Clinical trial results:
A 52-week, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole (OPC-14597) as Maintenance Treatment in Patients with Bipolar I Disorder

Summary

EudraCT number	2012-002870-30
Trial protocol	PL
Global end of trial date	09 April 2016

Results information

Result version number	v1 (current)
This version publication date	06 May 2017
First version publication date	06 May 2017

Trial information

Trial identification

Sponsor protocol code	31-08-250

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01567527
WHO universal trial number (UTN)	-
Other trial identifiers	IND No.: 114,284

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc
Sponsor organisation address	2440 Research Boulevard, Rockville, United States, MD 20850
Public contact	Otsuka Pharmaceutical Development & Commercialization, Inc., Otsuka Transparency Department, DT-inquiry@otsuka.jp
Scientific contact	Otsuka Pharmaceutical Development & Commercialization, Inc., Otsuka Transparency Department, DT-inquiry@otsuka.jp

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	09 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 April 2016
Global end of trial reached?	Yes
Global end of trial date	09 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a double-blind, placebo-controlled, randomized withdrawal trial to assess the time to recurrence of any mood episode in subjects with bipolar I disorder who had maintained stability on aripiprazole IM depot for at least 8 weeks.

Protection of trial subjects:

In accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline1 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.This trial was conducted in compliance with the protocol, ICH GCP and applicable local laws and regulatory requirements.
Note: All subjects were 18 to 65 years of age, inclusive, at time of informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Romania: 34
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 608
Worldwide total number of subjects	731
EEA total number of subjects	44

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)	726
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 1175 participants (including screen failures) at 103 trial sites in the following 7 countries: Canada, Japan, Republic of Korea, Poland, Romania, Taiwan, and the United States (US).

Pre-assignment

Screening details:

The trial consisted of a screening phase and 4 phases. In phases A-C (Conversion, Oral Stabilization and Depot Stabilization Phases), there was a single treatment group. In phase D (Double-blind, placebo-controlled phase), there were 2 treatment groups. All Outcome Measures were assessed in the double-blind, placebo-controlled phase of the study.

Period 1

Period 1 title	Oral Conversion Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All patients

Arm description:

During the Oral Conversion Phase, patients were cross-titrated from other antipsychotics to oral non-generic aripiprazole monotherapy.

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

Dosage and administration details:

Oral aripiprazole (The goal was to achieve a monotherapy target starting dose of 15mg/day at week 4 and no later than week 6) of the Conversion Phase.

Number of subjects in period 1	All patients
Started	466
Completed	367
Not completed	99
Withdrawn by the investigator	3
Consent withdrawn by subject	32
Adverse events	33
Met withdrawal criteria	10
Lost to follow-up	16
Protocol deviation	3
Lack of efficacy	2

Period 2

Period 2 title	Oral Aripiprazole Stabilization Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All patients

Arm description:

During the Oral Stabilization Phase, patients were stabilized on an oral dose of aripiprazole. 632 subjects entered the Oral Stabilization Phase (367 subjects entered from the Conversation Phase and 265 subjects entered the Oral Stabilization Phase directly)

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

Dosage and administration details:

Open-label oral aripiprazole monotherapy (Oral aripiprazole dose ranging from 15 to 30 mg daily)

Number of subjects in period 2	All patients
Started	367
Completed	425
Not completed	207
Withdrawn by the investigator	2
Consent withdrawn by subject	45
Adverse events	63
Met withdrawal criteria	41
Lost to follow-up	44
Lack of efficacy	12
Joined	265
Subjects entered Oral Stabilization Phase directly	265

Period 3

Period 3 title	IM Depot Stabilization Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Arms

Arm title	All patients

Arm description:

During the Depot Stabilization Phase, patients were stabilized on aripiprazole IM depot. The subjects were assigned to aripiprazole IM depot in the IM Depot Stabilization Phase for a minimum of 12 weeks and a maximum of 28 weeks. To proceed to the Double-blind, Placebo-controlled Phase, subjects were required to meet all the protocol-defined stability criteria for a minimum of 8 consecutive weeks (4 consecutive biweekly visits).

Arm type	Experimental
Investigational medicinal product name	Intramuscular (IM) Depot Aripiprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Single-blind fashion, aripiprazole IM depot 400 mg, irrespective of the final oral dose of aripiprazole in Phase B. A single decrease to 300 mg was permitted , as was a single return to 400 mg, if required, in addition oral aripiprazole during the first 2 weeks to maintain therapeutic levels

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: An unblinded site study drug manager prepared and administered the single-blind IM depot injections every 4 weeks throughout the IM Depot Stabilization Phase.

Number of subjects in period 3	All patients
Started	425
Completed	266
Not completed	159
Withdrawn by the investigator	6
Consent withdrawn by subject	56
Adverse events	37
Met withdrawal criteria	26
Sponsor discontinued study	1
Lost to follow-up	21
Protocol deviation	5
Lack of efficacy	7

Period 4

Period 4 title	Double-blind Placebo-controlled Phase
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Aripiprazole Depot

Arm description:

Patients received aripiprazole 300 mg or 400 mg depot intramuscularly up to 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Intramuscular (IM) Depot Aripiprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular (IM) Depot Aripiprazole Formulation 400 mg or 300 mg, once a month injection

Arm title	Placebo

Arm description:

Patients received placebo intramuscularly up to 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

IM Depot Placebo 400 mg or 300 mg, once a month injection.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: In this study, Period 4 (Double-blind Placebo controlled Phase) was chosen as the baseline period and Baseline measures are based on the participants from the Double-blind Placebo-controlled Phase.

Number of subjects in period 4[3]	Aripiprazole Depot	Placebo
Started	133	133
Completed	64	38
Not completed	69	95
Consent withdrawn by subject	13	10
AE without recurrence of any mood episode	7	1
Recurrence of any mood episode with AE	16	33
Recurrence of any mood episode without AE	19	35
Met withdrawal criteria	4	7
Lost to follow-up	8	5

Sponsor discontinued study	1	3
Protocol deviation	1	1

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Since the results presented are of Period 4, this was chosen as the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Aripiprazole Depot
Reporting group description:	
Patients received aripiprazole 300 mg or 400 mg depot intramuscularly up to 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Patients received placebo intramuscularly up to 52 weeks.	

Reporting group values	Aripiprazole Depot	Placebo	Total
Number of subjects	133	133	266
Age categorical			
Baseline measures are based on the participants from the Double-blind Placebo-controlled Phase			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	133	132	265
From 65-84 years	0	1	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	40.6	40.6	
standard deviation	± 10.8	± 11.2	-
Gender categorical			
Units: Subjects			
Female	83	70	153
Male	50	63	113
Age at first manic episode (years)			
Units: Years			
arithmetic mean	25.2	24.8	
standard deviation	± 10.3	± 9.9	-
Number of mood episodes past 12 months			
Units: Number			
arithmetic mean	2.2	2.2	
standard deviation	± 1.2	± 1.1	-
Duration of disease prior to enrollment (years)			
Units: Years			
arithmetic mean	12.1	13.6	
standard deviation	± 9.2	± 9.8	-
Number of prior hospitalizations for a mood episode			

Units: Number			
arithmetic mean	3.5	3.5	
standard deviation	± 3.9	± 4.1	-
YMRS Total Score			
Units: Number			
arithmetic mean	2.9	2.6	
standard deviation	± 3.5	± 3	-
MADRS Total Score			
Units: Number			
arithmetic mean	3	2.4	
standard deviation	± 3.4	± 3.4	-
CGI-BP Severity - Mania			
Units: Number			
arithmetic mean	1.5	1.4	
standard deviation	± 0.7	± 0.6	-

End points

End points reporting groups

Reporting group title	All patients

Reporting group description:

During the Oral Conversion Phase, patients were cross-titrated from other antipsychotics to oral non-generic aripiprazole monotherapy.

Reporting group title	All patients

Reporting group description:

During the Oral Stabilization Phase, patients were stabilized on an oral dose of aripiprazole. 632 subjects entered the Oral Stabilization Phase (367 subjects entered from the Conversation Phase and 265 subjects entered the Oral Stabilization Phase directly)

Reporting group title	All patients

Reporting group description:

During the Depot Stabilization Phase, patients were stabilized on aripiprazole IM depot. The subjects were assigned to aripiprazole IM depot in the IM Depot Stabilization Phase for a minimum of 12 weeks and a maximum of 28 weeks. To proceed to the Double-blind, Placebo-controlled Phase, subjects were required to meet all the protocol-defined stability criteria for a minimum of 8 consecutive weeks (4 consecutive biweekly visits).

Reporting group title	Aripiprazole Depot

Reporting group description:

Patients received aripiprazole 300 mg or 400 mg depot intramuscularly up to 52 weeks.

Reporting group title	Placebo

Reporting group description:

Patients received placebo intramuscularly up to 52 weeks.

Primary: Time from randomization to recurrence of any mood episode during Double-Bind Placebo Controlled phase

End point title	Time from randomization to recurrence of any mood episode during Double-Bind Placebo Controlled phase

End point description:

This endpoint was defined as meeting any of the following criteria:
1) Hospitalization for any mood episode OR
2) Any of the following:
a) YMRS total score ≥ 15 OR
b) MADRS total score ≥ 15 OR
c) CGI-BP-S score > 4 (overall score) OR
3) SAE of worsening disease (bipolar I disorder) OR
4) Discontinuation due to lack of efficacy or discontinuation due to an AE of worsening disease OR
5) Clinical worsening with the need for addition of a mood stabilizer, antidepressant treatment, antipsychotic medication, and/or increase greater than the allowed benzodiazepine doses for treatment of symptoms of an underlying mood disorder OR
6) Active suicidality, which is defined as a score of 4 or more on the MADRS item 10 OR an answer of "yes" on question 4 or 5 on the C-SSRS

End point type	Primary

End point timeframe:

Baseline of the Double-blind, Placebo-controlled Phase Up to the end of the study (Week 52)

End point values	Aripiprazole Depot	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	133		
Units: Recurrence Rate (%)				
number (not applicable)	26.5	51.1		

Statistical analyses

Statistical analysis title	Statistical analysis for Aripiprazole IM
Comparison groups	Aripiprazole Depot v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.451
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.299
upper limit	0.678

Statistical analysis title	Statistical analysis for IM Depot Placebo
Comparison groups	Aripiprazole Depot v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.475
upper limit	3.34

Secondary: Proportion of subjects meeting criteria for recurrence of any mood episode (manic, mixed, depressive)

End point title	Proportion of subjects meeting criteria for recurrence of any mood episode (manic, mixed, depressive)

End point description:

Recurrence of any mood episode (manic, mixed, depressive)

End point type	Secondary

End point timeframe:

Baseline of the Double-blind, Placebo-controlled Phase Up to the end of the study (Week 52)

End point values	Aripiprazole Depot	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	133		
Units: Percentage				
number (not applicable)	26.52	51.13		

Statistical analyses

Statistical analysis title	Statistical analysis for any mood episode
Comparison groups	Aripiprazole Depot v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-24.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.72
upper limit	-12.51

Secondary: Mean change from randomization to endpoint in the CGI-BP-S (mania) score

End point title	Mean change from randomization to endpoint in the CGI-BP-S (mania) score

End point description:

Change From Randomization to Endpoint in Clinical Global Impression - Bipolar Version-Severity Scores. The CGI-BP scale referred to the global impression of the subject with respect to bipolar disorder. The scale rated the subject’s Severity of Illness (CGI-BP-Severity: mania).

End point type	Secondary

End point timeframe:

Baseline of the Double-blind, Placebo-controlled Phase Up to the end of the study (Week 52)

End point values	Aripiprazole Depot	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	133		
Units: Number				
least squares mean (standard error)				
Week 2 (N = 123, 126)	-0.07 (± 0.039)	0.09 (± 0.059)		
Week 4 (N = 124, 121)	-0.01 (± 0.041)	0.1 (± 0.064)		
Week 6 (N = 117, 106)	-0.03 (± 0.049)	0.11 (± 0.069)		
Week 8 (N = 104, 100)	-0.01 (± 0.053)	0.19 (± 0.072)		
Week 10 (N = 103, 96)	0.02 (± 0.06)	0.11 (± 0.079)		
Week 12 (N = 95, 87)	0.03 (± 0.072)	0.13 (± 0.083)		
Week 14 (N = 99, 84)	-0.05 (± 0.063)	0.07 (± 0.079)		
Week 16 (N = 90, 82)	-0.1 (± 0.044)	0.09 (± 0.067)		
Week 18 (N = 87, 79)	-0.08 (± 0.05)	-0.01 (± 0.064)		
Week 20 (N = 83, 74)	-0.08 (± 0.05)	0.08 (± 0.069)		
Week 22 (N = 85, 71)	-0.12 (± 0.054)	0.21 (± 0.097)		
Week 24 (N = 79, 67)	-0.09 (± 0.049)	0.14 (± 0.079)		
Week 26 (N = 77, 62)	-0.11 (± 0.055)	0.19 (± 0.082)		
Week 28 (N = 81, 58)	-0.14 (± 0.05)	0.12 (± 0.077)		
Week 32 (N = 77, 56)	-0.13 (± 0.062)	0.09 (± 0.08)		
Week 36 (N = 72, 52)	-0.07 (± 0.06)	0.25 (± 0.103)		
Week 40 (N = 70, 51)	-0.06 (± 0.069)	0.24 (± 0.113)		
Week 44 (N = 69, 46)	-0.15 (± 0.058)	0.24 (± 0.107)		
Week 48 (N = 68, 43)	-0.11 (± 0.059)	0.11 (± 0.075)		
Week 52 (N = 64, 39)	-0.16 (± 0.058)	0.27 (± 0.126)		

Statistical analyses

Statistical analysis title	Statistical Ananlysis for week 52

Statistical analysis description:

Mixed model with fixed effects of treatment, region, week and interaction of treatment by week as terms and baseline by week as covariate. Heterogeneous compound symmetry covariance structure for observations within a subject is used.

Comparison groups	Aripiprazole Depot v Placebo

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Mixed model repeated measure analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.17

Secondary: Time from randomization to recurrence defined by hospitalization for a mood episode

End point title	Time from randomization to recurrence defined by hospitalization for a mood episode

End point description:

Analysis of Time from Randomization to Recurrence Defined by Hospitalization for a Mood Episode (Double-blind, Placebo-controlled Phase Efficacy Sample)

End point type	Secondary

End point timeframe:

Baseline of the Double-blind, Placebo-controlled Phase Up to the end of the study (Week 52)

End point values	Aripiprazole Depot	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	133		
Units: Recurrence rate (percentage)				
number (not applicable)	2.3	13.5		

Statistical analyses

Statistical analysis title	Statistical Analysis for Aripiprazole IM Depot
Comparison groups	Aripiprazole Depot v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.137

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.465

Statistical analysis title	Statistical Ananlysis for Placebo
Comparison groups	Placebo v Aripiprazole Depot
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	7.313
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.151
upper limit	24.865

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any AEs were recorded from the signing of informed consent onward.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Oral Aripiprazole Stabilization Phase

Reporting group description:

During the Oral Stabilization Phase, patients were stabilized on an oral dose of aripiprazole ranging from 15 mg to 30 mg daily.

Reporting group title	IM Depot Stabilization Phase

Reporting group description:

During the Depot Stabilization Phase, patients were stabilized on aripiprazole depot.

Reporting group title	Aripiprazole IM Depot- Double-blind, Placebo-controlled Phase

Reporting group description:

Patients received aripiprazole 300 mg or 400 mg depot intramuscularly

Reporting group title	Placebo-Double-blind, Placebo-controlled Phase

Reporting group description:

Patients received placebo intramuscularly for 52 weeks

Serious adverse events	Oral Aripiprazole Stabilization Phase	IM Depot Stabilization Phase	Aripiprazole IM Depot- Double-blind, Placebo-controlled Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 614 (5.70%)	36 / 425 (8.47%)	10 / 132 (7.58%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Accidental overdose			
subjects affected / exposed	1 / 614 (0.16%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 614 (0.16%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Nervous system disorders			
Akathisia			

subjects affected / exposed	1 / 614 (0.16%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Transient ischaemic attack			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiculopathy			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food poisoning			

subjects affected / exposed	1 / 614 (0.16%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic adhesions			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 614 (0.16%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Affect lability			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Affective disorder			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			

subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	2 / 614 (0.33%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar I disorder			
subjects affected / exposed	1 / 614 (0.16%)	4 / 425 (0.94%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	1 / 614 (0.16%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	17 / 614 (2.77%)	7 / 425 (1.65%)	2 / 132 (1.52%)
occurrences causally related to treatment / all	1 / 17	0 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	1 / 132 (0.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed mood			

subjects affected / exposed	1 / 614 (0.16%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	4 / 614 (0.65%)	8 / 425 (1.88%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 4	2 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptom			
subjects affected / exposed	2 / 614 (0.33%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	1 / 614 (0.16%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	3 / 614 (0.49%)	3 / 425 (0.71%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval abscess			
subjects affected / exposed	0 / 614 (0.00%)	1 / 425 (0.24%)	0 / 132 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo-Double-blind, Placebo-controlled Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 133 (18.80%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Accidental overdose			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain injury			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Food poisoning			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Pelvic adhesions			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholestasis				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Affect lability				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Affective disorder				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bipolar disorder				
subjects affected / exposed	3 / 133 (2.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Bipolar I disorder				
subjects affected / exposed	3 / 133 (2.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypomania				

subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	10 / 133 (7.52%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressed mood				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Depressive symptom				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Insomnia				

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vulval abscess			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Oral Aripiprazole Stabilization Phase	IM Depot Stabilization Phase	Aripiprazole IM Depot- Double-blind, Placebo-controlled Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	342 / 614 (55.70%)	287 / 425 (67.53%)	100 / 132 (75.76%)
Investigations			
Weight increased			
subjects affected / exposed	22 / 614 (3.58%)	47 / 425 (11.06%)	31 / 132 (23.48%)
occurrences (all)	23	47	31
Nervous system disorders			
Akathisia			
subjects affected / exposed	94 / 614 (15.31%)	74 / 425 (17.41%)	27 / 132 (20.45%)
occurrences (all)	99	82	32
Headache			
subjects affected / exposed	0 / 614 (0.00%)	0 / 425 (0.00%)	4 / 132 (3.03%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 614 (3.09%)	22 / 425 (5.18%)	0 / 132 (0.00%)
occurrences (all)	19	25	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	24 / 614 (3.91%)	30 / 425 (7.06%)	9 / 132 (6.82%)
occurrences (all)	24	36	9
Insomnia			
subjects affected / exposed	34 / 614 (5.54%)	41 / 425 (9.65%)	10 / 132 (7.58%)
occurrences (all)	35	47	11
Restlessness			
subjects affected / exposed	32 / 614 (5.21%)	24 / 425 (5.65%)	0 / 132 (0.00%)
occurrences (all)	34	25	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 614 (1.79%)	22 / 425 (5.18%)	10 / 132 (7.58%)
occurrences (all)	11	30	13

Non-serious adverse events	Placebo-Double-blind, Placebo-controlled Phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 133 (74.44%)		

Investigations Weight increased subjects affected / exposed occurrences (all)	 24 / 133 (18.05%) 25		
Nervous system disorders Akathisia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 17 / 133 (12.78%) 20 9 / 133 (6.77%) 10		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 0 / 133 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Restlessness subjects affected / exposed occurrences (all)	 6 / 133 (4.51%) 6 10 / 133 (7.52%) 12 0 / 133 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 13 / 133 (9.77%) 29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2012	Amendment Number 1: This amendment served to reflect a number of clarifications and additions to study procedures intended to enhance subject safety and accuracy of data. In addition, a number of administrative clarifications were made, including changes to text to enhance readability and correct typographical errors.
29 October 2013	Amendment Number 2: This second amendment reflected clarifications and additions to study procedures, statistical methods, and inclusion/exclusion criteria intended to enhance subject safety and accuracy of data. In addition, administrative clarifications were made, including changes to text to enhance readability and consistency and correct typographical errors.
19 June 2014	Amendment Number 3: This third amendment provided for continuation of the trial at Japanese sites if Trial 31-08-250 was terminated early for any reason other than safety in order to meet the randomization requirement specified by the Pharmaceutical and Medical Devices Agency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported