3
Skin and subcutaneous tissue disorders			
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 21 (4.76%) 1	0 / 21 (0.00%) 0
Renal and urinary disorders			

Pollakiuria subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	0 / 21 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1
Back pain subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	0 / 21 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1
Pain in extremity subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	1 / 21 (4.76%) 1
Pain in jaw subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	1 / 21 (4.76%) 3
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 21 (4.76%) 1	2 / 21 (9.52%) 2
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	0 / 21 (0.00%) 0	2 / 21 (9.52%) 2
Increased appetite subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 21 (4.76%) 1	0 / 21 (0.00%) 0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	7 / 21 (33.33%)		
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Pharyngeal erythema			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Apathy			

subjects affected / exposed occurrences (all) Hallucination, auditory subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Restlessness subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0		
Investigations Blood prolactin decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0		
Injury, poisoning and procedural complications Hand fracture subjects affected / exposed occurrences (all) Wound subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1 0 / 21 (0.00%) 0		
Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all) Palpitations subjects affected / exposed occurrences (all) Tachycardia	0 / 21 (0.00%) 0 0 / 21 (0.00%) 0		

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Hypotonia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Sedation			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Slow response to stimuli			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Eye disorders			

Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Vision blurred subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Abdominal pain subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Lip dry subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Vomiting subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Renal and urinary disorders			
Pollakiuria subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Pain in jaw			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Increased appetite			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2013	In protocol amendment 1, substantial revisions were made such as; To remove the option of allowing subjects to roll over into Study 31-10-274 if they terminated early due to lack of efficacy at Week 5 or later in the previous trial; To clarify the criteria for the exclusion of subjects based on QTc values; To increase the expected duration of the entire trial; To update the statistical methods; To clarify the process of breaking the blind; To update the sample handling for blood for metabolic profiling; To update the protocol with new OPDC standard sections on reporting of product quality complaints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 September 2013	The trial was terminated early based on the review of the recent data from placebo-controlled Trial 31-10-272 (aripiprazole QW) relative to the results of the placebo-controlled Trial 31-12-293 (aripiprazole once daily [QD]) in subjects 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. Therefore, OPDC discontinued trial 31-10-273 because the aripiprazole QW formulation will not be 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