



## Clinical trial results:

### A 52-Week, Open-label, Multicenter Study of the Safety and Tolerability of Aripiprazole Flexibly Dosed in the Treatment of Children and Adolescents with Autistic Disorder

#### Summary

EudraCT number	2017-000175-86
Trial protocol	Outside EU/EEA
Global end of trial date	05 June 2009

#### Results information

Result version number	v1 (current)
This version publication date	25 February 2018
First version publication date	25 February 2018

#### Trial information

##### Trial identification

Sponsor protocol code	CN138-180
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00365859
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Otsuka America Pharmaceutical Inc
Sponsor organisation address	2440 Research Blvd, Rockville, MD 20850, United States,
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Notes:

#### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	20 November 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2009
Global end of trial reached?	Yes
Global end of trial date	05 June 2009
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

The primary objective of this trial was to evaluate long-term safety and tolerability of aripiprazole flexibly dosed in the treatment of serious behavioral problems in children and adolescents with a diagnosis of autistic disorder.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The rights, safety, and well-being of the study patients were the most important consideration and prevailed over the interests of science and society.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	United States: 330
Worldwide total number of subjects	330
EEA total number of subjects	0

Notes:

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**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)	244
Adolescents (12-17 years)	86
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 353 patients (109 de novo & 244 (placebo 70 + aripiprazole 174) rollover patients) were enrolled. Of 109 de novo patients, 23 had baseline failures & only 86 entered the treatment phase. Totally 330 patients ( 86 de novo + 70 placebo + 174 aripiprazole) entered the treatment (single oral dose of Aripiprazole [2 to 15 mg/day] tablet)

### Pre-assignment

Screening details:

De novo patients had screening Phase of up to 42 days consisting of visit 1 (screening), visit 1a (washout period & interim screening) and visit 2 (baseline). Rollover patients had screening phase at visit 2 (screening & baseline, ). For rollover patients, screening and procedures were not repeated at visit 1 and 1a.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open label trial.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	De Novo

Arm description:

Patients who did not participate in studies CN138178 or CN138179 were included, provided that they met the entry criteria specified in the protocol. Patients with history of serious behavioral problems with a diagnosis of autistic disorders and were currently treated orally with aripiprazole 2gm/day .

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

Dosage and administration details:

All patients were assigned to aripiprazole (tablet) once daily oral treatment, which was flexibly dosed (2 to 15 mg/day) on the basis of treatment response and medication tolerability. All patients received 2 mg/day aripiprazole on Day 1 of this open-label, long-term study.

<b>Arm title</b>	Placebo Rollover
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Arm description:

Rollover patients who were treated orally with placebo in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study.

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

Dosage and administration details:

On Day 1 (the day after week 8 visit of the antecedent double-blind study), aripiprazole matching

placebo was administered at 2 mg/day

<b>Arm title</b>	Aripiprazole Rollover
Arm description: Rollover patients who were treated orally with aripiprazole in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study.	
Arm type	Experimental
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

All patients were assigned to aripiprazole (tablet) oral once daily treatment, which was flexibly dosed (2 to 15 mg/day) on the basis of treatment response and medication tolerability. Rollover patients received their first dose of study medication on Day 1 (the day after their Week 8 visit of the antecedent double-blind study). All rollover patients involved in the antecedent double-blind protocols (CN138178 or CN138179) had study medication re-titrated starting at 2 mg/day.

<b>Number of subjects in period 1</b>	De Novo	Placebo Rollover	Aripiprazole Rollover
Started	86	70	174
Completed	55	37	107
Not completed	31	33	67
Consent withdrawn by subject	7	5	15
Poor/noncompliance	2	1	2
Adverse event, non-fatal	9	11	15
Patient no longer met study criteria	1	-	1
Other	1	2	4
Lost to follow-up	2	8	21
Lack of efficacy	8	5	7
Administrative reason	1	1	2

## Baseline characteristics

### Reporting groups

Reporting group title	De Novo
Reporting group description:	
Patients who did not participate in studies CN138178 or CN138179 were included, provided that they met the entry criteria specified in the protocol. Patients with history of serious behavioral problems with a diagnosis of autistic disorders and were currently treated orally with aripiprazole 2gm/day .	
Reporting group title	Placebo Rollover
Reporting group description:	
Rollover patients who were treated orally with placebo in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study.	
Reporting group title	Aripiprazole Rollover
Reporting group description:	
Rollover patients who were treated orally with aripiprazole in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study.	

Reporting group values	De Novo	Placebo Rollover	Aripiprazole Rollover
Number of subjects	86	70	174
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	68	52	124
Adolescents (12-17 years)	18	18	50
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	9.7	9.8	9.7
standard deviation	± 3.2	± 3	± 3
Gender categorical			
Units: Subjects			
Female	16	8	19
Male	70	62	155

Reporting group values	Total		
Number of subjects	330		
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)	244		
Adolescents (12-17 years)	86		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	43		
Male	287		

## End points

### End points reporting groups

Reporting group title	De Novo
Reporting group description: Patients who did not participate in studies CN138178 or CN138179 were included, provided that they met the entry criteria specified in the protocol. Patients with history of serious behavioral problems with a diagnosis of autistic disorders and were currently treated orally with aripiprazole 2gm/day .	
Reporting group title	Placebo Rollover
Reporting group description: Rollover patients who were treated orally with placebo in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study.	
Reporting group title	Aripiprazole Rollover
Reporting group description: Rollover patients who were treated orally with aripiprazole in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study.	

### Primary: Safety and tolerability by assessment of the number of adverse events following oral treatment of Aripiprazole

End point title	Safety and tolerability by assessment of the number of adverse events following oral treatment of Aripiprazole <sup>[1]</sup>
End point description: To assess the safety and tolerability of oral treatment of Aripiprazole. Safety outcome measures included the incidence of death, serious adverse events (SAEs), treatment-emergent AEs and AEs leading to discontinuation. An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Safety and tolerability were assessed by vital sign measurements; body weight/BMI; ECGs; clinical laboratory evaluations; physical examinations; adverse events; and treatment discontinuations.	
End point type	Primary
End point timeframe: Adverse events (AEs) were collected from the screening visit to week 52	

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: Only summary statistics were presented. Frequencies and percentages are presented for categorical data. No formal statistical tests were planned.

End point values	De Novo	Placebo Rollover	Aripiprazole Rollover	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	70	171	
Units: Numbers				
All Treatment-Emergent Adverse Events (TEAEs)	75	63	148	
Treatment-Emergent Serious AEs	3	1	5	
Serious Related TEAEs	0	1	0	
TEAEs led to discontinuation	9	10	14	

## Statistical analyses

No statistical analyses for this end point

### Primary: Extrapyramidal symptoms (EPS)-related adverse events

End point title	Extrapyramidal symptoms (EPS)-related adverse events <sup>[2]</sup>
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End point description:

To assess the safety and tolerability of oral treatment of Aripiprazole by evaluating extrapyramidal symptoms (EPS) related AEs (including the change from baseline in the Simpson-Angus Rating Scale or Statistical Analysis Software (SAS) score, the abnormal involuntary movement scale (AIMS) score, and the Barnes Akathisia Scale).

End point type	Primary
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End point timeframe:

At week 0, week 8, week 26 and week 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only summary statistics are presented. Frequencies and percentages are presented for categorical data. No formal statistical tests were planned.

End point values	De Novo	Placebo Rollover	Aripiprazole Rollover	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	70	174	
Units: Number of participants				
Any EPS-Related Adverse Event (overall count)	16	6	26	
Parkinsonism Events (Total count)	5	4	10	
Tremor	4	3	3	
Extrapyramidal Disorder	1	0	4	
Cogwheel Rigidity	1	0	2	
Asterixis	0	0	1	
Masked Facies	0	1	0	
Akathisia Events (Total count)	3	1	12	
Psychomotor Hyperactivity	1	0	8	
Akathisia	3	1	4	
Dyskinetic Events (Total count)	6	0	3	
Dyskinesia	5	0	3	
Choreoathetosis	1	0	0	
Dystonic Events (Total count)	0	1	1	
Muscle Rigidity	0	1	0	
Muscle Spasms	0	0	1	
Residual Events (Total count)	2	0	0	
Muscle Twitching	2	0	0	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Aberrant Behavior Checklist (ABC) Subscale Score

End point title	Aberrant Behavior Checklist (ABC) Subscale Score
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End point description:

To evaluate the mean change from baseline in each of the 5 ABC (Aberrant Behavior Checklist) subscale score. ABC subscale score was used to assess and classify problem behaviors of children and adolescents with mental retardation. It is a 4-point scale with scores ranging from 0 (not at all a problem) to 3 (the problem is severe in degree) with 5 subscales (Irritability, Social Withdrawal, Stereotypic Behavior, Hyperactivity, and Inappropriate Speech). A negative change score signified improvement.

End point type	Secondary
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End point timeframe:

At screening, week 0, week 4, week 8 and once every 6 weeks until week 52

End point values	De Novo	Placebo Rollover	Aripiprazole Rollover	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	69	169	
Units: Mean				
arithmetic mean (standard deviation)				
ABC Irritability Subscale Score ( 0 to 45)	-6.5 (± 11.12)	-6.1 (± 11.25)	0.7 (± 9.72)	
ABC Hyperactivity Subscale Score (0 to 48)	-10 (± 10.55)	-8.3 (± 10.85)	0.3 (± 11.18)	
ABC Stereotypy Subscale Score (0 to 21)	-2.5 (± 4.67)	-1.9 (± 4.46)	0.1 (± 4.58)	
ABC Social Withdrawal Subscale Score (0 to 48)	-5.4 (± 9.07)	-3 (± 6.96)	-1.8 (± 6.09)	
ABC Inappropriate Speech Subscale Score (0 to 12)	-1.9 (± 2.66)	-1.8 (± 2.94)	-0.3 (± 2.5)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Global Impression (CGI) score

End point title	Clinical Global Impression (CGI) score
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End point description:

The CGI rating scale was used to evaluate participant's improvement over time. A baseline, CGI-s assessment was performed to rate the severity of the participant's condition on a 7-point scale ranging from 1 (no symptoms) to 7 ( very severe symptoms). At subsequent visits, the participant's improvement relative to the symptoms at baseline was assessed on a 7-point CGI-Improvement (CGI-I) scale ranging from 1 (very much improved) to 7 (very much worse). Since, the target symptoms for the medication was specifically for irritability, the CGI focused specifically on severity of irritability secondary to autistic disorder.

End point type	Secondary
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End point timeframe:

At screening and from week 0 to week 52 (for severity); from week 1 to week 52 (for improvement)

End point values	De Novo	Placebo Rollover	Aripiprazole Rollover	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	69	169	
Units: Mean				
arithmetic mean (standard deviation)				
CGI-Severity (CGI-S) Score	-0.8 (± 0.85)	-0.4 (± 1.06)	0 (± 1.01)	
CGI-Improvement (CGI-I) Score	2.7 (± 1.3)	2.4 (± 1.24)	2.5 (± 1.2)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

End point title	Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)
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End point description:

The CY-BOCS, a 10-item clinician-rated scale designed to measure the severity of obsessive-compulsive symptoms in participants below the age of 18. The CY-BOCS contains 5 items pertaining to obsessions (which were not used in this trial) and 5 items pertaining to compulsions, which rated each symptom domain in terms of time spent, interference with functioning, distress, resistance, and control. Each item was rated on a 5-point scale, from 0 (no symptoms or minimum severity) to 4 (extreme symptoms or maximum severity). A negative change score signifies improvement. Administration was modified for the purposes of this trial to allow for assessment based on an interview with the participant's parent or guardian. In this study, only compulsions were assessed due to communication difficulties in this patient population.

End point type	Secondary
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End point timeframe:

At week 0 and week 52

End point values	De Novo	Placebo Rollover	Aripiprazole Rollover	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	49	115	
Units: Mean				
arithmetic mean (standard deviation)				
CGI-Improvement Score	-2 (± 3.68)	-2.4 (± 5.06)	0.2 (± 3.81)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean change from baseline in the Pediatric Quality of Life Questionnaire (PedsQL)

End point title	Mean change from baseline in the Pediatric Quality of Life Questionnaire (PedsQL)
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End point description:

The PedsQL is a health-related quality-of-life instrument developed and validated for use with children

and adolescents. The primary analysis was the combined scales total across the age groups (child age 5 - 7, child age 8 - 12, and teen age 13 - 18), with a secondary analysis for separate age groups (child age 5 - 7, child 8 - 12 and teen age 13 - 18) and each separate scale (emotional functioning (5 items), social functioning (5 items) and cognitive functioning (6 items) were the scales used in PedsQL. The instructions asked the parent how much of a problem each item had occurred during the past 1 month. A 5-point response scale was used to rate each item (0 = never a problem, 4 = almost always a problem). Items were reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0), so that higher scores indicated better health-related quality of life.

End point type	Secondary
End point timeframe:	
At week 0 and week 52	

End point values	De Novo	Placebo Rollover	Aripiprazole Rollover	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	69	169	
Units: Response				
arithmetic mean (standard deviation)				
Combined Scales (Participant count = 65, 48 & 117)	12.2 (± 16.14)	2.9 (± 16.42)	1 (± 15.9)	
Emotional (Participant count = 65, 48 & 118)	12.7 (± 21.29)	4.9 (± 20.47)	-1.2 (± 19.28)	
Social (Participant count = 65, 48 & 117)	7.6 (± 23.83)	3.6 (± 25.92)	2.1 (± 22.49)	
Cognitive Function (Participant count=65,48 & 116)	16 (± 19.6)	0.6 (± 24.99)	1.6 (± 21.19)	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From week 1 to week 52

Adverse event reporting additional description:

For serious adverse events - From screening to week 52. Four patients entered treatment phase, but were not treated. hence, they were not included in the safety (AEs) analysis. One patient in de novo arm was discontinued from the study due to severe suicidal ideation. Thereby, only 85 subjects were included in the safety analysis.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12
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### Reporting groups

Reporting group title	De Novo
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Reporting group description:

Patients who did not participate in protocols CN138178 or CN138179. Patients with history of serious behavioral problems with a diagnosis of autistic disorders and were currently treated orally with aripiprazole 2gm/day . One participant was not dosed and thus was not included in the safety analysis analysis.

Reporting group title	Placebo Rollover
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Reporting group description:

Rollover patients who were treated orally with placebo in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study.

Reporting group title	Aripiprazole Rollover
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Reporting group description:

Rollover patients who were treated orally with aripiprazole in CN138178 or CN138179 at a dose of 2 mg/day on Day 1 of the study. Three participants did not receive medication and were not included in the safety analysis.

Serious adverse events	De Novo	Placebo Rollover	Aripiprazole Rollover
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 85 (3.53%)	1 / 70 (1.43%)	5 / 171 (2.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 85 (0.00%)	1 / 70 (1.43%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			

subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 85 (1.18%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impulsive Behaviour			
subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	1 / 85 (1.18%)	0 / 70 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Otitis Media Acute			

subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 70 (0.00%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Infection			
subjects affected / exposed	1 / 85 (1.18%)	0 / 70 (0.00%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	De Novo	Placebo Rollover	Aripiprazole Rollover
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 85 (88.24%)	63 / 70 (90.00%)	148 / 171 (86.55%)
Investigations			
Weight Increased			
subjects affected / exposed	20 / 85 (23.53%)	16 / 70 (22.86%)	40 / 171 (23.39%)
occurrences (all)	30	20	75
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 85 (8.24%)	7 / 70 (10.00%)	18 / 171 (10.53%)
occurrences (all)	13	11	32
Sedation			
subjects affected / exposed	8 / 85 (9.41%)	10 / 70 (14.29%)	9 / 171 (5.26%)
occurrences (all)	16	17	12
Drooling			
subjects affected / exposed	3 / 85 (3.53%)	3 / 70 (4.29%)	15 / 171 (8.77%)
occurrences (all)	5	5	23

Somnolence subjects affected / exposed occurrences (all)	4 / 85 (4.71%) 8	6 / 70 (8.57%) 12	3 / 171 (1.75%) 11
Lethargy subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 10	1 / 70 (1.43%) 1	2 / 171 (1.17%) 2
Dyskinesia subjects affected / exposed occurrences (all)	5 / 85 (5.88%) 8	0 / 70 (0.00%) 0	3 / 171 (1.75%) 5
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	6 / 85 (7.06%) 7	10 / 70 (14.29%) 12	23 / 171 (13.45%) 24
Fatigue subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 15	7 / 70 (10.00%) 14	9 / 171 (5.26%) 13
Irritability subjects affected / exposed occurrences (all)	4 / 85 (4.71%) 12	1 / 70 (1.43%) 3	11 / 171 (6.43%) 28
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	17 / 85 (20.00%) 19	12 / 70 (17.14%) 24	34 / 171 (19.88%) 65
Diarrhoea subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 9	8 / 70 (11.43%) 10	15 / 171 (8.77%) 21
Constipation subjects affected / exposed occurrences (all)	6 / 85 (7.06%) 10	4 / 70 (5.71%) 5	7 / 171 (4.09%) 8
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	10 / 85 (11.76%) 15	6 / 70 (8.57%) 7	15 / 171 (8.77%) 27
Epistaxis subjects affected / exposed occurrences (all)	8 / 85 (9.41%) 22	3 / 70 (4.29%) 12	10 / 171 (5.85%) 24

Nasal Congestion subjects affected / exposed occurrences (all)	10 / 85 (11.76%) 17	0 / 70 (0.00%) 0	11 / 171 (6.43%) 14
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	5 / 85 (5.88%) 7	3 / 70 (4.29%) 6	7 / 171 (4.09%) 8
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 19	8 / 70 (11.43%) 12	18 / 171 (10.53%) 24
Aggression subjects affected / exposed occurrences (all)	8 / 85 (9.41%) 12	6 / 70 (8.57%) 8	15 / 171 (8.77%) 26
Agitation subjects affected / exposed occurrences (all)	7 / 85 (8.24%) 9	2 / 70 (2.86%) 3	11 / 171 (6.43%) 12
Anxiety subjects affected / exposed occurrences (all)	3 / 85 (3.53%) 6	0 / 70 (0.00%) 0	9 / 171 (5.26%) 13
Tic subjects affected / exposed occurrences (all)	1 / 85 (1.18%) 2	6 / 70 (8.57%) 8	2 / 171 (1.17%) 4
Stereotypy subjects affected / exposed occurrences (all)	4 / 85 (4.71%) 4	1 / 70 (1.43%) 2	9 / 171 (5.26%) 15
Renal and urinary disorders Enuresis subjects affected / exposed occurrences (all)	5 / 85 (5.88%) 10	4 / 70 (5.71%) 6	6 / 171 (3.51%) 17
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	13 / 85 (15.29%) 21	10 / 70 (14.29%) 17	21 / 171 (12.28%) 34
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	11 / 85 (12.94%) 29	12 / 70 (17.14%) 27	16 / 171 (9.36%) 23

Ear Infection			
subjects affected / exposed	3 / 85 (3.53%)	2 / 70 (2.86%)	15 / 171 (8.77%)
occurrences (all)	5	2	21
Sinusitis			
subjects affected / exposed	8 / 85 (9.41%)	2 / 70 (2.86%)	10 / 171 (5.85%)
occurrences (all)	14	2	17
Gastroenteritis Viral			
subjects affected / exposed	5 / 85 (5.88%)	1 / 70 (1.43%)	8 / 171 (4.68%)
occurrences (all)	7	2	9
Metabolism and nutrition disorders			
Increased Appetite			
subjects affected / exposed	16 / 85 (18.82%)	8 / 70 (11.43%)	19 / 171 (11.11%)
occurrences (all)	20	18	35
Decreased Appetite			
subjects affected / exposed	6 / 85 (7.06%)	2 / 70 (2.86%)	7 / 171 (4.09%)
occurrences (all)	9	3	15

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2006	Amendment 01: <ul style="list-style-type: none"><li>• Decrease of washout period</li><li>• Removal of separate rater requirement</li><li>• Increase of sample size</li><li>• Addition of inclusion of de novo patients</li><li>• Changes to PedsQL</li><li>• Addition of CGSQ</li><li>• Clarify requirements for mental age assessment</li><li>• Withdrawal of CGI as safety objective</li><li>• Administrative and typographical changes</li></ul>
17 June 2007	Amendment 02: <ul style="list-style-type: none"><li>• Clarification regarding de novo patients' entrance criteria</li><li>• Decrease number of days that efficacy evaluations will be included for analysis</li><li>• Mental age requirement specifications</li><li>• Collection of insulin collection and evaluation</li><li>• Window visits defined</li><li>• Allowance of use of historical ADI-R</li><li>• Extension of enrollment period</li><li>• DSMB to receive efficacy data for review only</li><li>• Addition of mental age assessment at baseline if not done at screening</li><li>• Administrative and typographical changes</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: