Clinical trial results:
A Long-term, Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Flexible-Dose Oral Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia or Child and Adolescent Patients with Bipolar I Disorder, Manic or Mixed Episode with or without Psychotic Features

Summary

EudraCT number	2010-018911-13
Trial protocol	PL BG HU
Global end of trial date	07 September 2014

Results information

Result version number	v2 (current)
This version publication date	09 April 2016
First version publication date	12 August 2015
Version creation reason	• New data added to full data set New data added to full data set.

Trial information

Trial identification

Sponsor protocol code	31-09-267

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01122927
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, Maryland, United States, 20850
Public contact	Dorota Plewicka , Covance CAPS Ltd, 47 578213 25, dorota.plewicka@covance.com
Scientific contact	Dorota Plewicka , Covance CAPS Ltd, 47 578213 25, dorota.plewicka@covance.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	27 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2014
Global end of trial reached?	Yes
Global end of trial date	07 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to further characterize the long-term safety and tolerability of aripiprazole in adolescent subjects with schizophrenia and child and adolescent subjects with bipolar I disorder, manic or mixed episode, with or without psychotic features.

Protection of trial subjects:

The trial was conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH-GCP), and applicable local laws and regulatory requirements. Written informed consent was obtained from each participant's legally acceptable representative as applicable for local laws, and informed assent was obtained from all participants, as applicable for local laws. Informed consent/assent, as applicable for local laws, was obtained and documented prior to initiation of any procedures that were performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medications. All participants received copies of their signed and dated Informed consent forms (ICFs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2010
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	United States: 105
Country: Number of subjects enrolled	Bulgaria: 70
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	India: 93
Country: Number of subjects enrolled	Philippines: 12
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Romania: 17
Country: Number of subjects enrolled	Russian Federation: 73
Country: Number of subjects enrolled	Serbia: 12
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Ukraine: 98

Worldwide total number of subjects	524
EEA total number of subjects	130

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)	18
Adolescents (12-17 years)	493
Adults (18-64 years)	13
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 524 participants at 118 trial sites in 13 countries.

Pre-assignment

Screening details:

524 participants entered this trial (297 participants in the conversion phase and 510 participants in the open-label treatment phase). In the latter, 362 were de novo participants (280 participants entered into the conversion phase) and 148 rolled over from Trial 2010-020987-39. 416 participants had schizophrenia and 94 had bipolar disorder.

Period 1

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

Blinding implementation details:

Not applicable for this open-label trial.

Arms

Arm title	All Participants

Arm description:

Data for all the participants were analyzed.

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 were administered oral aripiprazole titrated from 10 to 30 milligram per day (mg/day), with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Number of subjects in period 1	All Participants
Started	524
Completed	198
Not completed	326
Physician decision	14
Consent withdrawn by subject	72
Adverse Event	36
Lost to follow-up	21
Sponsor Discontinued Trial	165
Met Withdrawal Criteria	10
Protocol deviation	1
Lack of efficacy	7

Baseline characteristics

Reporting groups	
Reporting group title	All Participants
Reporting group description:	
Data for all the participants were analyzed.	

Reporting group values	All Participants	Total	
Number of subjects	524	524	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	18	18	
Adolescents (12-17 years)	493	493	
Adults (18-64 years)	13	13	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	15.2		
standard deviation	± 1.6	-	
Gender categorical Units: Subjects			
Female	208	208	
Male	316	316	

End points

End points reporting groups

Reporting group title	All Participants

Reporting group description:

Data for all the participants were analyzed.

Subject analysis set title	Open-label Treatment Phase
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were administered oral aripiprazole titrated from 10 to 30 milligram per day (mg/day), with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Subject analysis set title	Tanner score at Baseline of 1
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who entered this phase had received oral aripiprazole titrated from 10 to 30 mg/day, with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Subject analysis set title	Tanner score at Baseline of 2
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who entered this phase had received oral aripiprazole titrated from 10 to 30 mg/day, with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Subject analysis set title	Tanner score at Baseline of 3
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who entered this phase had received oral aripiprazole titrated from 10 to 30 mg/day, with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Subject analysis set title	Tanner score of Baseline of 4
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who entered this phase had received oral aripiprazole at a target dose of 10 to 30 mg/day, with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Subject analysis set title	Tanner score of Baseline of 5
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who entered this phase had received oral aripiprazole titrated from 10 to 30 mg/day, with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Primary: Number of participants with adverse events (AEs)

End point title	Number of participants with adverse events (AEs)[1]

End point description:

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

End point type	Primary

End point timeframe:

Adverse events were recorded from the time of the informed consent was signed until the follow-up visit 30 (± 3) days after the end of trial.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis provided for Number of participants with adverse events (AEs).

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Participants				
Participants with TEAEs	349			
Participants with serious TEAEs	49			
Participants with severe TEAEs	33			
Discontinued due to AEs	32			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of laboratory values of potential clinical relevance

End point title	Incidence of laboratory values of potential clinical relevance

End point description:

The laboratory values were one of the parameters to measure the safety and tolerability of individual participants. Incidence of TEAEs of potential clinical relevance include abnormal values in serum chemistry, hematology, urinalyses and prolactin tests that were identified based on pre-defined criteria. Abnormal laboratory values in participants were reported as SAE/AEs and are reported in the SAE/non-serious AE section of this report.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Participants				
Chemistry-Alanine transaminase	11			
Chemistry-Aspartate transaminase	8			
Chemistry-Bilirubin, total	20			
Chemistry-Calcium	30			
Chemistry-Chloride	158			
Chemistry-Cholesterol, total, fasting	68			
Chemistry-Creatine phosphokinase, total	40			
Chemistry-Glutamyl transferase	78			
Chemistry-HDL cholesterol, fasting	128			
Chemistry-LDL cholesterol, calculation	2			

Chemistry-Phosphorus inorganic	135			
Chemistry-Protein, total serum	81			
Chemistry-Triglycerides, fasting	46			
Hematology-Eosinophils	19			
Hematology-Hemoglobin	14			
Hematology-White blood cell count	9			
Urinalysis-Protein, urine	348			
Urinalysis-Specific gravity	188			
Others-Insulin	49			
Others-Insulin, fasting	78			
Others-Prolactin	324			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of physical examination findings of potential clinical relevance

End point title	Incidence of physical examination findings of potential clinical relevance

End point description:

The physical examination evaluation was one of the parameters to measure the safety and tolerability of individual participants. Incidence of TEAEs of potential clinical relevance include abnormal changes in the following body systems: head, ears, eyes, nose, and throat; thorax; abdomen; urogenital; extremities; neurological; and skin and mucosae.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of vital signs of potential clinical relevance

End point title	Incidence of vital signs of potential clinical relevance

End point description:

Vital signs are taken at Baseline, Weeks 1, 2, 3, 4, 6, 8, and Months 3, 4, 6, 9, 12, 15, 18, 21, 24 of Phase 2 (Visits beyond Month 12 only for de novo subjects). Assessments included orthostatic (supine and standing) blood pressure (BP) measured as millimeter of mercury [mmhg]), heart rate and body temperature. Incidence of TEAEs of potential clinical relevance included abnormal values in heart rate (measured as beats per minutes [bpm]), systolic and diastolic blood pressure, respiratory rate and

weight that were identified based on pre-defined criteria. Abnormal vital signs in participants were reported as SAE/AEs and are reported in the SAE/non-serious AE section of this report.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Participants				
Heart rate supine-Increase ≥15 bpm	1			
Heart rate supine-Decrease ≥15 bpm	1			
Heart rate standing-Increase ≥15 bpm	4			
Heart rate standing-Decrease ≥15 bpm	0			
Systolic supine BP-Increase ≥20 mmHg	36			
Systolic supine BP-Decrease ≥20 mmHg	31			
Systolic standing BP-Increase ≥20mmHg	38			
Systolic standing BP-Decrease ≥20mmHg	40			
Diastolic supine BP-Increase ≥15 mmHg	41			
Diastolic supine BP-Decrease ≥15mmHg	19			
Diastolic standing BP-Increase ≥15mmHg	53			
Diastolic standing BP-Decrease ≥15mmHg	13			
Weight gain ≥7%	195			
Weight loss ≥7%	45			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline by Week in Abnormal Involuntary Movement Scale (AIMS)

End point title	Mean change from Baseline by Week in Abnormal Involuntary Movement Scale (AIMS)

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N=486)	-0.02 (± 0.24)			
Week 2 (N=507)	-0.01 (± 0.25)			
Week 3 (N=507)	0.01 (± 0.36)			
Week 4 (N=507)	-0.01 (± 0.27)			
Week 6 (N=507)	0.02 (± 0.56)			
Week 8 (N=507)	-0.02 (± 0.28)			
Month 3 (N=507)	0 (± 0.31)			
Month 6 (N=507)	-0.02 (± 0.4)			
Month 9 (N=506)	0.01 (± 0.55)			
Month 12 (N=507)	-0.02 (± 0.41)			
Month 15 (N=360)	-0.01 (± 0.43)			
Month 18 (N=360)	-0.04 (± 0.35)			
Month 21 (N=360)	-0.01 (± 0.52)			
Month 24 (N=360)	-0.04 (± 0.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline by Week in Simpson-Angus Scale (SAS) total score

End point title	Mean change from Baseline by Week in Simpson-Angus Scale (SAS) total score

End point description:

The SAS is a rating scale used to measure EPS. The SAS scale consists of a list of 10 symptoms of parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia), with each item rated from 0 to 4, with 0 being normal and 4 being the worst. The SAS Total score is sum of ratings for all 10 items, with possible Total scores from 0 to 40.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N=486)	-0.08 (± 0.89)			
Week 2 (N=507)	-0.11 (± 1.22)			
Week 3 (N=507)	-0.08 (± 1.23)			
Week 4 (N=507)	-0.18 (± 1.37)			
Week 6 (N=507)	-0.12 (± 1.49)			
Week 8 (N=507)	-0.21 (± 1.34)			
Month 3 (N=507)	-0.23 (± 1.56)			
Month 6 (N=507)	-0.31 (± 1.48)			
Month 9 (N=506)	-0.35 (± 1.5)			
Month 12 (N=507)	-0.36 (± 1.51)			
Month 15 (N=360)	-0.43 (± 1.78)			
Month 18 (N=360)	-0.48 (± 1.74)			
Month 21 (N=360)	-0.49 (± 1.82)			
Month 24 (N=360)	-0.53 (± 1.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline by Week in Barnes Akathisia Rating Scale (BARS) score

End point title	Mean change from Baseline by Week in Barnes Akathisia Rating Scale (BARS) score

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N=487)	-0.02 (± 0.26)			
Week 2 (N=507)	-0.02 (± 0.35)			
Week 3 (N=507)	-0.02 (± 0.35)			

Week 4 (N=507)	-0.03 (± 0.33)			
Week 6 (N=507)	-0.03 (± 0.36)			
Week 8 (N=507)	-0.02 (± 0.41)			
Month 3 (N=507)	0 (± 0.45)			
Month 6 (N=507)	-0.03 (± 0.44)			
Month 9 (N=506)	-0.04 (± 0.43)			
Month 12 (N=507)	-0.04 (± 0.42)			
Month 15 (N=360)	-0.02 (± 0.47)			
Month 18 (N=360)	-0.05 (± 0.48)			
Month 21 (N=360)	-0.04 (± 0.5)			
Month 24 (N=360)	-0.05 (± 0.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with cognitive impairment for each New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT)

End point title	Number of participants with cognitive impairment for each New York Assessment for Adverse Cognitive Effects of Neuropsychiatric Treatment (NY-AACENT)

End point description:

The NY-AACENT is not a validated scale. It was included in this trial because of concerns that regulatory authorities (the European Committee for Medicinal Products for Human Use [CHMP] and the Paediatric Sub-Committee of the European Medicinal Agency [PDCO]) had regarding drug induced cognitive impairment. No validated scale addressing these issues was available at the time of the trial. The NY-AACENT was used to detect changes in cognitive function subsequent to pharmacological or similar treatments for neurological or psychiatric problems. It was specifically designed to be used in paediatric populations (ages 12 to 17), but could have been utilized with other age groups, as appropriate.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Participants				
Working memory	237			
Attention/vigilance	306			
Verbal learning/memory	233			
Visual learning/memory	138			
Reasoning and problem solving	308			
Speed of processing	276			
Social congnition	307			

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline and Post-Baseline Tanner Staging

End point title	Baseline and Post-Baseline Tanner Staging

End point description:

Tanner staging was completed together with the physical examination by the same trial-affiliated clinician in the most inconspicuous manner for the participant as possible. Tanner staging assessment consisted of 2 domains (pubic hair and breast development) for girls and 3 domains (pubic hair, penis development, and testes development) for boys. A participant who reached Stage 5 (both in pubic hair and genitalia) did not need to continue with Tanner Staging assessment and the Tanner Staging scales of this participant were imputed as 5 for all of the following scheduled time points up to and including the completion visit/early termination (ET) visit. The clinician arrived at a single score summarizing the domains (not individual domain scores) when evaluating the participant. The total shift data for last visit is presented below.

End point type	Secondary

End point timeframe:

Baseline to Last Visit

End point values	Tanner score at Baseline of 1	Tanner score at Baseline of 2	Tanner score at Baseline of 3	Tanner score of Baseline of 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	24	79	196
Units: Participants				
Last Vist (Post-Baseline score of 1) (N= 1)	1	0	0	0
Last Vist (Post-Baseline score of 2) (N= 9)	4	5	0	0
Last Vist (Post-Baseline score of 3) (N= 39)	2	9	28	0
Last Vist (Post-Baseline score of 4) (N= 134)	0	7	33	94
Last Vist (Post-Baseline score of 5) (N= 327)	0	3	18	102

End point values	Tanner score of Baseline of 5			
Subject group type	Subject analysis set			
Number of subjects analysed	204			
Units: Participants				
Last Vist (Post-Baseline score of 1) (N= 1)	0			
Last Vist (Post-Baseline score of 2) (N= 9)	0			

Last Vist (Post-Baseline score of 3) (N= 39)	0			
Last Vist (Post-Baseline score of 4) (N= 134)	0			
Last Vist (Post-Baseline score of 5) (N= 327)	204			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline for Columbia-Suicide Severity Rating Scale (C-SSRS) in Suicidal Ideation Intensity Total Score

End point title	Mean change from Baseline for Columbia-Suicide Severity Rating Scale (C-SSRS) in Suicidal Ideation Intensity Total Score

End point description:

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

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 1 (N= 487)	-0.4 (± 2.1)			
Week 2 (N= 483)	-0.4 (± 2.2)			
Week 3 (N= 477)	-0.4 (± 2.2)			
Week 4 (N= 491)	-0.4 (± 2.2)			
Week 6 (N= 488)	-0.3 (± 2.1)			
Week 8 (N= 484)	-0.4 (± 2)			
Month 3 (N= 478)	-0.3 (± 2.2)			
Month 4 (N= 472)	-0.3 (± 2.1)			
Month 6 (N= 458)	-0.2 (± 2.5)			
Month 9 (N= 407)	-0.2 (± 1.8)			
Month 12 (N= 302)	-0.3 (± 2)			
Month 15 (N= 261)	-0.2 (± 1.9)			
Month 18 (N= 247)	-0.1 (± 2)			
Month 21 (N= 212)	-0.1 (± 1.8)			
Month 24 (N= 180)	0 (± 1.9)			

Last Visit (N= 507)	-0.1 (± 2.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who discontinued due to all adverse events

End point title	Percentage of participants who discontinued due to all adverse events

End point description:

The time to discontinuations due to all causes other than sponsor terminating the trial was measured from the date of entering the open-label treatment phase to the date of ET for discontinued participants in the open-label treatment phase (ie, time to discontinuation = date of discontinuation [or date of completion for completed participants] − date of participant entering the open-label treatment phase + 1). If the participants completed the trial or were discontinued due to the sponsor terminating the trial, they were censored at the time of completion or trial termination, respectively.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Discontinuation rate				
number (not applicable)				
From study P3109266 (N= 148)	3.4			
De Novo (N= 362)	7.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Positive and Negative Symptoms Score (PANSS) total score

End point title	Mean change from Baseline in Positive and Negative Symptoms Score (PANSS) total score

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS total score was the sum of the rating scores for 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items from the PANSS panel. The PANSS total score ranged from 30 (best possible outcome) to 210 (worst possible outcome).

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 414)	-9.98 (± 14.66)			
Month 24 (N= 267)	-12.52 (± 15.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS positive subscale score

End point title	Mean change from Baseline in PANSS positive subscale score

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS positive subscale score was the sum of the rating scores for the 7 positive scale items from the PANSS panel. The 7 positive symptom constructs are delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. The PANSS Positive Subscale ranges from 7 (absence of symptoms) to 49 (extremely severe symptoms).

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 414)	-2.57 (± 4.96)			
Month 24 (N= 267)	-2.91 (± 5.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in PANSS negative subscale score

End point title	Mean change from Baseline in PANSS negative subscale score

End point description:

The PANSS consisted of three subscales: a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 (absence of symptoms) and a score of 7 (extremely severe symptoms). The PANSS negative subscale score was the sum of the rating scores for the 7 negative scale items from the PANSS panel. The 7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking. The PANSS Negative Subscale ranges from 7 (absence of symptoms) to 49 (extremely severe symptoms).

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 414)	-2.79 (± 4.17)			
Month 24 (N= 267)	-3.48 (± 4.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Clinical Global Impression-Severity (CGI-S) Score

End point title	Mean change from Baseline in Clinical Global Impression-Severity (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 study physician 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 ill at all; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill participants.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 414)	-0.66 (± 0.96)			
Month 24 (N= 267)	-0.77 (± 1.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean in Clinical Global Impression-Improvement (CGI-I) score

End point title	Mean in Clinical Global Impression-Improvement (CGI-I) score

End point description:

The efficacy of trial medication were rated for each participant using the CGI-I scale. The study physician must rate the participant's total improvement whether or not it is due entirely to drug treatment. All responses were compared to the participant's condition at baseline. Response choices include: 0 = not assessed; 1 =very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 =minimally worse; 6 = much worse; and 7 = very much worse.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	510			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 408)	2.62 (± 1.16)			
Month 24 (N= 263)	2.38 (± 1.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Young Mania Rating Scale (YMRS) score

End point title	Mean change from Baseline in Young Mania Rating Scale (YMRS) score

End point description:

The YMRS consists of 11 items assessing the core symptoms of mania and was used to assess participants with bipolar I disorder, manic and mixed episodes with or without psychotic features: elevated mood, increased motor activity - energy, sexual interest, sleep, irritability, speech (rate and

amount), language - thought disorder, content, disruptive - aggressive behavior, appearance, and insight. Each item had 5 or 9 grades of severity, with lower scores indicating milder symptoms. The number of raters within each trial center was to be kept to a minimum. The YMRS Total Score (range 0 to 44) is the sum of the rating scores for 11 items for assessing the core symptoms of mania. A missing value for any YMRS assessment item(s) could have resulted in a missing YMRS Total Score. A higher YMRS Total Score represents greater severity. In this study, 94 participants had bipolar disorder, this explains the N=94 in the table below and these were de novo participants.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	94			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 93)	-9.71 (± 10.23)			
Month 24 (N= 93)	-10.02 (± 10.21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Clinical Global Impression Scale - Bipolar (CGI-BP) version severity score

End point title	Mean change from Baseline in Clinical Global Impression Scale - Bipolar (CGI-BP) version severity score

End point description:

The CGI-BP scale refers to the global impression of the subject with respect to bipolar disorder. The scale rated the subject's Severity of Illness (CGI-BP-Severity: mania, depression, and overall bipolar illness) and Change From Preceding Phase (CGI-BP-Improvement: mania, depression, and overall bipolar illness) based on a 7- or 8-point scale. Severity of Illness (CGI-BP-Severity) was rated at all visits. At each visit other than Day 0 (Baseline), the Change From Preceding Phase (CGI-BP-Improvement) was judged with respect to participant's condition at Baseline. The CGI-BP Severity Scores (range 1 to 7), as well as CGI-BP Improvement Scores (range 1 to 7) are single-item rating scores, with higher scores representing greater severity or less improvement. Data for 94 de novo participants were available with bipolar disorder.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	94			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 93)	-1.26 (± 1.33)			
Month 24 (N= 93)	-1.3 (± 1.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Clinical Global Impression Scale - Bipolar version improvement score

End point title	Mean change from Baseline in Clinical Global Impression Scale - Bipolar version improvement score

End point description:

The CGI-BP scale refers to the global impression of the subject with respect to bipolar disorder. The scale rated the subject's Severity of Illness (CGI-BP-Severity: mania, depression, and overall bipolar illness) and Change From Preceding Phase (CGI-BP-Improvement: mania, depression, and overall bipolar illness) based on a 7- or 8-point scale. Severity of Illness (CGI-BP-Severity) was rated at all visits. At each visit other than Day 0 (Baseline), the Change From Preceding Phase (CGI-BP-Improvement) was judged with respect to participant's condition at Baseline. The CGI-BP Severity Scores (range 1 to 7), as well as CGI-BP Improvement Scores (range 1 to 7) are single-item rating scores, with higher scores representing greater severity or less improvement. Only 40 participants had data at Baseline to explain the N=40 in the table below and these were de novo participants.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	94			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 93)	2.27 (± 1.28)			
Month 24 (N= 93)	2.17 (± 1.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in General Behavior Inventory (GBI) Scale Total Score for Mania and Depression in both Parent/Guardian and Subject versions

of the scale

End point title	Mean change from Baseline in General Behavior Inventory (GBI) Scale Total Score for Mania and Depression in both Parent/Guardian and Subject versions of the scale

End point description:

The GBI is a self-report inventory with 73 items focusing on mood-related behaviors, including depressive, hypomanic, and biphasic symptoms. For this trial, two 20-item subscales were utilized: one was completed by the parent/guardian or legal representative, as applicable for local laws, and the other was completed by the participant. Responses were given on a 4-point Likert scale, with 0 being never or hardly ever and 3 being very often or almost constantly. The GBI Total Score for mania (range 0 to 30) is the sum of scores for items 1 to 10 and the GBI Total Score for depression (range 0 to 30) is the sum of scores for items 11 to 20 in the GBI Parent/Guardian or Subject Version panel. Scores from the Parent/Guardian and participant Versions were summarized separately. A missing value for any GBI assessment items could have resulted in a missing GBI Total Score. High scores represent greater psychopathology. Data was only available for 80 de novo participants with bipolar disorder.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	80			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 78)	-1.62 (± 7.2)			
Month 24 (N= 78)	-1.82 (± 7.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in the Attention Deficit Hyperactive Disorders Rating (ADHD-RS-IV) scale score

End point title	Mean change from Baseline in the Attention Deficit Hyperactive Disorders Rating (ADHD-RS-IV) scale score

End point description:

The ADHD-RS-IV is a reliable and easy-to-administer instrument both for diagnosing ADHD in children and adolescents and for assessing treatment response. Containing 18 items, the scale was linked directly to DSM-IV-TR diagnostic criteria for ADHD. There were 3 versions of the scale: a parent questionnaire on home behaviors (English), a parent questionnaire on home behaviors (Spanish), and a teacher questionnaire on classroom behaviors. For this trial, the parent questionnaire on home behaviors (English) was utilized. The ADHD-RS-IV Total Score (range 0 to 54) is the sum of rating scores for 18 items, with higher scores representing greater severity. A missing value for any ADHD-RS-IV assessment items could have resulted in a missing ADHD-RS-IV Total Score. Data were only available for 82 participants with bipolar disorder and these were de novo participants.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	82			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 81)	-3.25 (± 10.43)			
Month 24 (N= 81)	-2.53 (± 10.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Children's Global Assessment Scale (CGAS) in Bipolar (de novo participants)

End point title	Mean change from Baseline in Children's Global Assessment Scale (CGAS) in Bipolar (de novo participants)

End point description:

The CGAS is a 100-point rating scale measuring psychological, social, and school functioning for children aged 6 to 17. It was adapted from the Adults Global Assessment Scale. The Global Assessment Scale was 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. The CGAS was developed by Schaffer and colleagues to provide a global measure of severity of disturbance in children and adolescents. The CGAS Score (range 1 to 100) is a single-item score for rating a child’s general level of functioning on a health-illness continuum, with higher scores representing better functioning.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	Open-label Treatment Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	94			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Month 12 (N= 93)	14.17 (± 16.01)			
Month 24 (N= 93)	14 (± 16.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of suicidality, suicidal behaviour and suicidal ideation

End point title	Incidence of suicidality, suicidal behaviour and suicidal ideation

End point description:

Suicidality was defined as reporting at least one occurrence of any suicidal behavior or suicidal ideation. Suicidal behavior was defined as reporting any type of suicidal behaviors (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior). Suicidal ideation was defined as reporting any type of suicidal ideation. The below reported N value is the number of participants with specified suicidal ideation/behavior at the given time point.

End point type	Secondary

End point timeframe:

Baseline to Month 24

End point values	All Participants			
Subject group type	Reporting group			
Number of subjects analysed	507			
Units: Participants				
number (not applicable)				
Complete suicidality	0			
Suicidality	32			
Suicidal behavior	5			
Emergence of suicidal behavior	3			
Suicidal ideation	31			
Emergence of suicidal ideation	19			
Emergence of serious suicial ideation	2			
Worsening of suicidal ideation	26			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the signing of the informed consent until the follow-up visit 30 (± 3) days after the end of trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Conversion Phase

Reporting group description:

Participants who entered this phase were converted from his or her antipsychotic to the minimum target dose of 10 mg/day aripiprazole monotherapy and continue to increase the dose up to a maximum of 30 mg/day, or for tolerability reasons, to reduce the aripiprazole dose to no less than 5 mg/day.

Reporting group title	Open-label Treatment Phase

Reporting group description:

Participants who entered this phase had received oral aripiprazole at a target dose of 10 to 30 mg/day, with a minimum dose of 5 mg/day, based on individual participant's response and tolerability considerations.

Serious adverse events	Conversion Phase	Open-label Treatment Phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 297 (0.67%)	49 / 510 (9.61%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine phosphokinase			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congenital, familial and genetic disorders			
Gilbert’s syndrome			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth disorder			
subjects affected / exposed	1 / 297 (0.34%)	0 / 510 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 297 (0.00%)	18 / 510 (3.53%)	
occurrences causally related to treatment / all	0 / 0	7 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	0 / 297 (0.00%)	8 / 510 (1.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 297 (0.00%)	7 / 510 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	0 / 297 (0.00%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 297 (0.00%)	3 / 510 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, auditory			
subjects affected / exposed	0 / 297 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 297 (0.00%)	2 / 510 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar I disorder			
subjects affected / exposed	1 / 297 (0.34%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			

subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood swings			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self injurious behaviour			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Laryngitis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 297 (0.00%)	1 / 510 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Conversion Phase	Open-label Treatment Phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 297 (13.47%)	194 / 510 (38.04%)	
Investigations			
Weight increased			
subjects affected / exposed	1 / 297 (0.34%)	38 / 510 (7.45%)	
occurrences (all)	1	50	
Nervous system disorders			
Headache			
subjects affected / exposed	23 / 297 (7.74%)	67 / 510 (13.14%)	
occurrences (all)	32	87	
Somnolence			
subjects affected / exposed	20 / 297 (6.73%)	33 / 510 (6.47%)	
occurrences (all)	22	39	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 297 (1.35%)	30 / 510 (5.88%)	
occurrences (all)	4	53	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 297 (2.02%)	32 / 510 (6.27%)	
occurrences (all)	6	53	
Schizophrenia			
subjects affected / exposed	1 / 297 (0.34%)	30 / 510 (5.88%)	
occurrences (all)	1	36	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 297 (1.68%)	34 / 510 (6.67%)	
occurrences (all)	5	43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2010	In protocol amendment 1, provided instructions for titrating de novo subjects who were treated with a marketed long-acting intramuscular depot antipsychotic for <1 cycle plus 14 days or <60 days prior to screening. Updated the number of participants expected to rollover from Trial 31-09-266 from 180 to 63. Added child and adolescent participants with bipolar I disorder, manic or mixed episode with or without psychotic features to the trial population. Added the restrictions on treatment with benzodiazepines or propranolol within 8 hours or treatment with anticholinergic agents within 12 hours prior to all trial assessments during any phase of the trial. Added sections on YMRS, CGI-BP, GBI, ADHD-RS-IV, and K-SADS-PL to instruct investigators on these assessments. Instructed investigators to identify and to report participants (within 24 hours) who met the criteria for potential drug induced liver damage (Hy's Law). Provided additional instructions on how long birth control was to be used for female participants of childbearing potential and female partners of male participants and included birth control depot injections as an acceptable form of birth control. Provided time windows for prohibited concomitant antidepressants prior to entry into the conversion phase or the open-label treatment phase. Clarified that all participants require a K-SADS-PL assessment prior to entering the conversion phase or the open-label treatment phase of Trial 31-09-267.
14 December 2010	In protocol amendment 2, Changed the trial designation from Phase 4 to Phase 3. Added 3 safety rating scales to the protocol: the Clinician Pediatric Adverse Event Rating Scale (PAERS), Sexual Adverse Event Scale (SAES), and NY-AACENT scales. Excluded participants who used clozapine at any time. Excluded participants with a positive cannabis test at screening. Excluded participants who used an intramuscular depot long-acting antipsychotic within 6 months of beginning trial treatment. Excluded participants with evidence of subclinical hypothyroidism. Updated the number of participants required to be screened. Changed the wording for parent or guardian to parent/guardian or legal representative, as applicable for local laws.
28 March 2011	In protocol amendment 3, Changed the exclusionary QTc value from ≥ 420 to ≥450 msec. Clarified that a clinically significant fasting blood glucose level, requiring trial exclusion was ≥125 mg/dL. Added statement that participants who previously screen failed due to QTc ≥ 420 msec were allowed to be rescreened. Changed second hypothyroidism to hyperthyroidism in the inclusion criteria 12. Added procedure at ET or completion visits that participants were discontinued in the Interactive voice response system/Interactive web response system (IVRS/IWRS). Added documentation of birth control status at the follow-up visit. Changed Phase 3 to Phase 2 in the following sentence: "The incidence of the symptom items recorded in the three adverse event scales at each visit will be summarized for the Phase 2 Safety Sample by disease under study and by treatment group (aripiprazole and placebo) for the Phase 3 Safety Sample." Removed the planned summary of Tanner Staging scores using their cross frequencies at baseline and postbaseline by treatment group. Added protocol dates to the footer and added the Investigational New Drug (IND) number to the title page and protocol synopsis. Removed all references to the SAES and PAERS from the protocol. Updated the ECG language. Clarified which medications are prohibited. Changed the number of trial sites from up to 75 to approximately 75 sites. Clarified the titration requirements for rollover subjects from Trial 31-09-266. Clarified the use of titration cards for participants on < 5 and 5 mg/day of branded aripiprazole. Clarified that oral aripiprazole was not to be dispensed at Week 6/end of the conversion phase. Clarified that a rollover participants CGI-I baseline score was based on the participants status at the last visit of Trial 31-09-266.

21 March 2012	In protocol amendment 4, Increased the sample size to meet the requirement set forth as a key binding element of the European Medicines Agency (EMA) P/99/2011 Aripiprazole Paediatric Investigational Plan to provide 2 years of safety data for at least 100 subjects, including Tanner Staging and cognitive AEs. Adjusted the assumptions for screening failure rate and the discontinuation rate in the conversion phase based on actual trial data. Updated the amendment with new safety information and aripiprazole Investigator Brochure, Version No. 15. Deleted the version of MedDRA that was to be used to code AEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 September 2014	The study was terminated by the Sponsor as the European Medicines Agency P/99/2011Aripiprazole PIP which directed the sponsor to provide 2 years of safety data for at least 100 participants. The objective was met in April 2014.	-

Notes:

Limitations and caveats

None reported