Clinical trial results:
A 52-week, Multicenter, Open-label Study to Evaluate the Effectiveness of Aripiprazole Intramuscular Depot as Maintenance Treatment in Patients with Schizophrenia "ASPIRE OPEN-LABEL" (Aripiprazole Intramuscular Depot Progam in Schizophrenia)

Summary

EudraCT number	2008-002699-83
Trial protocol	BE FI HU AT EE DK FR GB BG SK
Global end of trial date	07 October 2013

Results information

Result version number	v1 (current)
This version publication date	29 May 2016
First version publication date	29 May 2016

Trial information

Trial identification

Sponsor protocol code	1031-08-248

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00731549
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Timothy Peters-Strickland, Otsuka Pharmaceutical Development & Commercialization, Inc., 001 609 249-6559,
Scientific contact	Timothy Peters-Strickland, Otsuka Pharmaceutical Development & Commercialization, Inc., 001 609 249-6559,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2013
Global end of trial reached?	Yes
Global end of trial date	07 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety and tolerability of aripiprazole intramuscular (IM) Depot administered every 4 weeks for 52 weeks to participants with schizophrenia. The secondary objective was to evaluate the efficacy.

Protection of trial subjects:

In accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline, and the applicable local laws and regulatory requirements of the countries in which the trial was conducted, copies of the protocol, amendments, and informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC) for each investigational site or country, as appropriate, prior to trial start or prior to implementation of the amendment at that site or country.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 125
Country: Number of subjects enrolled	Estonia: 27
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	United States: 354
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Romania: 34
Country: Number of subjects enrolled	Slovakia: 20
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Argentina: 19
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Chile: 53
Country: Number of subjects enrolled	Croatia: 24
Country: Number of subjects enrolled	India: 50
Country: Number of subjects enrolled	Korea, Republic of: 36

Country: Number of subjects enrolled	Mexico: 26
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	Philippines: 18
Country: Number of subjects enrolled	Puerto Rico: 8
Country: Number of subjects enrolled	Russian Federation: 83
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	South Africa: 31
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Thailand: 10
Worldwide total number of subjects	1081
EEA total number of subjects	324

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)	0
Adults (18-64 years)	1081
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This open label Phase 3 study enrolled participants from the maintenance phase of study 2008-002675-27 (31-07-246) and study 2008-002676-10 (31-07-247) and new participants. Participants received aripiprazole IM depot as maintenance treatment. 1081 participants were treated in the open-label maintenance phase.

Pre-assignment

Screening details:

Screening phase (applicable if enrolled late/new participants received antipsychotic treatment other than aripiprazole), conversion phase (Phase 1, to convert from other antipsychotics to aripiprazole), oral stabilization phase (Phase 2-aripiprazole 10-30 milligram [mg]), and open-label IM phase (Phase 3-aripiprazole 400 mg IM depot).

Period 1

Period 1 title	Open-label maintenance phase (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Aripiprazole 400/300 mg IM depot

Arm description:

Participants received open-label aripiprazole 400/300 mg IM depot into gluteal muscle every 4 weeks for a maximum of 52 weeks. Flexible dosing with aripiprazole 300 mg and 400 mg was permitted in order to maximize retention of participants. Participants also received supplemental oral aripiprazole (10 mg to 20 mg daily) for the first two weeks to maintain therapeutic plasma concentrations.

Arm type	Experimental
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	OPC-14597, Lu AF41155
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intramuscular use

Dosage and administration details:

Participants received open-label aripiprazole 400/300 mg IM depot into gluteal muscle every 4 weeks for a maximum of 52 weeks. Flexible dosing with aripiprazole 300 mg and 400 mg was permitted in order to maximize retention of participants. Participants also received supplemental oral aripiprazole (10 mg to 20 mg daily) for the first two weeks to maintain therapeutic plasma concentrations.

Number of subjects in period 1	Aripiprazole 400/300 mg IM depot
Started	1081
Completed	858
Not completed	223
Physician decision	16
Consent withdrawn by subject	89
Lack of efficacy with adverse event	37
Met withdrawal criteria	24

Lack of efficacy without adverse event	6
Adverse event	31
Lost to follow-up	19
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Open-label maintenance phase
Reporting group description:	
Participants received open-label aripiprazole 400/300 mg IM depot into gluteal muscle every 4 weeks for a maximum of 52 weeks. Flexible dosing with apipiprazole 300 mg and 400 mg was permitted in order to maximize retention of participants. Participants also received supplemental oral aripiprazole (10 mg to 20 mg daily) for the first two weeks to maintain therapeutic plasma concentrations.	

Reporting group values	Open-label maintenance phase	Total	
Number of subjects	1081	1081	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1081	1081	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	41.2		
standard deviation	± 10.6	-	
Gender categorical			
Units: Subjects			
Female	439	439	
Male	642	642	

End points

End points reporting groups

Reporting group title	Aripiprazole 400/300 mg IM depot

Reporting group description:

Participants received open-label aripiprazole 400/300 mg IM depot into gluteal muscle every 4 weeks for a maximum of 52 weeks. Flexible dosing with aripiprazole 300 mg and 400 mg was permitted in order to maximize retention of participants. Participants also received supplemental oral aripiprazole (10 mg to 20 mg daily) for the first two weeks to maintain therapeutic plasma concentrations.

Primary: Percentage of stable participants at Baseline who remained stable at endpoint (last visit).

End point title	Percentage of stable participants at Baseline who remained stable at endpoint (last visit).[1]

End point description:

"Stable" was defined as meeting all of the following criteria: Outpatient status; Positive and negative syndrome scale (PANSS) total score ≤ 80; Lack of specific psychotic symptoms on the PANSS as measured by a score of ≤ 4 on each of the following items (possible scores of 1 to 7 for each item): 1) conceptual disorganization 2) suspiciousness 3) hallucinatory behaviour 4) unusual thought content; Clinical Global Impression of Severity (CGI-S) ≤ 4 (moderately ill); and Clinical Global Impression for Severity of Suicidality (CGI-SS) ≤ 2 (mildly suicidal) on Part 1 and ≤ 5 (minimally worsened) on Part 2. The percentage of stable participants at baseline who remained stable at endpoint (last visit) is described here. All participants who entered the open-label phase and had at least one post-baseline efficacy evaluation were included. N defines number of stable participants at baseline who were evaluated at the specified trial week.

End point type	Primary

End point timeframe:

Baseline to Week 52/Last visit

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 was planned for this endpoint

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Percentage of participants				
number (not applicable)				
Baseline (N=1075)	100			
Week 2 (N=1023)	99.02			
Week 4 (N=1045)	99.14			
Week 8 (N=1009)	98.51			
Week 12 (N=988)	97.47			
Week 16 (N=951)	98.42			
Week 20 (N=919)	98.15			
Week 24 (N=880)	99.2			
Week 28 (N=854)	98.95			
Week 32 (N=838)	99.16			
Week 36 (N=814)	99.26			
Week 40 (N=807)	99.5			
Week 44 (N=784)	99.11			

Week 48 (N=751)	99.2			
Week 52 (N=671)	98.96			
Last visit (N=1072)	94.96			

Statistical analyses

No statistical analyses for this end point

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 criteria" defined as meeting; 1) Clinical Global Impression of Improvement (CGI-I) ≥ 5 (minimally worse), AND increase to score of >4 and absolute increase of ≥ 2 on individual PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content); or increase to score >4 and absolute increase of ≥ 4 on combined 4 PANSS items on any of these PANSS items (conceptual disorganization, hallucinatory behaviour, suspiciousness, unusual thought content) OR 2) Hospitalization due to worsening of psychotic symptoms, but excluding hospitalization for psychosocial reasons, OR 3) CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2, OR 4) Violent behaviour resulting in clinically relevant self-injury, injury to another person, or property damage. All participants who entered open label phase and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Every week visit until Last visit.

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Percentage of participants				
number (not applicable)				
Week 2 (N=1028)	0.49			
Week 4 (N=1049)	0.48			
Week 8 (N=1011)	0.79			
Week 12 (N=988)	1.52			
Week 16 (N=948)	0.84			
Week 20 (N=920)	1.09			
Week 24 (N=883)	0.45			
Week 28 (N=857)	0.58			
Week 32 (N=838)	0.36			
Week 36 (N=814)	0.25			
Week 40 (N=808)	0.25			
Week 44 (N=783)	0.26			
Week 48 (N=750)	0.27			
Week 52 (N=668)	0.3			
Last visit (N=1079)	4.17			
Overall (N=1079)	8.25			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving remission.

End point title	Percentage of participants achieving remission.

End point description:

Remission is defined as a score of ≤ 3 on each of the following specific PANSS items, maintained for a period of six months: delusions, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms/posturing, blunted affect, social withdrawal, and lack of spontaneity. All participants who entered the open label maintenance phase and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Overall from every visit until Last visit

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: percentage of participants				
number (not applicable)	51.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants stable at Baseline and remaining stable at Week 28.

End point title	Percentage of participants stable at Baseline and remaining stable at Week 28.

End point description:

"Stable" was defined as meeting all of the following criteria: Outpatient status; PANSS total score ≤ 80; Lack of specific psychotic symptoms on the PANSS as measured by a score of ≤ 4 on each of the following items (possible scores of 1 to 7 for each item): 1) conceptual disorganization 2) suspiciousness 3) hallucinatory behaviour 4) unusual thought content; Clinical Global Impression of Severity (CGI-S) ≤ 4 (moderately ill); and Clinical Global Impression for Severity of suicidality (CGI-SS) ≤ 2 (mildly suicidal) on Part 1 and ≤ 5 (minimally worsened) on Part 2. All participants who entered the open label maintenance phase and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Baseline to Week 28

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Percentage of participants				
number (not applicable)				
Baseline (N=1075) Week 28 (N=854)	100 98.95			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with time to first exacerbation of psychotic symptoms/impending relapse

End point title	Percentage of participants with time to first exacerbation of psychotic symptoms/impending relapse

End point description:

Participants who first time meet relapse criteria were considered as having an event at date of exacerbation of psychotic symptoms/impending relapse. Time to first event was calculated as the earliest date of meeting one of relapse criteria. Limited concurrent treatment with oral aripiprazole was permitted as rescue therapy. All participants who entered the open label maintenance phase and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1079			
Units: Percentage of participants				
number (not applicable)	8.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline to endpoint (last visit) in Positive and Negative Syndrome Scale (PANSS) Total Score.

End point title	Mean change from Baseline to endpoint (last visit) in Positive

	and Negative Syndrome Scale (PANSS) Total Score.

End point description:

PANSS total score (range 30-210) is the sum of the rating scores for 7 positive scale items, 7 negative scale items and 16 general psychopathology scale items from the PANSS scale. PANSS positive subscale score (range 7-49) is the sum of the rating scores for the 7 positive scale items from the PANSS scale. PANSS negative subscale score (range 7-49) is the sum of the rating scores for the 7 negative scale items from the PANSS scale. The severity of each scale is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms. All participants who entered the open label maintenance phase and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 52 and last visit

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 12 (N=987)	-1.69 (± 6.21)			
Week 24 (N=882)	-2.55 (± 7.08)			
Week 52 (N=669)	-3.55 (± 7.75)			
Last visit (N=1078)	-1.72 (± 10.21)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Mean change from Baseline in Clinical Global Impression of Severity (CGI-S) Score.

End point description:

To assess CGI-S, the rater or physician will answer the following question: "Considering your total clinical experience with this particular population, how mentally ill is the participant at this time?" Response choices include: 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. All participants who entered the open label maintenance phase 3 and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 52 and last visit

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 12 (N=987)	-0.11 (± 0.52)			
Week 24 (N=883)	-0.17 (± 0.53)			
Week 52 (N=668)	-0.24 (± 0.56)			
Last visit (N=1079)	-0.14 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline to endpoint in PANSS positive and negative subscales.

End point title	Mean change from Baseline to endpoint in PANSS positive and negative subscales.

End point description:

PANSS positive subscale score (range 7-49) is the sum of the rating scores for the 7 positive scale items from the PANSS scale. Positive subscale consists of 7 positive symptom constructs: delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, and hostility). PANSS negative subscale score (range 7-49) is the sum of the rating scores for the 7 negative scale items from the PANSS scale. Negative subscale consists of 7 negative symptom constructs: blunted affect, emotional withdrawal, poor rapport, passive pathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking). The severity of each scale is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms. All participants who entered the open label maintenance phase and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 52 and last visit.

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 12 positive subscale score (N=987)	-0.42 (± 2.11)			
Week 24 positive subscale score (N=882)	-0.68 (± 2.26)			
Week 52 positive subscale score (N=669)	-1.04 (± 2.53)			
Last visit positive subscale score (N=1078)	-0.49 (± 3.38)			
Week 12 negative subscale score (N=987)	-0.4 (± 2.4)			

Week 24 negative subscale score (N=882)	-0.53 (± 2.52)			
Week 52 negative subscale score (N=669)	-0.8 (± 2.94)			
Last visit negative subscale score (N=1078)	-0.46 (± 3.19)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Clinical Global Impression of Improvement (CGI-I) Score.

End point title	Mean Clinical Global Impression of Improvement (CGI-I) Score.

End point description:

To assess CGI-I the rater or physician will rate the participant's total improvement whether or not it is due entirely to drug treatment. All responses will be compared to the participants 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. All participants who entered the open label maintenance phase 3 and have at least one post-baseline efficacy evaluation are included.

End point type	Secondary

End point timeframe:

Weeks 2, 4, 12, 24, 52 and last visit

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Baseline (N=1081)	3.48 (± 0.82)			
Week 2 (N=1026)	3.52 (± 0.85)			
Week 4 (N=1049)	3.49 (± 0.86)			
Week 12 (N=987)	3.42 (± 0.92)			
Week 24 (N=882)	3.33 (± 0.98)			
Week 52 (N=669)	3.25 (± 0.99)			
Last visit (N=1079)	3.35 (± 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who discontinued due to all causes.

End point title	Percentage of participants who discontinued due to all causes.

End point description:

Participants who discontinued due to any cause were noted. Limited concurrent treatment with oral

aripiprazole was permitted as rescue therapy for participants not meeting stability criteria. Rescue therapy was initiated at 10 or 15 mg daily for participants receiving aripiprazole IM depot 300 mg and at 10 mg daily for participants receiving aripiprazole IM depot 400 mg. Dose of oral aripiprazole could be increased after one week to 15 mg for efficacy needs or decreased to 5 mg for tolerability at any point during oral rescue therapy. Rescue therapy was not to be given for more than 4 weeks between 3 consecutive IM depot injections. Rescue therapy could be discontinued when the participant achieved two consecutive weeks of stability, or oral rescue dose could be decreased for an additional week at investigator's discretion, if the 4-week limit for the rescue therapy episode had not been reached. No more than 3 episodes of rescue therapy were permitted.

End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	Aripiprazole 400/300 mg IM depot			
Subject group type	Reporting group			
Number of subjects analysed	1081			
Units: Percentage of participants				
number (not applicable)	20.6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of the open label maintenance phase until the end of treatment visit.

Adverse event reporting additional description:

A treatment emergent adverse event was defined as an adverse event (AE) that began after the start of study medication (aripiprazole IM depot/oral tablets), or an AE that continued from Baseline and became serious, related to study treatment, or resulted in death, discontinuation, interruption or reduction of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Aripiprazole 400/300 mg IM depot

Reporting group description:

Participants received open-label aripiprazole 400/300 milligrams (mg) IM depot into gluteal muscle every 4 weeks for a maximum of 52 weeks. Flexible dosing with apipiprazole 300 mg and 400 mg was permitted in order to maximize retention of participants. Participants also received supplemental oral aripiprazole (10 mg to 20 mg daily) for the first two weeks to maintain therapeutic plasma concentrations.

Serious adverse events	Aripiprazole 400/300 mg IM depot		
Total subjects affected by serious adverse events			
subjects affected / exposed	95 / 1081 (8.79%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer recurrent			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemangioma of liver			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Non-small cell lung cancer metastatic				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal cancer metastatic				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tongue neoplasm				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arteriosclerosis				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hypertension				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Facial pain				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 1081 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anxiety			

subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination, auditory				
subjects affected / exposed	2 / 1081 (0.19%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Homicidal ideation				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	15 / 1081 (1.39%)			
occurrences causally related to treatment / all	0 / 17			
deaths causally related to treatment / all	0 / 0			
Schizoaffective disorder				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Schizophrenia				
subjects affected / exposed	21 / 1081 (1.94%)			
occurrences causally related to treatment / all	3 / 23			
deaths causally related to treatment / all	0 / 0			
Schizophrenia, paranoid type				

subjects affected / exposed	5 / 1081 (0.46%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	2 / 1081 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	3 / 1081 (0.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			
subjects affected / exposed	2 / 1081 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Multiple injuries			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac failure			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	2 / 1081 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Loss of consciousness				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ruptured cerebral aneurysm				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tremor				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Open angle glaucoma				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uveitis				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Dyspepsia				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				

subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomach mass			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	2 / 1081 (0.19%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 1081 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	2 / 1081 (0.19%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Genital candidiasis			

subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis viral				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pilonidal cyst				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 1081 (0.37%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syphilis				
subjects affected / exposed	1 / 1081 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	2 / 1081 (0.19%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 1081 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Aripiprazole 400/300 mg IM depot		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	254 / 1081 (23.50%)		
Nervous system disorders			
Headache			
subjects affected / exposed	82 / 1081 (7.59%)		
occurrences (all)	121		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	73 / 1081 (6.75%)		
occurrences (all)	98		
Insomnia			
subjects affected / exposed	71 / 1081 (6.57%)		
occurrences (all)	92		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	76 / 1081 (7.03%)		
occurrences (all)	94		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2008	Part 1: A number of additions to trial procedures intended to enhance participant safety and accuracy of data were made: Replaced Brief Assessment of Cognition in Schizophrenia with Trails A, Tower of London, and Letter-Number Span cognition assessments; revised post-treatment follow-up to include phone calls 20 and 26 weeks after the last visit; added assessment of haemoglobin A1c if fasting glucose was ≥125 milligrams/decilitre (mg/dL) and/or the urinalysis was positive for glucose; included varenicline as a prohibited concomitant medication; added assessment of electrocardiogram (ECG) at the end of the Conversion Phase for participants who terminated prematurely from the Conversion Phase; added individual durations of pregnancy monitoring based on formulation of aripiprazole; added details for the determination of starting dose in the Oral Stabilization Phase based on the participant's prior history with the double-blind trials and oral aripiprazole; added descriptions for determination of body mass index and waist circumference; added requirement for withdrawal of participants who continued to meet exacerbation of psychotic symptoms/impending relapse criteria after receiving 3 episodes of oral aripiprazole tablet rescue therapy. Participants not meeting stability criteria, but not in impending relapse could continue in the trial at the investigator's discretion; added requirement that participants meeting exacerbation of psychotic symptoms/impending relapse criteria must receive oral aripiprazole tablet rescue therapy.
29 July 2008	Part 2: Revised exclusion criterion related to abstinence/contraceptive use based on half-life of aripiprazole; clarified that participants who receiving aripiprazole in combination with any other antipsychotic(s) must enter the Conversion Phase in order to discontinue other antipsychotic(s). Only participants who received aripiprazole as monotherapy after the last visit of Trials 246/247 or at screening of Trial 31-08-248 (if applicable) could progress directly to the Oral Stabilization Phase; revised key secondary efficacy endpoints based on feedback from the Food and Drug Administration and adjusted statistical methods accordingly; clarified rules for rescue therapy; replaced Columbia Suicide Severity Rating Scale(C-SSRS) in protocol appendix; specified that a modified version of the CSSRS-European Version would be used for this trial to reduce redundant data capture and replace the sample form in the appendix with the modified form; removed table of trial day intervals for determination of visit dates; clarified that the last visit of the Open-label IM Depot Maintenance Phase was required to occur 379 days (1 year plus 2 weeks) after the first dose of open-label aripiprazole IM depot; clarified that Investigator Assessment and Patient Satisfaction with Medication Questionnaire -Modified should be completed only for participants who participated in the Conversion Phase of Trial 248 or de novo participants who had not been enrolled in Trials 246/247 so that treatment with aripiprazole IM depot could be compared with other antipsychotic(s) taken prior to entry into Trial 31-08-248; clarified that participants receiving more than one benzodiazepine at screening could qualify for the trial if they discontinued one of the benzodiazepines during the screening period; clarified that investigator- and subject-rated assessments of injection site were to be based on the site of the most recent injection; ECGs would be obtained "approximately" 5 minutes apart.

18 November 2009	Part 1: Updated general information on aripiprazole in introductory sections based on most recent Investigator Brochure and completed clinical study reports; revised trial design description to clarify antipsychotic medication requirements at screening (including definition of "lapse" in aripiprazole or antipsychotic medication at time of trial entry), as these requirements related to participant entry into the Conversion Phase vs directly into the Oral Stabilization Phase of the trial; clarified language regarding "non-generic oral aripiprazole monotherapy (trial drug)."; added a table delineating recommendation for switching from other generic oral aripiprazole to non-generic oral aripiprazole monotherapy; changed nomenclature of "additional" participants to "new" participants (participants who had not been enrolled in either Trial 31-07-246 or Trial 31-07-247 who enroll in Trial 31-08-248 as their first aripiprazole IM depot trial); Clarified Personal and Social Performance Scale as "other" assessments rather than "efficacy" assessments; added that a pharmacokinetic blood sample was to be collected in the event of a serious adverse event in the Open-label IM Depot Maintenance Phase (aripiprazole IM depot phase only); clarified that the aripiprazole IM depot injection site would be evaluated before and after each injection. Immediately prior to the first aripiprazole IM depot injection site, the anticipated injection site was to be evaluated; added assessment of C-SSRS at all postbaseline visits, rather than as determined by CGI-SS score, and renaming the "postbaseline C-SSRS" as "C-SSRS since last visit."; refined exclusion criteria regarding screening ECG values for QTc interval; Clarified information that should be included in source documentation; clarified that prolactin levels would be assessed at Week 6/end of the Conversion Phase/ET; clarified that participants who discontinued any phase of the trial were not eligible to be rescreened to enter the trial
18 November 2009	Part 2: Included explanation that the Letter-Number Span assessment of cognition was not able to be completed in countries with Cyrillic and character-based languages; included a requirement for the physical examination to include the genitourinary body system with the option that the assessment could be performed within 1 year prior to the end of the screening period provided that documentation of the examination and records of results were provided to the trial investigator. A genitourinary examination was required annually (every 52 weeks) during the trial; clarified allowances/restrictions regarding concomitant medications (zolpidem extended-release, propranolol); added instruction to investigators regarding subject false-positive drug screen results during the trial; revised statistical analysis methods; replaced PANSS and C-SSRS in protocol appendix with most current versions; revised Resource Utilization Questionnaire; added Subject Experience with IM Depot Medication survey; clarified initiation of rescue therapy strategy; updated trial design to include the long-term extension trial; clarified the stability assessment to be done at Weeks 3, 6, and 10; increased the number of participants from 500 to 500-800. In addition, a number of administrative clarifications were made, including changes to text to enhance readability and correct typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported