Clinical trial results:
A 12-week, Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Aripiprazole Intramuscular Depot (OPC-14597, Lu AF41155) in the Acute Treatment of Adults With Schizophrenia

Summary

EudraCT number	2012-003805-86
Trial protocol	LV
Global end of trial date	30 August 2013

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	15 August 2015

Trial information

Trial identification

Sponsor protocol code	31-12-291

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01663532
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, Maryland 20850
Public contact	Timothy Peters-Strickland, Otsuka Pharmaceutical Development & Commercialization, Inc, +1 609 249-6559, Timothy.Peters-Strickland@otsuka-us.com
Scientific contact	Timothy Peters-Strickland, Otsuka Pharmaceutical Development & Commercialization, Inc, +1 609 249-6559, Timothy.Peters-Strickland@otsuka-us.com

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	16 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2013
Global end of trial reached?	Yes
Global end of trial date	30 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall efficacy of aripiprazole intramuscular (IM) depot as acute treatment in participants with schizophrenia. The secondary objective of this trial was to evaluate the safety and tolerability of aripiprazole IM depot as acute treatment in participants with schizophrenia.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	United States: 327
Country: Number of subjects enrolled	Latvia: 2
Worldwide total number of subjects	340
EEA total number of subjects	13

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	339
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

340 participants were enrolled from 41 trial sites (37 in the United States, 2 in Croatia and 2 in Latvia).

Pre-assignment

Screening details:

This trial included a 13-Day Screening phase (which includes washout from previous antipsychotics for 7 days and/or washout from other prohibited medications), a 12-Week acute treatment phase, and a 14 (±2) Day safety follow-up.

Period 1

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

Blinding implementation details:

In this trial, participants and all other investigational site personnel, Sponsor employees, and other trial personnel remained blinded to the identity of the treatment assignments until every participant had completed trial treatment and the database had been locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aripiprazole IM Depot 400/300mg

Arm description:

Participants randomized to aripiprazole IM depot received aripiprazole IM depot 400 milligram (mg) as the initial dose with a single decrease to aripiprazole IM depot 300 mg permitted for tolerability per the study physician. The study treatment was injected into gluteal muscle every 4 weeks (Baseline/Day, Week 4, Week 8) during the 12-Week Acute Treatment Phase (ie, 3 IM depot injections). For 14 days beginning with the first injection, participants received concomitant oral aripiprazole (10 to 20 mg/day based on the study physician's clinical judgment).

Arm type	Experimental
Investigational medicinal product name	Aripiprazole
Investigational medicinal product code	
Other name	OPC-14597, Lu AF41155
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Aripiprazole IM depot 400 mg was administered as the initial dose with a single decrease to aripiprazole IM depot 300 mg permitted for tolerability per the study physician. The study treatment was injected into gluteal muscle every 4 weeks (Baseline/Day, Week 4, Week 8) during the 12-Week Acute Treatment Phase (ie, 3 IM depot injections). For 14 days beginning with the first injection, participants received concomitant oral aripiprazole (10 to 20 mg/day based on the study physician's clinical judgment).

Arm title	Placebo

Arm description:

Participants randomized to Placebo group received matching placebo. For 14 days beginning with the first injection, participants received concomitant oral placebo.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Matching placebo was injected into the gluteal muscle every 4 weeks (Baseline/Day, Week 4, Week 8) during the 12-Week Acute Treatment Phase (ie, 3 IM depot injections). For 14 days beginning with the first injection, participants received concomitant oral placebo.

Number of subjects in period 1	Aripiprazole IM Depot 400/300mg	Placebo
Started	168	172
Completed	94	65
Not completed	74	107
Physician decision	1	1
Consent withdrawn by subject	35	17
Met withdrawal criteria	7	6
Adverse event	7	13
Lost to follow-up	9	10
Lack of efficacy	15	60

Baseline characteristics

Reporting groups	
Reporting group title	Aripiprazole IM Depot 400/300mg
Reporting group description:	
Participants randomized to aripiprazole IM depot received aripiprazole IM depot 400 milligram (mg) as the initial dose with a single decrease to aripiprazole IM depot 300 mg permitted for tolerability per the study physician. The study treatment was injected into gluteal muscle every 4 weeks (Baseline/Day, Week 4, Week 8) during the 12-Week Acute Treatment Phase (ie, 3 IM depot injections). For 14 days beginning with the first injection, participants received concomitant oral aripiprazole (10 to 20 mg/day based on the study physician's clinical judgment).	
Reporting group title	Placebo
Reporting group description:	
Participants randomized to Placebo group received matching placebo. For 14 days beginning with the first injection, participants received concomitant oral placebo.	

Reporting group values	Aripiprazole IM Depot 400/300mg	Placebo	Total
Number of subjects	168	172	340
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	42.1	42.7	
standard deviation	± 11	± 10.9	-
Gender categorical Units: Subjects			
Female	38	33	71
Male	130	139	269

End points

End points reporting groups

Reporting group title	Aripiprazole IM Depot 400/300mg

Reporting group description:

Participants randomized to aripiprazole IM depot received aripiprazole IM depot 400 milligram (mg) as the initial dose with a single decrease to aripiprazole IM depot 300 mg permitted for tolerability per the study physician. The study treatment was injected into gluteal muscle every 4 weeks (Baseline/Day, Week 4, Week 8) during the 12-Week Acute Treatment Phase (ie, 3 IM depot injections). For 14 days beginning with the first injection, participants received concomitant oral aripiprazole (10 to 20 mg/day based on the study physician's clinical judgment).

Reporting group title	Placebo

Reporting group description:

Participants randomized to Placebo group received matching placebo. For 14 days beginning with the first injection, participants received concomitant oral placebo.

Primary: Change from Baseline to Week 10 in Positive and Negative Syndrome Scale (PANSS) Total Score.

End point title	Change from Baseline to Week 10 in Positive and Negative Syndrome Scale (PANSS) Total Score.

End point description:

The PANSS consisted of three subscales that contained a total of 30 symptom constructs. For each symptom construct, severity was rated on a 7-point scale, with a score of 1 that indicated the absence of symptoms and a score of 7 indicated extremely severe symptoms. The PANSS total score was the sum of the rating scores for 7 positive subscale items, 7 negative subscale items, and 16 general psychopathology subscale items from the PANSS panel. PANSS Total Score ranged from 30 (best possible outcome) to 210 (worst possible outcome). The primary statistical comparison was performed using the Mixed Effect Model Repeated Measure (MMRM) approach.

End point type	Primary

End point timeframe:

Baseline to Week 10

End point values	Aripiprazole IM Depot 400/300mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	167		
Units: Units on a scale				
least squares mean (standard error)				
Week 1 (N=162, 167)	-8.9 (± 0.9)	-5 (± 0.9)		
Week 2 (N=144, 157)	-15.2 (± 1.2)	-8.3 (± 1.2)		
Week 4 (N= 134, 140)	-19 (± 1.4)	-9.8 (± 1.3)		
Week 6 (N= 126, 117)	-21.5 (± 1.5)	-10.3 (± 1.5)		
Week 8 (N= 108, 96)	-23.7 (± 1.6)	-9.7 (± 1.6)		
Week 10 (N= 99, 81)	-26.8 (± 1.6)	-11.7 (± 1.6)		
Week 12 (N=99, 68)	-27.2 (± 1.7)	-12.6 (± 1.8)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 1

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. Data for only 162 and 167 participants from aripiprazole and placebo groups were available. MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0005 [2]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	-1.7

Notes:

[1] - Null hypothesis of change from Baseline in PANSS total score of aripiprazole IM depot 400/300mg group is same as that of placebo group was tested. The sample size estimated a 1:1 randomization ratio (aripiprazole IM depot 400/300mg: placebo) to achieve 90% power and to preserve a nominal alpha level of 0.05 given a treatment difference of -7.5 points in change from Baseline with standard deviation of 20 points between aripiprazole and placebo using a two-sided z-test.

[2] - Kenward-Rodger degree of freedom was used to test treatment effects and p-value was not adjusted as this is a primary efficacy endpoint.

Statistical analysis title	Statistical analysis at Week 2

Statistical analysis description:

Null hypothesis of change from Baseline in PANSS total score of aripiprazole IM depot 400/300mg group is same as that of placebo group was tested. The sample size estimated a 1:1 randomization ratio (aripiprazole IM depot 400/300mg: placebo) to achieve 90% power and to preserve a nominal alpha level of 0.05 given a treatment difference of -7.5 points in change from Baseline with standard deviation of 20 points between aripiprazole and placebo using a two-sided z-test.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001 [4]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10
upper limit	-4

Notes:

[3] - Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. Data for only 162 and 167 participants from aripiprazole and placebo groups were available. MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

[4] - Kenward-Rodger degree of freedom was used to test the treatment effects and p-value was not adjusted as this is a primary efficacy endpoint.

Statistical analysis title	Statistical analysis at Week 4

Statistical analysis description:

Null hypothesis of change from Baseline in PANSS total score of aripiprazole IM depot 400/300mg group is same as that of placebo group was tested. The sample size estimated a 1:1 randomization ratio (aripiprazole IM depot 400/300mg: placebo) to achieve 90% power and to preserve a nominal alpha level of 0.05 given a treatment difference of -7.5 points in change from Baseline with standard deviation of 20 points between aripiprazole and placebo using a two-sided z-test.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.8
upper limit	-5.6

Notes:

[5] - Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. Data for only 162 and 167 participants from aripiprazole and placebo groups were available. MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.
[6] - Kenward-Rodger degree of freedom was used to test the treatment effects and p-value was not adjusted as this is a primary efficacy endpoint.

Statistical analysis title	Statistical analysis at Week 6

Statistical analysis description:

Null hypothesis of change from Baseline in PANSS total score of aripiprazole IM depot 400/300mg group is same as that of placebo group was tested. The sample size estimated a 1:1 randomization ratio (aripiprazole IM depot 400/300mg: placebo) to achieve 90% power and to preserve a nominal alpha level of 0.05 given a treatment difference of -7.5 points in change from Baseline with standard deviation of 20 points between aripiprazole and placebo using a two-sided z-test.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	-7.3

Notes:

[7] - Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. Data for only 162 and 167 participants from aripiprazole

and placebo groups were available. MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.
[8] - Kenward-Rodger degree of freedom was used to test the treatment effects and p-value was not adjusted as this is a primary efficacy endpoint.

Statistical analysis title	Statistical analysis at Week 8

Statistical analysis description:

Null hypothesis of change from Baseline in PANSS total score of aripiprazole IM depot 400/300mg group is same as that of placebo group was tested. The sample size estimated a 1:1 randomization ratio (aripiprazole IM depot 400/300mg: placebo) to achieve 90% power and to preserve a nominal alpha level of 0.05 given a treatment difference of -7.5 points in change from Baseline with standard deviation of 20 points between aripiprazole and placebo using a two-sided z-test.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	-9.6

Notes:

[9] - Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. Data for only 162 and 167 participants from aripiprazole and placebo groups were available. MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.
[10] - Kenward-Rodger degree of freedom was used to test the treatment effects and p-value was not adjusted as this is a primary efficacy endpoint.

Statistical analysis title	Statistical analysis at Week 10

Statistical analysis description:

Null hypothesis of change from Baseline in PANSS total score of aripiprazole IM depot 400/300mg group is same as that of placebo group was tested. The sample size estimated a 1:1 randomization ratio (aripiprazole IM depot 400/300mg: placebo) to achieve 90% power and to preserve a nominal alpha level of 0.05 given a treatment difference of -7.5 points in change from Baseline with standard deviation of 20 points between aripiprazole and placebo using a two-sided z-test.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-15.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.4
upper limit	-10.8

Notes:

[11] - Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. Data for only 162 and 167 participants from aripiprazole and placebo groups were available. MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.
[12] - Kenward-Rodger degree of freedom was used to test the treatment effects and p-value was not adjusted as this is a primary efficacy endpoint.

Statistical analysis title	Statistical analysis at Week 12

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. Data for only 162 and 167 participants from aripiprazole and placebo groups were available. MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.3
upper limit	-10

Secondary: Change from Baseline to Week 10 in Clinical Global Impression-Severity Scale (CGI-S) Score

End point title	Change from Baseline to Week 10 in Clinical Global Impression-Severity Scale (CGI-S) Score

End point description:

The severity of illness for each participants were rated using the CGI-S scale. The study physician were to answer the following question: "Considering your total experience with this particular population, how mentally ill is the patient at this time?" Response choices included were: 0= not assessed; 1= normal; not at all ill; 2= borderline mentally ill; 3= mildly ill; 4= moderately ill; 5= markedly ill; 6= severely ill; and 7= among the most extremely ill participants.

End point type	Secondary

End point timeframe:

Baseline to Week 10

End point values	Aripiprazole IM Depot 400/300mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	168		
Units: Units on a scale				
least squares mean (standard error)				

Week 1 (N= 162, 168)	-0.4 (± 0.1)	-0.2 (± 0.1)		
Week 2 (N= 144, 157)	-0.8 (± 0.1)	-0.4 (± 0.1)		
Week 4 (N= 134, 140)	-1 (± 0.1)	-0.4 (± 0.1)		
Week 6 (N= 126, 117)	-1.2 (± 0.1)	-0.5 (± 0.1)		
Week 8 (N= 108, 96)	-1.3 (± 0.1)	-0.6 (± 0.1)		
Week 10 (N= 99, 81)	-1.4 (± 0.1)	-0.6 (± 0.1)		
Week 12 (N=99, 68)	-1.4 (± 0.1)	-0.6 (± 0.1)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 1

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. After the comparison for primary efficacy endpoint was statistically significant, the comparison of change from Baseline in CGI severity score was conducted at same alpha level 0.05.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [13]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1

Notes:

[13] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 2

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. After the comparison for primary efficacy endpoint was statistically significant, the comparison of change from Baseline in CGI severity score was conducted at same alpha level 0.05.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [14]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.2

Notes:

[14] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 4

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. After the comparison for primary efficacy endpoint was statistically significant, the comparison of change from Baseline in CGI severity score was conducted at same alpha level 0.05.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [15]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.4

Notes:

[15] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 6

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. After the comparison for primary efficacy endpoint was statistically significant, the comparison of change from Baseline in CGI severity score was conducted at same alpha level 0.05.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.5

Notes:

[16] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 8

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. After the comparison for primary efficacy endpoint was statistically significant, the comparison of change from Baseline in CGI severity score was conducted at same alpha level 0.05.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.5

Notes:

[17] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 10

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. After the comparison for primary efficacy endpoint was statistically significant, the comparison of change from Baseline in CGI severity score was conducted at same alpha level 0.05.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.6

Notes:

[18] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 12

Statistical analysis description:

Efficacy sample was defined as the ITT population which included randomized participants who took at

least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. After the comparison for primary efficacy endpoint was statistically significant, the comparison of change from Baseline in CGI severity score was conducted at same alpha level 0.05.

Comparison groups	Placebo v Aripiprazole IM Depot 400/300mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.5

Secondary: Change from Baseline to Week 10 in PANSS Positive Subscale Score.

End point title	Change from Baseline to Week 10 in PANSS Positive Subscale Score.

End point description:

The PANSS consisted of three subscales that contained a total of 30 symptom constructs. For each symptom construct, severity is rated on a 7-point scale, with a score of 1 indicated the absence of symptoms and a score of 7 indicated extremely severe symptoms. In positive subscale, the 7 positive symptom constructs were: delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility. PANSS Positive Subscale Score ranges from 7 (absence of symptoms) to 49 (extremely severe symptoms).

End point type	Secondary

End point timeframe:

Baseline to Week 10

End point values	Aripiprazole IM Depot 400/300mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	167		
Units: Units on a scale				
least squares mean (standard error)				
Week 1 (N= 162, 167)	-3.5 (± 0.3)	-2.1 (± 0.3)		
Week 2 (N= 144, 157)	-5.7 (± 0.4)	-3.4 (± 0.4)		
Week 4 (N= 134, 140)	-7 (± 0.5)	-3.9 (± 0.4)		
Week 6 (N= 126, 117)	-8.2 (± 0.5)	-4.4 (± 0.5)		
Week 8 (N= 108, 96)	-8.9 (± 0.5)	-4.1 (± 0.5)		
Week 10 (N= 99, 81)	-10 (± 0.5)	-4.9 (± 0.5)		
Week 12 (N=99, 68)	-9.9 (± 0.6)	-4.8 (± 0.6)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 1

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [19]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	-0.6

Notes:

[19] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 2

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	-1.3

Notes:

[20] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 4

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [21]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	-2

Notes:

[21] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 6

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	-2.6

Notes:

[22] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 8

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-4.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	-3.4

Notes:

[23] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 10

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [24]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	-3.7

Notes:

[24] - MMRM analysis with treatment, pooled centers, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured
covariate was performed.

Statistical analysis title	Statistical analysis at Week 12

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	-3.6

Secondary: Change from Baseline to Week 10 in PANSS Negative Subscale Score.	
End point title	Change from Baseline to Week 10 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 indicated- absence of symptoms and a score of 7 indicated- 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 were: blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking. PANSS Negative Subscale Score ranges from 7 (absence of symptoms) to 49 (extremely severe symptoms).

End point type	Secondary

End point timeframe:

Baseline to Week 10

End point values	Aripiprazole IM Depot 400/300mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	167		
Units: Units on a scale				
least squares mean (standard error)				
Week 1 (N= 162, 167)	-1.6 (± 0.2)	-0.7 (± 0.2)		
Week 2 (N= 144, 157)	-2.4 (± 0.3)	-1.2 (± 0.3)		
Week 4 (N= 134, 140)	-3.1 (± 0.4)	1.3 (± 0.4)		
Week 6 (N= 126, 117)	-3.5 (± 0.4)	1.3 (± 0.4)		
Week 8 (N= 108, 96)	-4 (± 0.4)	-1.4 (± 0.4)		
Week 10 (N= 99, 81)	-4.5 (± 0.5)	-1.6 (± 0.5)		
Week 12 (N=99, 68)	-4.7 (± 0.4)	-2.2 (± 0.5)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 1

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023 [25]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.3

Notes:

[25] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 2

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032 [26]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-0.4

Notes:

[26] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 4

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	-0.8

Statistical analysis title	Statistical analysis at Week 6

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [27]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	-1.3

Notes:

[27] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 8

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Placebo v Aripiprazole IM Depot 400/300mg
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [28]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-1.4

Notes:

[28] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 10

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo

Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [29]
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	-1.6

Notes:

[29] - MMRM analysis with treatment, pooled centres, Week and treatment-by-Week, and Baseline-by-Week interaction as an unstructured covariate was performed.

Statistical analysis title	Statistical analysis at Week 12

Statistical analysis description:

Efficacy sample was defined as the intent to treat (ITT) population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	MMRM
Parameter estimate	Treatment difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-1.3

Secondary: Change from Baseline to Week 10 in Personal and Social Performance Scale (PSP) Score.

End point title	Change from Baseline to Week 10 in Personal and Social Performance Scale (PSP) Score.

End point description:

The PSP was a validated clinician scale that measured personal and social functioning in 4 domains: socially useful activities eg, work and study), personal and social relationships, self-care, disturbing and aggressive behaviours. Impairement in each of these domains was rated as absent, mild, manifest, marked, severe, or very severe. These ratings were then converted to a total score based on a 100-point scale using algorithms to identify the appropriate 10-point interval and the study physician's judgement to determine the total score within the 10-point interval. Participants with a PSP total score of 71 to 100 were considered to have mild functional difficulty. Scores of 31 to 70 represented varying degrees of disability (31 to 70) and ratings of 1 to 30 indicated minimal functioning that required intense support and/or supervision.

End point type	Secondary

End point timeframe:

Baseline to Week 10

End point values	Aripiprazole IM Depot 400/300mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	146		
Units: Units on a scale				
least squares mean (standard error)	12.3 (± 1.2)	5.2 (± 1.2)		

Statistical analyses

Statistical analysis title	Statistial analysis at Week 10

Statistical analysis description:

Efficacy sample included participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had one Post-Baseline efficacy assessment. Last Observation Carried Forward (LOCF) was used to impute the missing data with the recorded value obtained at the preceding visit.

Comparison groups	Placebo v Aripiprazole IM Depot 400/300mg
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.1
upper limit	10.1

Notes:

[30] - Analysis of Covariance (ANVOVA) model with treatment and pooled centres as factors and Baseline value as covariate for the comparison at other visits.

Secondary: Clinical Global Impression-Improvement Scale (CGI-I) Score at Week 10

End point title	Clinical Global Impression-Improvement Scale (CGI-I) Score at Week 10

End point description:

The efficacy of study treatment was rated for each subject using the CGI-I scale. The rater or investigator rated the participant's total improvement whether or not it was due entirely to study treatment. All responses were compared with the participant's condition at Baseline (ie, randomization). Response choices included: 0 = not assessed, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

End point type	Secondary

End point timeframe:

Week 10

End point values	Aripiprazole IM Depot 400/300mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	168		
Units: Units on a scale				
least squares mean (standard error)	2.7 (± 1.2)	3.7 (± 1.3)		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 10

Statistical analysis description:

Efficacy sample was defined as the ITT population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. LOCF was used to impute the missing data with the recorded value obtained at the preceding visit.

Comparison groups	Placebo v Aripiprazole IM Depot 400/300mg
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [31]
Method	Cochran-Mantel-Haenszel

Notes:

[31] - Cochran-Mantel-Haenszel (CMH) raw mean scores differ test (Van Elteren test) controlling for pooled centres.

Secondary: Responder rate at Week 10 based on PANSS Total Score.

End point title	Responder rate at Week 10 based on PANSS Total Score.

End point description:

Responder rate was defined as ≥30% reduction from Baseline in PANSS Total Score. PANSS Total Score ranged from 30 (best possible outcome) to 210 (worst possible outcome).

End point type	Secondary

End point timeframe:

Week 10

End point values	Aripiprazole IM Depot 400/300mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	167		
Units: Participants				
number (not applicable)	60	24		

Statistical analyses

Statistical analysis title	Statistical analysis at Week 10

Statistical analysis description:

Efficacy sample was defined as the ITT population which included randomized participants who took at least one injection of double-blind (aripiprazole IM depot or placebo) and had at least one Post-Baseline efficacy assessment. LOCF was used to impute the missing data with the recorded value obtained at the preceding visit.

Comparison groups	Aripiprazole IM Depot 400/300mg v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [32]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (net)
Point estimate	22.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.9
upper limit	32.4

Notes:

[32] - CMH test controlling by region (pooled sites).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored from signing of the ICF until Safety Follow-up visit 14 (± 2) days after the last treatment.

Adverse event reporting additional description:

One participant was randomly assigned to aripiprazole IM depot 400 mg/ 300 mg, but was not treated and did not have any post-randomization assessments and was not included in safety or efficacy assessments.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Aripiprazole IM Depot 400/300mg

Reporting group description:

Participants randomized to aripiprazole IM depot received aripiprazole IM depot 400 milligram (mg) as the initial dose with a single decrease to aripiprazole IM depot 300 mg permitted for tolerability per the study physician. The study treatment was injected into gluteal muscle every 4 weeks (Baseline/Day, Week 4, Week 8) during the 12-Week Acute Treatment Phase (ie, 3 IM depot injections). For 14 days beginning with the first injection, participants received concomitant oral aripiprazole (10 to 20 mg/day based on the study physician's clinical judgment).

Reporting group title	Placebo

Reporting group description:

Participants randomized to Placebo group received matching placebo. For 14 days beginning with the first injection, participants received concomitant oral placebo.

Serious adverse events	Aripiprazole IM Depot 400/300mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 167 (4.79%)	6 / 172 (3.49%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 167 (0.00%)	1 / 172 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			

subjects affected / exposed	2 / 167 (1.20%)	2 / 172 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	3 / 167 (1.80%)	3 / 172 (1.74%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Substance abuse			
subjects affected / exposed	1 / 167 (0.60%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 167 (0.60%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 167 (0.60%)	0 / 172 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aripiprazole IM Depot 400/300mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	91 / 167 (54.49%)	68 / 172 (39.53%)	
Investigations			
Weight increased			
subjects affected / exposed	28 / 167 (16.77%)	12 / 172 (6.98%)	
occurrences (all)	29	12	
Nervous system disorders			
Akathisia			
subjects affected / exposed	19 / 167 (11.38%)	6 / 172 (3.49%)	
occurrences (all)	20	6	

Headache			
subjects affected / exposed	24 / 167 (14.37%)	28 / 172 (16.28%)	
occurrences (all)	39	39	
Sedation			
subjects affected / exposed	9 / 167 (5.39%)	2 / 172 (1.16%)	
occurrences (all)	9	2	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	9 / 167 (5.39%)	1 / 172 (0.58%)	
occurrences (all)	13	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	16 / 167 (9.58%)	12 / 172 (6.98%)	
occurrences (all)	20	19	
Dyspepsia			
subjects affected / exposed	10 / 167 (5.99%)	11 / 172 (6.40%)	
occurrences (all)	14	14	
Toothache			
subjects affected / exposed	9 / 167 (5.39%)	8 / 172 (4.65%)	
occurrences (all)	9	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 167 (5.99%)	10 / 172 (5.81%)	
occurrences (all)	10	13	
Psychiatric disorders			
Agitation			
subjects affected / exposed	9 / 167 (5.39%)	11 / 172 (6.40%)	
occurrences (all)	26	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2012	Added Eudra CT number. Removed all references to interim analysis. Updated Schedule of Assessments to reflect administration of oral investigational medicinal product (IMP)during Screening Phase if needed to establish tolerability to aripiprazole. Clarified that no Week 12 data could be collected more than 100 days after first dose of IM depot IMP in addition to clarifying maximum amount of time allowed between injections. Corrected minor formatting errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported