



## Clinical trial results:

### A Randomized, Placebo-controlled Trial to Evaluate the Long-term (ie, Maintenance) Efficacy of Oral Aripiprazole in the Treatment of Pediatric Subjects with Tourette's Disorder

#### Summary

EudraCT number	2018-002270-48
Trial protocol	HU
Global end of trial date	30 June 2020

#### Results information

Result version number	v1
This version publication date	08 January 2021
First version publication date	08 January 2021

#### Trial information

##### Trial identification

Sponsor protocol code	31-14-204
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03661983
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, 20850
Public contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 844-687-8522, OtsukaRMReconciliation@rmpdc.org
Scientific contact	Global Clinical Development, Otsuka Pharmaceutical Development & Commercialization, Inc., +1 844-687-8522, OtsukaRMReconciliation@rmpdc.org

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 June 2020
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate the long-term efficacy of aripiprazole once-daily treatment with oral tablets in pediatric subjects with TD.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2018
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: 9
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	United States: 23
Worldwide total number of subjects	36
EEA total number of subjects	4

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)	22
Adolescents (12-17 years)	14
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 13 investigative sites in Canada, the United States and Hungary from Oct 13, 2018 to Jun 30, 2020.

### Pre-assignment

Screening details:

Pediatric participants with a diagnosis of Tourette's Disorder were enrolled in this to receive oral aripiprazole in an Open-label Stabilization Phase and a Double-blind Randomized Withdrawal Phase and then followed for safety up to 30 days post-last dose.

### Period 1

Period 1 title	Open Label Stabilization Phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Open Label Stabilization Phase: Aripiprazole
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Arm description:

Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received aripiprazole matching-placebo tablets, orally as per the regimen specified in the arm description.

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:

Participants received aripiprazole tablets, orally as per the regimen specified in the arm description.

<b>Number of subjects in period 1</b>	Open Label Stabilization Phase: Aripiprazole
Started	36
Completed	25
Not completed	11
Adverse event, non-fatal	5

Withdrawal by Parent/Guardian	2
Study Terminated by Sponsor	3
Lack of efficacy	1

## Period 2

Period 2 title	Double-blind Randomized Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Double Blind Phase: Aripiprazole Full Dose

### Arm description:

Participants who met stabilization criteria and randomized to receive full dose of aripiprazole i.e. 5 mg or 10 mg for <50 kg participants, and 10 mg or 20 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.

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:

Participants received aripiprazole tablets, orally as per the regimen specified in the arm description.

<b>Arm title</b>	Double Blind Phase: Aripiprazole Half Dose
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### Arm description:

Participants who met stabilization criteria and randomized to receive half dose of aripiprazole i.e. 2 mg or 5 mg for <50 kg participants, and 5 mg or 10 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.

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:

Participants received aripiprazole tablets, orally as per the regimen specified in the arm description.

<b>Arm title</b>	Double Blind Phase: Placebo
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### Arm description:

Participants who met randomization criteria and randomized to receive aripiprazole matching-placebo tablets, 2 daily, orally, up to 12 weeks in Double-Blind Phase.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received aripiprazole matching-placebo tablets, orally as per the regimen specified in the arm description.

Number of subjects in period 2	Double Blind Phase: Aripiprazole Full Dose	Double Blind Phase: Aripiprazole Half Dose	Double Blind Phase: Placebo
Started	9	8	8
Completed	7	7	0
Not completed	2	1	8
Disease Relapse	-	-	6
Adverse event, non-fatal	1	-	-
Withdrawal by Parent/Guardian	-	-	1
Study Terminated by Sponsor	1	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Open Label Stabilization Phase: Aripiprazole
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Reporting group description:

Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase.

Reporting group values	Open Label Stabilization Phase: Aripiprazole	Total	
Number of subjects	36	36	
Age categorical			
Units: Subjects			
Children (2-11 years)	22	22	
Adolescents (12-17 years)	14	14	
Age continuous			
Units: years			
arithmetic mean	10.9		
standard deviation	± 3.0	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	30	30	
Ethnicity			
Units: Subjects			
Hispanic or Latino	7	7	
Not Hispanic or Latino	29	29	
Unknown or Not Reported	0	0	
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	32	32	
More than one race	0	0	
Unknown or Not Reported	2	2	

## End points

### End points reporting groups

Reporting group title	Open Label Stabilization Phase: Aripiprazole
Reporting group description: Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase.	
Reporting group title	Double Blind Phase: Aripiprazole Full Dose
Reporting group description: Participants who met stabilization criteria and randomized to receive full dose of aripiprazole i.e. 5 mg or 10 mg for <50 kg participants, and 10 mg or 20 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.	
Reporting group title	Double Blind Phase: Aripiprazole Half Dose
Reporting group description: Participants who met stabilization criteria and randomized to receive half dose of aripiprazole i.e. 2 mg or 5 mg for <50 kg participants, and 5 mg or 10 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to 12 weeks in Double-Blind Phase.	
Reporting group title	Double Blind Phase: Placebo
Reporting group description: Participants who met randomization criteria and randomized to receive aripiprazole matching-placebo tablets, 2 daily, orally, up to 12 weeks in Double-Blind Phase.	

### Primary: Percentage of Participants With Relapse During the Double-blind Randomized Withdrawal Phase

End point title	Percentage of Participants With Relapse During the Double-blind Randomized Withdrawal Phase <sup>[1]</sup>
End point description: Relapse was defined as a loss of $\geq 50\%$ of the improvement experienced during the open-label stabilization phase (i.e., improvement at the last assessment of Yale Global Tic Severity Scale [YGTSS] before randomization) on the Yale Global Tic Severity Scale Total Tic Score (YGTSS TTS). Intent to Treat (ITT) Sample included all participants who were randomized and received at least 1 dose of randomized IMP were included in this dataset and were analyzed according to the treatment group they were randomized to.	
End point type	Primary
End point timeframe: From Randomization up to 12 weeks in Double-blind Randomized Withdrawal Phase	

#### 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 planned for this endpoint.

End point values	Double Blind Phase: Aripiprazole Full Dose	Double Blind Phase: Aripiprazole Half Dose	Double Blind Phase: Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	8	8	
Units: percentage of participants				
number (not applicable)	0	0	75.0	



## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after last dose of study drug (Up to approximately 36 weeks)

Adverse event reporting additional description:

Open-label Safety Sample included all participants that had administered at least 1 dose of IMP during the open-label stabilization phase. Randomized Safety Sample included all participants who received at least 1 dose of randomized IMP during double-blind randomized withdrawal phase were included and analyzed according to the treatment received.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	Open Label Stabilization Phase: Aripiprazole
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Reporting group description:

Participants began treatment with aripiprazole at a 2.0 mg/day dose, with the dose titrated to 5.0 mg/day after 2 days. Subsequent dose adjustments were based on the participant's weight to achieve optimum control of tics up to the maximum recommended doses based on the United States Labeling, up to Week 8 and then continued on the most stabilized dose up to minimum Week 14 or maximum Week 20. Participants who met stabilization criteria were randomized to Double-blind Randomization Phase.

Reporting group title	Double Blind Phase: Aripiperazole Full Dose
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Reporting group description:

Participants who met stabilization criteria and randomized to receive full dose of aripiprazole i.e. 5 mg or 10 mg for <50 kg participants, and 10 mg or 20 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to Week 32.

Reporting group title	Double Blind Phase: Aripiperazole Half Dose
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Reporting group description:

Participants who met stabilization criteria and randomized to receive half dose of aripiprazole i.e. 2 mg or 5 mg for <50 kg participants, and 5 mg or 10 mg for >50 kg participants (2 tablets a day), based on stabilized dose in open-label stabilization phase, up to Week 32.

Reporting group title	Double Blind Phase: Placebo
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Reporting group description:

Participants who met randomization criteria and randomized to receive aripiprazole matching-placebo tablets, 2 daily, orally, up to Week 32.

Serious adverse events	Open Label Stabilization Phase: Aripiprazole	Double Blind Phase: Aripiperazole Full Dose	Double Blind Phase: Aripiperazole Half Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Suicidal Ideation			

subjects affected / exposed	0 / 36 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Double Blind Phase: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Psychiatric disorders			
Suicidal Ideation			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Open Label Stabilization Phase: Aripiprazole	Double Blind Phase: Aripiprazole Full Dose	Double Blind Phase: Aripiprazole Half Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 36 (47.22%)	3 / 9 (33.33%)	3 / 8 (37.50%)
Investigations			
Weight increased			
subjects affected / exposed	3 / 36 (8.33%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 36 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 36 (2.78%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	5 / 36 (13.89%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	5	0	1

Headache subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 4	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Sedation subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 7	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Enuresis subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Irritability subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Restlessness subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Infections and infestations Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 9 (0.00%) 0	1 / 8 (12.50%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 9 (0.00%) 0	1 / 8 (12.50%) 1

<b>Non-serious adverse events</b>	Double Blind Phase: Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 8 (25.00%)		
Investigations Weight increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Injury, poisoning and procedural complications Upper limb fracture subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Sedation subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0  0 / 8 (0.00%) 0  0 / 8 (0.00%) 0		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)  Enuresis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1  0 / 8 (0.00%) 0		

Irritability			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Pharyngitis streptococcal			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2018	The following updates were made as per Amendment 01: Added a Week 10 visit to the double-blind phase. Allowed for remote visits (i.e., telemedicine) for selected trial visits. Decreased the number of Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) assessments and vital signs measurements. Added waist circumference. Specified that the C-SSRS is the children's version. Added the option of micro-sampling for clinical laboratory tests. Added an interim analysis (IA). Revised language regarding sample size calculation and primary endpoint analysis. Clarified inclusion/exclusion criteria. Deleted Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) contact information in the appendices. Deleted sample assessment scales in the appendices. Updated the protocol to conform to the Otsuka template and style guide. Corrected minor typographical errors.
20 June 2018	The following updates were made as per Amendment 01: Added the EudraCT number. Increased the number of proposed sites. Specified that randomization will be stratified by region and body weight. Clarified exclusion criterion #17. Removed the option for the screening visit to be conducted remotely. Removed the option for remote visits during the open-label stabilization phase after the Week 12 visit. Clarified dose titration and specify when and how dose adjustments are permitted. Added language regarding relapse. Specified conditions for the measurement of blood pressure. Removed triplicate electrocardiograms (ECGs) so that only one ECG is done. Added details regarding Columbia-Suicide Severity Rating Scale (C-SSRS) results. Added missing clinical laboratory assessments. Corrected minor typographical errors and add clarifications to text.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 June 2020	This trial was terminated early due to the withdrawal of post-marketing commitment (PMC) to FDA. The planned interim analysis was not conducted either.	-

Notes:

### Limitations and caveats

None reported