Clinical trial results:
A Long-Term Multicenter, Randomized, Double-blind, Placebo Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia

Summary

EudraCT number	2010-020987-39
Trial protocol	Outside EU/EEA
Global end of trial date	12 December 2013

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	31-09-266

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01149655
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, Maryland 20850
Public contact	Matthew Media Group, Matthew Media Group, ATTAINstudyinfo@mmgct.com
Scientific contact	Matthew Media Group, Matthew Media Group, ATTAINstudyinfo@mmgct.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000235-PIP02-10
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	12 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2013
Global end of trial reached?	Yes
Global end of trial date	12 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of aripiprazole compared with placebo, as measured by time to exacerbation of psychotic symptoms/impending relapse, in adolescent schizophrenic subjects who have maintained stability for 2 consecutive weekly time points on oral aripiprazole with at least 7 weeks of treatment. The secondary objective was to evaluate the safety and tolerability of oral aripiprazole as maintenance treatment in adolescent participants with schizophrenia.

Protection of trial subjects:

The study was conducted in accordance with the protocol, legal and regulatory requirements, as well as in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting clinical studies. Consistent with ethical principles for the protection of human research participants, no study procedures were performed on study candidates until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this study were submitted to and approved by the institutional review board (IRB) or independent ethics committee (IEC) for each respective trial site or country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Russian Federation: 89
Country: Number of subjects enrolled	United States: 12
Country: Number of subjects enrolled	India: 59
Country: Number of subjects enrolled	Philippines: 15
Country: Number of subjects enrolled	Taiwan: 2
Worldwide total number of subjects	201
EEA total number of subjects	21

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)	0
Adolescents (12-17 years)	201
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 244 participants were screened, 201 entered the trial and 146 were randomized into the double-blind maintenance phase. The participants were recruited from 69 trial sites in the United States of America, Russia, Romania, India, Philippines, Malaysia, and Taiwan.

Pre-assignment

Screening details:

Participants were titrated to oral aripiprazole in Period 1. Participants who converted to aripiprazole and who already received aripiprazole were in Period 2. Participants met stability criteria were randomized in 2:1 ratio (aripiprazole: placebo) in Period 3. Disposition presented for the overall study.

Period 1

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

Blinding implementation details:

During the double-blind phase, treatment assignment code list was available only to an independent biostatistician and the clinical supply operations group. All other personnel were blinded to the identity of the treatment assignments until every participant had completed trial treatment and the database was locked.

Arms

Arm title	All participants

Arm description:

Data for all participants was analysed

Arm type	Experimental
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	
Other name	Abilify, OPC-14597
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who had received oral aripiprazole 2 to 10 milligram (mg) for 2 Weeks in combination with any other antipsychotic were in conversion phase. Participants who had converted to aripiprazole monotherapy period 1 (conversion phase) and had received aripiprazole monotherapy for schizophrenia at screening were in period 2, provided the prescribed aripiprazole dose did not exceed 30 mg per day for 2 Weeks. Participants in period 3 were randomized in a 2:1 (aripiprazole: placebo) ratio and had received oral aripiprazole titrated from 10 to 30 mg/day as double-blind maintenance treatment for up to 52 weeks.

Number of subjects in period 1	All participants
Started	201
Completed	21
Not completed	180
Physician decision	6
Consent withdrawn by subject	20

Sponsor discontinued trial	97
Adverse event without lack of efficacy	11
Met withdrawal criteria	8
Lost to follow-up	1
Lack of efficacy or relapse	37

Baseline characteristics

Reporting groups	
Reporting group title	All participants
Reporting group description:	
Data for all participants was analysed	

Reporting group values	All participants	Total	
Number of subjects	201	201	
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	15.1		
standard deviation	± 1.2	-	
Gender categorical Units: Subjects			
Female	68	68	
Male	133	133	

End points

End points reporting groups

Reporting group title	All participants
Reporting group description:	
Data for all participants was analysed	
Subject analysis set title	Aripiprazole double-blind maintenance
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The Intent-to-Treat (ITT) data set comprised all participants randomized to the double-blind treatment.	
Subject analysis set title	Placebo double-blind maintenance
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT data set comprised all subjects randomized to the double-blind treatment.	

Primary: Overall relapse rate (in percent) from randomization to exacerbation of psychotic symptoms/impending relapse.

End point title	Overall relapse rate (in percent) from randomization to exacerbation of psychotic symptoms/impending relapse.
End point description:	
Overall relapse rate from randomization, as assessed by Clinical Global Impression of Improvement (CGI-I) score ≥5, Positive and Negative Syndrome Scale (PANSS) scores for hostility or uncooperativeness ≥5, or ≥20% increase in PANSS Total Score. Impending relapse was defined as meeting any of the following 5 criteria: 1) CGI-I score of ≥ 5 (minimally worse) and increase in individual PANSS items to a score > 4 with an absolute increase of ≥ 2 on that specific item or absolute increase of ≥ 4 on the combined 4 PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content). OR 2) CGI-I score of 6 or 7 (much or very much worse) OR 3) Hospitalization due to worsening of illness OR 4) Any suicidal behaviour or answers of "yes" to Questions 4 or 5 on the suicidal ideation section of the C-SSRS OR 5) Violent or aggressive behaviour resulting in clinically significant injury. The intent-to-treat (ITT) population was analysed.	
End point type	Primary
End point timeframe:	
Baseline to Week 55/End of Double-Blind phase visit	

End point values	All participants	Aripiprazole double-blind maintenance	Placebo double-blind maintenance	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	146	98	48	
Units: Percent				
number (not applicable)	25.3	19.39	37.5	

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 52
Statistical analysis description:	
ITT data set was used for the analysis. Participants who were lost to follow-up or who were still in the study at the end of Week 52 were considered as censored on their date of last efficacy evaluation. The ITT set comprised participants randomized to the double-blind phase. Total number of exacerbation of	

psychotic symptoms/impending relapse was estimated using a 2:1 randomization ratio to achieve at least 80% power and to preserve overall nominal alpha level of 0.05 (2-sided).

Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0161
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.461
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.242
upper limit	0.879

Notes:

[1] - Hazard ratios and their 95% confidence intervals were derived from the Cox Proportional Hazard model with treatment as term. Hazard ratio < 1 is in favour of oral aripiprazole 10-30 mg group for superiority test.

Secondary: Percentage of participants meeting exacerbation of psychotic symptoms/impending relapse criteria.

End point title	Percentage of participants meeting exacerbation of psychotic symptoms/impending relapse criteria.

End point description:

Impending relapse was defined as meeting any of the following 5 criteria: 1) CGI-I score of ≥ 5 (minimally worse) and increase in individual PANSS items to a score > 4 with an absolute increase of ≥ 2 on that specific item or absolute increase of ≥ 4 on the combined 4 PANSS items. OR 2) CGI-I score of 6 or 7 (much or very much worse) OR 3) Hospitalization due to worsening of illness OR 4) Any suicidal behaviour or answers of "yes" to Questions 4 or 5 on the suicidal ideation section of the C-SSRS OR 5) Violent or aggressive behaviour resulting in clinically significant injury. The ITT data set comprised of all participants who were randomised to the double-blind phase.

End point type	Secondary

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Percentage				
number (not applicable)				
CGI-I + PANSS	16.33	33.33		
CGI-I of 6 of 7	11.22	25		
Hospitalisation	1.02	10.42		
Suicidal behaviour	1.02	0		
Violent behaviour	4.08	10.42		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who had achieved remission.

End point title	Percentage of participants who had achieved remission.

End point description:

Percentage of participants who had achieved remission, where remission was defined as a score of ≤ 3 on each of the following specific PANSS items, maintained for a period of 6 months: delusions, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms/ posturing, blunted affect, social withdrawal, and lack of spontaneity. The ITT data set comprised of all participants who were randomised to the double-blind phase. For evaluation of remission, 48 of 98 aripiprazole participants and 19 of 48 placebo participants met the 6 month threshold for remission analysis. Of those, 21 of 48 aripiprazole participants and 8 of 19 placebo participants met criteria for remission.

End point type	Secondary

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	19		
Units: Percentage of participants				
number (not applicable)	43.8	42.1		

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 52

Statistical analysis description:

The ITT data set comprised of participants who were randomized to the double-blind treatment. For evaluation of remission, 48 of 98 aripiprazole participants and 19 of 48 placebo participants met the 6 month threshold for remission analysis. Of those, 21 of 48 aripiprazole participants and 8 of 19 placebo participants met criteria for remission.

Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.9025
Method	Chi-squared

Notes:

[2] - The expected total number of exacerbation of psychotic symptoms/impending relapse was estimated using a 2:1 (aripiprazole:placebo) randomization ratio to achieve at least 80% power and to preserve an overall nominal alpha level of 0.05 (2-sided).

Secondary: Percentage of participants who discontinued due to all reasons other than sponsor discontinued Study.

End point title	Percentage of participants who discontinued due to all reasons other than sponsor discontinued Study.

End point description:

Percentage of participants discontinued due to all reasons other than sponsor discontinued study were noted. The ITT data set comprised of all participants who were randomised to the double-blind phase.

End point type	Secondary

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Percentage				
number (not applicable)	25.51	47.92		

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Week 52
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0076
Method	Logrank

Secondary: Mean change from Baseline to endpoint in PANSS total score.

End point title	Mean change from Baseline to endpoint in PANSS total score.

End point description:

The PANSS consisted of 3 subscales with a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicates (absence of symptoms) and a score of 7 indicates (extremely severe symptoms). The symptom constructs for each subscale were positive subscale, negative subscale and general psychopathology subscale. The PANSS Total Score ranged from 30 (best possible outcome) to 210 (worst possible outcome). The ITT data set comprised of participants randomized to double-blind period. LOCF (last observation carried forward) method was used to impute missing data. Week 1 had only 95 and 45 participants analysed.

End point type	Secondary

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98[3]	48[4]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1	0.22 (± 5.62)	-0.27 (± 4.66)		
Week 2	0.09 (± 5.77)	-0.58 (± 6.01)		
Week 3	-0.36 (± 6.41)	1.81 (± 9.66)		
Week 4	-0.64 (± 6.9)	1.56 (± 11.13)		
Week 6	-1.2 (± 8.28)	2.92 (± 13.39)		
Week 8	-1.62 (± 9.2)	3.71 (± 14.29)		
Week 10	-1.2 (± 9.61)	3.9 (± 14.8)		
Week 12	-0.19 (± 10.57)	4.52 (± 16.17)		
Week 14	-0.18 (± 11.06)	5.5 (± 17.21)		
Week 16	-0.78 (± 11.72)	5.56 (± 17.33)		
Week 18	-0.68 (± 12.3)	5.57 (± 17.24)		
Week 20	-0.57 (± 12.46)	6.06 (± 17.84)		
Week 22	-0.31 (± 12.37)	6.1 (± 18.98)		
Week 24	-0.36 (± 12.36)	5.92 (± 19.22)		
Week 26	-0.88 (± 12.41)	5.81 (± 19.65)		
Week 28	-0.85 (± 12.52)	5.65 (± 19.82)		
Week 30	-0.96 (± 12.71)	5.6 (± 19.96)		
Week 32	-0.99 (± 12.74)	6.21 (± 20.43)		
Week 34	-1.12 (± 13.05)	5.79 (± 19.85)		
Week 36	-0.55 (± 13.04)	5.4 (± 20.2)		
Week 38	-0.84 (± 13.17)	5.21 (± 20.27)		
Week 40	-0.92 (± 13.21)	5.1 (± 20.34)		
Week 42	-1.14 (± 13.26)	4.94 (± 20.36)		
Week 44	-0.96 (± 13.32)	4.88 (± 20.47)		
Week 46	-1.02 (± 13.35)	4.83 (± 20.54)		
Week 48	-0.99 (± 13.34)	4.67 (± 20.72)		
Week 50	-1.19 (± 13.43)	4.71 (± 20.66)		
Week 52	-1.31 (± 13.47)	4.79 (± 20.6)		

Notes:

[3] - At Week 1, data were available for 55 participants

[4] - At Week 1, data were available for 45 participants

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline to endpoint in PANSS negative subscale.

End point title	Mean change from Baseline to endpoint in PANSS negative subscale.

End point description:

The PANSS consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms). The 7 negative symptom constructs were blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking. The PANSS Total Score ranged from 30 (best possible outcome) to 210 (worst possible outcome). The ITT data set comprised of participants randomized to the double-blind phase. LOCF method was used to impute missing data. Week 1 participants analysed were 94 and 45.

End point type	Secondary

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (Aripiprazole N= 95, Placebo N= 45)	0.03 (± 1.57)	-0.09 (± 1.4)		
Week 2	-0.07 (± 1.68)	-0.23 (± 2.35)		
Week 3	-0.39 (± 1.89)	0.48 (± 3.17)		
Week 4	-0.27 (± 2.12)	0.44 (± 3.41)		
Week 6	-0.42 (± 2.37)	0.9 (± 3.57)		
Week 8	-0.41 (± 2.37)	0.77 (± 3.76)		
Week 10	-0.33 (± 2.47)	0.71 (± 3.82)		
Week 12	-0.38 (± 2.91)	0.79 (± 0.79)		
Week 14	-0.41 (± 3.13)	1.15 (± 4.63)		
Week 16	-0.51 (± 3.31)	1.19 (± 4.77)		
Week 18	-0.47 (± 3.45)	1.19 (± 4.77)		
Week 20	-0.47 (± 3.54)	1.1 (± 4.93)		
Week 22	-0.43 (± 3.55)	1.06 (± 5.26)		
Week 24	-0.42 (± 3.54)	0.79 (± 5.41)		
Week 26	-0.54 (± 3.6)	0.81 (± 5.43)		
Week 28	-0.51 (± 3.63)	0.83 (± 5.43)		
Week 30	-0.56 (± 3.57)	0.67 (± 5.55)		
Week 32	-0.52 (± 3.6)	0.98 (± 5.89)		
Week 34	-0.64 (± 3.68)	0.56 (± 0.56)		
Week 36	-0.47 (± 3.71)	0.65 (± 5.69)		
Week 38	-0.62 (± 0.37)	0.54 (± 5.84)		
Week 40	-0.64 (± 3.78)	0.54 (± 5.78)		
Week 42	0.77 (± 3.79)	0.42 (± 5.75)		
Week 44	-0.72 (± 3.87)	0.46 (± 5.76)		

Week 46	-0.68 (± 3.84)	0.35 (± 5.83)		
Week 48	-0.73 (± 3.83)	0.33 (± 5.88)		
Week 50	-0.8 (± 3.84)	0.29 (± 5.96)		
Week 52	-0.78 (± 3.81)	0.4 (± 5.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of responders in each treatment group

End point title	Percentage of responders in each treatment group

End point description:

Percentage of responders in each treatment group (i.e, response defined as meeting stability criteria). Participants stabilized on aripiprazole (trial drug) within the approved dose range of 10 to 30 mg/day and are tolerable based on clinical judgment. The ITT data set comprised of all participants who were randomised to the double-blind phase.

End point type	Secondary

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Percentage				
number (not applicable)				
Week 1 (Arirpiprazole N= 95, Placebo	96.8	97.8		
Week 2 (N= 91, 46)	92.3	95.7		
Week 3 (N= 86, 45)	93	86.7		
Week 4 (N= 91, 43)	93.4	90.7		
Week 6 (N= 87, 41)	90.8	92.7		
Week 8 (N= 82, 38)	97.6	89.5		
Week 10 (N= 74, 32)	94.6	93.8		
Week 12 (N= 71, 30)	94.4	93.3		
Week 14 (N= 68, 26)	94.1	92.3		
Week 16 (N= 65, 25)	96.9	96		
Week 18 (N= 59, 23)	94.9	91.3		
Week 20 (N= 57, 23)	94.7	91.3		
Week 22 (N= 55, 21)	92.7	95.2		
Week 24 (N= 51, 19)	98	100		
Week 26 (N= 48, 19)	97.9	100		
Week 28 (N= 42, 17)	97.6	100		
Week 30 (N= 40, 16)	95	100		
Week 32 (N= 39, 16)	94.9	93.8		
Week 34 (N= 38, 14)	94.7	100		
Week 36 (N= 36, 15)	94.4	100		
Week 38 (N= 33, 12)	100	100		

Week 40 (N= 29, 11)	100	100		
Week 42 (N= 27, 11)	100	100		
Week 44 (N= 21, 8)	100	100		
Week 46 (N= 18, 8)	88.9	100		
Week 48 (N= 17, 8)	94.1	100		
Week 50 (N= 17, 6)	88.2	100		
Week 52 (N= 14, 7)	100	100		
Last Visit (N= 98, 48)	77.6	64.6		

Statistical analyses

Statistical analysis title	Statistical analysis 1 at Last Visit

Statistical analysis description:

Statistical Analysis for Last Visit. The total number of exacerbation of psychotic symptoms/impending relapse was estimated using a 2:1 (aripiprazole:placebo) randomization ratio to achieve at least 80% power and to preserve an overall nominal alpha level of 0.05 (2-sided).

Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0962
Method	Chi-squared

Other pre-specified: Mean change from Baseline to endpoint in CGI-S score.

End point title	Mean change from Baseline to endpoint in CGI-S score.

End point description:

The severity of illness for each participant was rated using the CGI-S scale. To assess CGI-s, the Investigator answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" Response choices included: 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 participants. The ITT data set comprised of participants randomised to the double-blind phase. LOCF method was used to impute missing data. Week 1 participants analysed were 94 and 45 and Week 2 to Week 52 participants analysed were 97 and 48.

End point type	Other pre-specified

End point timeframe:

Baseline to Week 52/End of Double-Blind Phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (Aripiprazole N= 94, Placebo N= 45)	0.01 (± 0.23)	0.02 (± 0.34)		

Week 2 (N= 97, 48)	0 (± 0.32)	0.02 (± 0.44)		
Week 3	0.01 (± 0.4)	0.13 (± 0.64)		
Week 4	0.03 (± 0.44)	0.1 (± 0.69)		
Week 6	0.44 (± 0.52)	0.15 (± 0.77)		
Week 8	0.04 (± 0.63)	0.19 (± 0.79)		
Week 10	0.02 (± 0.71)	0.25 (± 0.81)		
Week 12	0.05 (± 0.77)	0.31 (± 0.85)		
Week 14	0.03 (± 0.78)	0.35 (± 1.04)		
Week 16	0.02 (± 0.83)	0.33 (± 1.06)		
Week 18	0.04 (± 0.83)	0.35 (± 1.06)		
Week 20	0.05 (± 0.85)	0.4 (± 1.12)		
Week 22	0.08 (± 0.87)	0.38 (± 1.14)		
Week 24	0.06 (± 0.88)	0.35 (± 1.18)		
Week 26	0.05 (± 0.89)	0.35 (± 1.18)		
Week 28	0.05 (± 0.92)	0.33 (± 1.19)		
Week 30	0.04 (± 0.91)	0.33 (± 1.19)		
Week 32	0.04 (± 0.92)	0.31 (± 1.21)		
Week 34	0.05 (± 0.93)	0.29 (± 1.22)		
Week 36	0.07 (± 0.95)	0.29 (± 1.22)		
Week 38	0.07 (± 0.95)	0.29 (± 1.22)		
Week 40	0.07 (± 0.95)	0.29 (± 1.22)		
Week 42	0.06 (± 0.94)	0.29 (± 1.22)		
Week 44	0.08 (± 0.95)	0.31 (± 1.21)		
Week 46	0.07 (± 0.95)	0.31 (± 1.21)		
Week 48	0.06 (± 0.94)	0.29 (± 1.22)		
Week 50	0.05 (± 0.95)	0.27 (± 1.25)		
Week 52	0.05 (± 0.95)	0.29 (± 1.22)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean CGI-I score at endpoint.

End point title	Mean CGI-I score at endpoint.

End point description:

Baseline for the double-blind maintenance phase was defined as the last visit with available data in the stabilization phase, and the CGI-I scale was completed prior to or on the first dose date in the double-blind maintenance phase. Response choices included: 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. The ITT data set comprised of participants randomised to double-blind phase. LOCF method was used to impute missing data. Week 1 participants analysed were 94 and 45 and Week 2 to Week 52 participants analysed were 97 and 48.

End point type	Other pre-specified

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline	2.4 (± 0.8)	2.52 (± 0.82)		
Week 1 (Aripiprazole N= 94, Placebo N= 45)	3.49 (± 0.84)	3.51 (± 0.84)		
Week 2 (N= 97, 48)	3.48 (± 0.88)	3.52 (± 0.95)		
Week 3	3.47 (± 0.89)	3.63 (± 1.06)		
Week 4	3.6 (± 0.92)	3.6 (± 1.2)		
Week 6	3.53 (± 1)	3.73 (± 1.3)		
Week 8	3.46 (± 1.09)	3.83 (± 1.45)		
Week 10	3.38 (± 1.13)	3.9 (± 1.49)		
Week 12	3.45 (± 1.19)	3.96 (± 1.44)		
Week 14	3.44 (± 1.23)	4.04 (± 1.56)		
Week 16	3.32 (± 1.25)	4 (± 1.57)		
Week 18	3.35 (± 1.29)	4.02 (± 1.58)		
Week 20	3.4 (± 1.3)	4.08 (± 1.54)		
Week 22	3.43 (± 1.34)	4.04 (± 1.6)		
Week 24	3.41 (± 1.31)	4.08 (± 1.6)		
Week 26	3.41 (± 1.34)	4.04 (± 1.6)		
Week 28	3.43 (± 1.34)	4.02 (± 4.02)		
Week 30	3.44 (± 1.36)	4 (± 1.66)		
Week 32	3.46 (± 1.37)	3.98 (± 1.68)		
Week 34	3.47 (± 1.36)	3.94 (± 1.71)		
Week 36	3.48 (± 1.39)	3.94 (± 1.71)		
Week 38	3.45 (± 1.38)	3.94 (± 1.71)		
Week 40	3.45 (± 1.38)	3.92 (± 1.72)		
Week 42	3.45 (± 1.38)	3.92 (± 1.72)		
Week 44	3.45 (± 1.38)	3.94 (± 1.71)		
Week 46	3.46 (± 1.37)	3.94 (± 1.71)		
Week 48	3.46 (± 1.38)	3.92 (± 1.72)		
Week 50	3.46 (± 1.38)	3.92 (± 1.72)		
Week 52	3.42 (± 1.39)	3.92 (± 1.72)		

Statistical analyses

Statistical analysis title	Statistical analysis at Baseline
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3862 [5]
Method	Cochran-Mantel-Haenszel

Notes:
[5] - The Cochran-Mantel-Haenszel (CMH) method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 1
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8861 [6]
Method	Cochran-Mantel-Haenszel

Notes:
[6] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 2
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8189 [7]
Method	Cochran-Mantel-Haenszel

Notes:
[7] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 3
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3689 [8]
Method	Cochran-Mantel-Haenszel

Notes:
[8] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 4
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9723 [9]
Method	Cochran-Mantel-Haenszel

Notes:
[9] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 6
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2985 [10]
Method	Cochran-Mantel-Haenszel

Notes:

[10] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 8
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0883 [11]
Method	Cochran-Mantel-Haenszel

Notes:

[11] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 10
Comparison groups	Placebo double-blind maintenance v Aripiprazole double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0228 [12]
Method	Cochran-Mantel-Haenszel

Notes:

[12] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 12
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0274 [13]
Method	Cochran-Mantel-Haenszel

Notes:

[13] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 14
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0135 [14]
Method	Cochran-Mantel-Haenszel

Notes:

[14] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 16
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059 [15]
Method	Cochran-Mantel-Haenszel

Notes:

[15] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 18
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0076 [16]
Method	Cochran-Mantel-Haenszel

Notes:

[16] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 20
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0065 [17]
Method	Cochran-Mantel-Haenszel

Notes:

[17] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 22
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0175 [18]
Method	Cochran-Mantel-Haenszel

Notes:

[18] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 24
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0107 [19]
Method	Cochran-Mantel-Haenszel

Notes:

[19] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 26
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118 [20]
Method	Cochran-Mantel-Haenszel

Notes:

[20] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 28
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0232 [21]
Method	Cochran-Mantel-Haenszel

Notes:

[21] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 30
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0337 [22]
Method	Cochran-Mantel-Haenszel

Notes:

[22] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 32
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0507 [23]
Method	Cochran-Mantel-Haenszel

Notes:

[23] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 34
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0791 [24]
Method	Cochran-Mantel-Haenszel

Notes:

[24] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 36
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0898 [25]
Method	Cochran-Mantel-Haenszel

Notes:

[25] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 38
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0686 [26]
Method	Cochran-Mantel-Haenszel

Notes:

[26] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 40
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0833 [27]
Method	Cochran-Mantel-Haenszel

Notes:

[27] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 42
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0824 [28]
Method	Cochran-Mantel-Haenszel

Notes:

[28] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 44
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0686 [29]
Method	Cochran-Mantel-Haenszel

Notes:

[29] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 46
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0737 [30]
Method	Cochran-Mantel-Haenszel

Notes:

[30] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 48
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0893 [31]
Method	Cochran-Mantel-Haenszel

Notes:

[31] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 50
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0706 [32]
Method	Cochran-Mantel-Haenszel

Notes:

[32] - CMH method was based on raw mean score statistics.

Statistical analysis title	Statistical analysis at Week 52
Comparison groups	Aripiprazole double-blind maintenance v Placebo double-blind maintenance
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0657 [33]
Method	Cochran-Mantel-Haenszel

Notes:

[33] - CMH method was based on raw mean score statistics.

Other pre-specified: Mean change from Baseline to endpoint in PANSS positive subscale.

End point title	Mean change from Baseline to endpoint in PANSS positive subscale.

End point description:

The PANSS consisted of 3 subscales were a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 indicated (absence of symptoms) and a score of 7 indicated (extremely severe symptoms). The 7 positive symptom constructs were delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS Total Score ranged from 30 (best possible outcome) to 210 (worst possible outcome). The ITT data set comprised of participants randomised to

the double-blind phase. LOCF method was used to impute missing data. Week 1 participants analysed were 94 and 45.

End point type	Other pre-specified

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (Aripiprazole N= 95, Placebo N= 45)	0.08 (± 1.84)	0.07 (± 2.41)		
Week 2	0.09 (± 2.05)	-0.04 (± 2.87)		
Week 3	0.01 (± 2.36)	0.56 (± 3.34)		
Week 4	-0.12 (± 2.65)	0.58 (± 3.8)		
Week 6	-0.2 (± 2.9)	1.1 (± 4.85)		
Week 8	-0.19 (± 3.23)	1.56 (± 5.11)		
Week 10	-0.16 (± 3.28)	1.63 (± 5.45)		
Week 12	0.23 (± 3.58)	1.96 (± 5.78)		
Week 14	0.28 (± 3.77)	2.27 (± 6.03)		
Week 16	0.32 (± 3.77)	2.17 (± 6.05)		
Week 18	0.24 (± 3.98)	2.15 (± 6.14)		
Week 20	0.18 (± 4)	2.44 (± 6.32)		
Week 22	0.39 (± 4.12)	2.6 (± 6.44)		
Week 24	0.38 (± 4.23)	2.65 (± 6.36)		
Week 26	0.22 (± 4.23)	2.58 (± 6.45)		
Week 28	0.17 (± 4.28)	2.56 (± 6.51)		
Week 30	0.22 (± 4.41)	2.6 (± 6.59)		
Week 32	0.18 (± 4.45)	2.71 (± 6.64)		
Week 34	0.29 (± 4.45)	2.58 (± 2.58)		
Week 36	0.22 (± 4.55)	2.48 (± 6.6)		
Week 38	0.27 (± 4.56)	2.46 (± 6.63)		
Week 40	0.24 (± 4.52)	2.44 (± 6.69)		
Week 42	0.27 (± 4.52)	2.35 (± 6.73)		
Week 44	0.27 (± 4.52)	2.33 (± 6.76)		
Week 46	0.21 (± 4.52)	2.42 (± 6.69)		
Week 48	0.3 (± 4.53)	2.29 (± 6.77)		
Week 50	0.2 (± 4.52)	2.33 (± 6.75)		
Week 52	0.16 (± 4.55)	6.75 (± 6.75)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean change from Baseline to endpoint in Children's Global Assessment Scale (CGAS).

End point title	Mean change from Baseline to endpoint in Children's Global Assessment Scale (CGAS).

End point description:

The CGAS was developed by Schaffer and colleagues to provide a global measure of severity of disturbance in children and adolescents. The CGAS is a rating scale for evaluating the overall functioning of a participant during a specified time period on a continuum from psychological or psychiatric sickness to health. The CGAS is a valid and reliable tool for rating a child's general level of functioning on a health-illness continuum. CGAS score (range 1-100) was a single item score for rating a child's general level of functioning on a health-illness continuum, with higher scores represented better functioning. The ITT data set comprised of participants randomised to the double-blind phase. LOCF method was used to impute missing data. Week 1 participants analysed were 95 and 45.

End point type	Other pre-specified

End point timeframe:

Baseline to Week 52/End of Double-Blind phase visit.

End point values	Aripiprazole double-blind maintenance	Placebo double-blind maintenance		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	48		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (Aripiprazole N= 95, Placebo N= 45)	0 (± 2.74)	-0.09 (± 2.02)		
Week 2	-0.1 (± 3.9)	-0.31 (± 4.03)		
Week 3	0.35 (± 4.36)	-1.04 (± 7.21)		
Week 4	0.29 (± 5.22)	-1.23 (± 7.78)		
Week 6	0.4 (± 6.01)	-2.08 (± 9.14)		
Week 8	0.98 (± 6.9)	-2.4 (± 9.93)		
Week 10	1.11 (± 7.47)	-2.31 (± 11.63)		
Week 12	1.08 (± 8.21)	-2.85 (± 11.4)		
Week 14	1.06 (± 8.49)	-3.52 (± 12.4)		
Week 16	1.57 (± 8.69)	-2.69 (± 12.96)		
Week 18	1.55 (± 9.41)	-2.9 (± 13.07)		
Week 20	1.28 (± 9.88)	-4.06 (± 14.84)		
Week 22	1.17 (± 10.15)	-3.77 (± 15.05)		
Week 24	1.33 (± 10.33)	-3.67 (± 15.2)		
Week 26	1.61 (± 10.37)	-3.69 (± 15.29)		
Week 28	1.73 (± 10.73)	-3.75 (± 15.26)		
Week 30	1.92 (± 10.89)	-3.44 (± 15.45)		
Week 32	1.86 (± 11.03)	-3.33 (± 15.47)		
Week 34	2.05 (± 11.19)	-3 (± 15.85)		
Week 36	1.87 (± 11.41)	-3.1 (± 15.7)		
Week 38	2 (± 11.59)	-2.85 (± 15.95)		

Week 40	1.9 (± 11.68)	-2.85 (± 15.99)		
Week 42	1.9 (± 11.74)	-2.69 (± 16.17)		
Week 44	1.83 (± 11.86)	-2.67 (± 16.18)		
Week 46	2.13 (± 11.74)	-2.67 (± 16.17)		
Week 48	2.17 (± 11.79)	-2.4 (± 16.42)		
Week 50	2.29 (± 11.74)	-2.31 (± 16.51)		
Week 52	2.35 (± 11.85)	-2.25 (± 16.58)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the time the informed consent form was signed (with 4-Week Post-Trial Follow-up).

Adverse event reporting additional description:

Serious adverse event was any untoward medical occurrence that results in death, was life-threatening, required inpatient hospitalisation or prolonged hospitalisation. An AE was an exacerbation of existing problem or any new problem, experienced by a participant when enrolled in a trial, whether or not it was considered drug related by physician.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Aripiprazole-Conversion Phase

Reporting group description:

Participants had received oral aripiprazole 2 to 10 mg for 2 Weeks in combination with any other antipsychotic were in conversion phase.

Reporting group title	Aripiprazole-Stabilisation Phase

Reporting group description:

Participants who had converted to aripiprazole monotherapy period 1 (conversion phase) and had received aripiprazole monotherapy for schizophrenia at screening were in period 2, provided the prescribed aripiprazole dose did not exceed 30 mg (milligrams) per day for 2 Weeks.

Reporting group title	Aripiprazole-Double Blind Maintenance Treatment

Reporting group description:

Participants who met stability criteria in period 2 (stabilisation phase) had received oral aripiprazole 10 to 30 mg/day for 52 Weeks in period 3 (double-blind maintenance treatment).

Reporting group title	Placebo-Double Blind Maintenance Treatment

Reporting group description:

Participants who met stability criteria in period 2 (stabilisation phase) had received placebo for 52 Weeks in period 3 (double-blind maintenance treatment).

Serious adverse events	Aripiprazole-Conversion Phase	Aripiprazole-Stabilisation Phase	Aripiprazole-Double Blind Maintenance Treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 186 (1.08%)	4 / 183 (2.19%)	3 / 98 (3.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	0 / 98 (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
Psychiatric disorders			

Hallucinations, mixed			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	0 / 98 (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
Psychotic disorder			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	2 / 98 (2.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	1 / 186 (0.54%)	2 / 183 (1.09%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo-Double Blind Maintenance Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 48 (12.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Hallucinations, mixed			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			

subjects affected / exposed	5 / 48 (10.42%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Aripiprazole-Conversion Phase	Aripiprazole-Stabilisation Phase	Aripiprazole-Double Blind Maintenance Treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 186 (27.96%)	56 / 183 (30.60%)	41 / 98 (41.84%)
Investigations			
Weight increased			
subjects affected / exposed	0 / 186 (0.00%)	13 / 183 (7.10%)	8 / 98 (8.16%)
occurrences (all)	0	14	8
Nervous system disorders			
Akathisia			
subjects affected / exposed	11 / 186 (5.91%)	14 / 183 (7.65%)	3 / 98 (3.06%)
occurrences (all)	11	16	3
Headache			
subjects affected / exposed	12 / 186 (6.45%)	13 / 183 (7.10%)	6 / 98 (6.12%)
occurrences (all)	14	13	6
Somnolence			
subjects affected / exposed	19 / 186 (10.22%)	12 / 183 (6.56%)	0 / 98 (0.00%)
occurrences (all)	23	12	0
Tremor			
subjects affected / exposed	6 / 186 (3.23%)	13 / 183 (7.10%)	4 / 98 (4.08%)
occurrences (all)	6	16	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 186 (0.00%)	0 / 183 (0.00%)	1 / 98 (1.02%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 186 (8.60%)	14 / 183 (7.65%)	5 / 98 (5.10%)
occurrences (all)	16	16	5
Psychotic disorder			

subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	7 / 98 (7.14%)
occurrences (all)	1	0	7
Schizophrenia			
subjects affected / exposed	1 / 186 (0.54%)	6 / 183 (3.28%)	9 / 98 (9.18%)
occurrences (all)	1	6	9
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 186 (0.00%)	0 / 183 (0.00%)	7 / 98 (7.14%)
occurrences (all)	0	0	8

Non-serious adverse events	Placebo-Double Blind Maintenance Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 48 (52.08%)		
Investigations			
Weight increased			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	5		
Nervous system disorders			
Akathisia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Somnolence			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	5		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Psychiatric disorders			
Insomnia			

subjects affected / exposed	9 / 48 (18.75%)		
occurrences (all)	14		
Psychotic disorder			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Schizophrenia			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	8		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2011	This amendment included a new warning from the European Summary of Product Characteristics on venous thromboembolism and an explanation of the occurrence of suicidal behaviour in participants with psychotic illnesses; to provide clearer instructions to investigators on trial procedures; to correct several errors in the protocol that were inconsistent with the Schedule of Trial Assessments.
20 November 2012	The aim of this amendment was: to reduce the statistical power of the trial from 90% to 80% while keeping the randomization ratio at 2:1 to limit the number of participants exposed to placebo. Consequently, the total number of events was reduced from 49 to 37. The total number of randomized participants was decreased from 138 to 105: in the aripiprazole group, from 96 to 70, and in the placebo group, from 48 to 35; to reduce the number of interim analyses from two to one; to extend the 2-year recruitment period by 1 year, making it a 3-year recruitment period; to add a missing "not" to Inclusion Criterion #3 "as long as the subject does not require prohibited medication."; to update the protocol amendment with information from the aripiprazole Investigator Brochure, Version No. 16; to update the protocol amendment with text from the new protocol template; to remove mention of collecting thyroid stimulating hormone at the conversion phase baseline visit; to make clarifications about the following: (1) stability criterion 5, (2) the intent-to-treat Population, (3) the rationale for using aripiprazole doses higher than 15 mg, (4) the minimum duration of aripiprazole exposure needed with the 2 weeks of stabilization, and (5) the rationale for an interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 October 2013	The sponsor terminated the trial after the 37th event of exacerbation of psychotic symptoms/impending relapse occurred. This was to reduced the overall risk to participants by minimizing exposure to placebo.	-

Notes:

Limitations and caveats

None reported