



Clinical trial results:

A 52-week, Multicenter, Open-label Study to Evaluate the Effectiveness of an Intramuscular Depot Formulation of Aripiprazole (OPC-14597) as Maintenance Treatment in Patients with Bipolar I Disorder

Summary

EudraCT number	2012-004334-42
Trial protocol	HU
Global end of trial date	18 November 2016

Results information

Result version number	v1 (current)
This version publication date	18 December 2017
First version publication date	18 December 2017

Trial information

Trial identification

Sponsor protocol code	31-08-252
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01710709
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Otsuka Pharmaceutical Development & Commercialization, Inc.
Sponsor organisation address	2440 Research Boulevard, Rockville, Maryland, United States, 20850
Public contact	Senior Director, Global Clinical Development, Joan Amatniek, MD, MS, 609 512-4464, joan.amatniek@otsuka-us.com
Scientific contact	Senior Director, Global Clinical Development, Joan Amatniek, MD, MS, 609 512-4464, joan.amatniek@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	07 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2016
Global end of trial reached?	Yes
Global end of trial date	18 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial evaluated effectiveness via assessment of safety and tolerability (primary objective) and efficacy (secondary objective) of aripiprazole IM depot as measured by maintenance of stability in subjects with bipolar I disorder.

Protection of trial subjects:

The study was conducted according to the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline and the applicable local laws and regulatory requirements of the countries in which the trial was conducted. Informed consent was obtained from all subjects in writing before any trial related procedures were performed. Prior to start, copies of the protocol, any amendments, and the informed consent form (ICF) were reviewed and approved by the governing institutional review board (IRB) or independent ethics committee (IEC). Essential information was fully explained in layman's language to the subject by the investigator or a qualified designee.

Note: All subjects were 18 years and older at time of informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 6
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	United States: 322
Country: Number of subjects enrolled	Japan: 75
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Malaysia: 10
Worldwide total number of subjects	464
EEA total number of subjects	47

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)	458
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who had completed trial 31-08-250 (rollover - 85 participants) and who had not participated (de novo - 379 participants) were enrolled in the IM Depot Maintenance Phase and received at least 1 dose of IMP.

Pre-assignment

Screening details:

For de novo participants, screening took place from Days -42 to -2

Period 1

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

Arms

Arm title	Phase C: Open-label IM Depot Maintenance Phase
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Arm description:

All De novo participants received open-label aripiprazole 400/300 mg IM depot and the participants who completed Trial 31-08-250 entered phase C on aripiprazole IM depot 400 mg, regardless of their last dose of IM depot. De novo participants also received daily supplemental oral aripiprazole (10 to 20 mg daily for non-Japanese sites; 6 to 18 mg for Japanese sites) for the first 2 weeks to maintain therapeutic plasma concentrations. For participants who completed Trial 31-08-250 (some of whom had received double-blind placebo), the use of supplemental oral aripiprazole for the first ≤ 2 weeks was at the investigator's discretion based on the clinical status of the participant. Administration of rescue therapy was recommended for participants who did not meet stability criteria during the IM Depot Maintenance Phase, unless in the investigator's judgment withdrawal from the trial was considered more appropriate.

Arm type	Experimental
Investigational medicinal product name	aripiprazole
Investigational medicinal product code	OPC-14597
Other name	Abilify Maintena
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Prior to injection, vials of aripiprazole IM depot 400 mg were reconstituted with a designated quantity of sterile water for injection. Participants received the drug through intramuscular route. The dosage details are given below:

Initially 400 mg, every 4 weeks for ≤ 52 weeks; flexible dosing with 300 mg and 400 mg was permitted as often as necessary during the treatment period. De novo participants also received oral aripiprazole during the first 2 weeks to maintain therapeutic levels

Number of subjects in period 1	Phase C: Open-label IM Depot Maintenance Phase
Started	464
Completed	291
Not completed	173
Consent withdrawn by subject	53
Adverse Event	48

Protocol Violation	5
Lost to follow-up	29
Participant met withdrawal criteria	33
Participant withdrawn by investigator	2
Lack of efficacy	3

Baseline characteristics

Reporting groups

Reporting group title	Phase C: Open-label IM Depot Maintenance Phase
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Reporting group description:

All De novo participants received open-label aripiprazole 400/300 mg IM depot and the participants who completed Trial 31-08-250 entered phase C on aripiprazole IM depot 400 mg, regardless of their last dose of IM depot. De novo participants also received daily supplemental oral aripiprazole (10 to 20 mg daily for non-Japanese sites; 6 to 18 mg for Japanese sites) for the first 2 weeks to maintain therapeutic plasma concentrations. For participants who completed Trial 31-08-250 (some of whom had received double-blind placebo), the use of supplemental oral aripiprazole for the first ≤ 2 weeks was at the investigator's discretion based on the clinical status of the participant. Administration of rescue therapy was recommended for participants who did not meet stability criteria during the IM Depot Maintenance Phase, unless in the investigator's judgment withdrawal from the trial was considered more appropriate.

Reporting group values	Phase C: Open-label IM Depot Maintenance Phase	Total	
Number of subjects	464	464	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	458	458	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	41.1		
standard deviation	± 11.8	-	
Gender categorical			
Units: Subjects			
Female	268	268	
Male	196	196	

End points

End points reporting groups

Reporting group title	Phase C: Open-label IM Depot Maintenance Phase
Reporting group description:	
All De novo participants received open-label aripiprazole 400/300 mg IM depot and the participants who completed Trial 31-08-250 entered phase C on aripiprazole IM depot 400 mg, regardless of their last dose of IM depot. De novo participants also received daily supplemental oral aripiprazole (10 to 20 mg daily for non-Japanese sites; 6 to 18 mg for Japanese sites) for the first 2 weeks to maintain therapeutic plasma concentrations. For participants who completed Trial 31-08-250 (some of whom had received double-blind placebo), the use of supplemental oral aripiprazole for the first ≤ 2 weeks was at the investigator's discretion based on the clinical status of the participant. Administration of rescue therapy was recommended for participants who did not meet stability criteria during the IM Depot Maintenance Phase, unless in the investigator's judgment withdrawal from the trial was considered more appropriate.	

Primary: Number of participants with Adverse Events

End point title	Number of participants with Adverse Events ^[1]
End point description:	
An adverse event (AE) is defined as any untoward medical occurrence in a participant enrolled in the clinical trial and which does not necessarily have to have a causal relationship with the investigational medicinal product (IMP). Any adverse events (AEs) were recorded from the signing of informed consent onward. At each visit, the occurrences of AEs and the participant's recorded AE information were assessed. AEs were assessed as a criteria for safety and tolerability.	
Analysis Population Description:	
IM Depot Maintenance Phase Safety Sample: All participants who received at least 1 dose of aripiprazole IM depot in the IM Depot Maintenance Phase. TEAEs = Treatment-emergent adverse events (used in the result table).	
End point type	Primary
End point timeframe:	
At baseline, Phase C trial weeks 1 to 52/early termination (ET) and post-treatment follow-up	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: No statistical analysis was specified for this endpoint.	

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	464			
Units: Participants				
number (not applicable)				
Participants with adverse events	374			
Participants with TEAEs	374			
Participants with serious TEAEs	30			
Participants with non- serious TEAEs	367			
Participants with severe TEAEs	41			
Discontinuation of IMP due to AEs	47			
Discontinuation fo IMP due to AEs/death	48			
Deaths	1			

Statistical analyses

No statistical analyses for this end point

Primary: Injection Site Pain Measured by mean Visual Analog Scale (VAS) scores

End point title	Injection Site Pain Measured by mean Visual Analog Scale (VAS) scores ^[2]
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End point description:

Injection-site pain was evaluated by mean visual analog scale (VAS) scores as reported by the participant after each injection at visits where an injection occurred. The degree of pain at the most recent injection site was measured by VAS. The rating scale ranged from 0 (no pain) to 100 (unbearably painful). Participants were followed for 1 hour post-injection and then VAS was completed. Injection evaluations were completed on the same day that the injection was administered

Analysis Population Description

All participants who received at least one dose of aripiprazole IM depot. It is equivalent to safety set (SAF). Number analyzed (n) = Total number of participants with at least one observation of the given parameter (used in result table)

End point type	Primary
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End point timeframe:

At baseline and Phase C trial weeks 4, 8, 12 to 48

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was specified for this endpoint.

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	464			
Units: Participants				
arithmetic mean (standard deviation)				
1ST Injection (n= 462)	4.9 (± 10.7)			
2ND Injection (n= 435)	4.1 (± 8.4)			
3RD Injection (n= 422)	3.4 (± 7.5)			
4TH Injection (n= 402)	3.6 (± 8.6)			
5TH Injection (n= 387)	2.9 (± 7.9)			
6TH Injection (n= 366)	2.4 (± 5.8)			
7TH Injection (n= 353)	2.6 (± 7)			
8TH Injection (n= 293)	2.4 (± 4.9)			
9TH Injection (n= 284)	2.6 (± 6.6)			
10TH Injection (n= 264)	2.5 (± 7.5)			
11TH Injection (n= 255)	2.4 (± 6.3)			
12TH Injection (n= 247)	1.8 (± 4.3)			
13TH Injection (n= 223)	2.2 (± 5.5)			
Last Injection (n= 463)	2.4 (± 5.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with Clinically Significant Abnormal Laboratory Test results

End point title	Number of participants with Clinically Significant Abnormal Laboratory Test results ^[3]
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End point description:

Standard safety variables to be analyzed were included clinical laboratory tests.

Analysis Population Description

All participants who received at least 1 dose of aripiprazole IM depot in the IM Depot Maintenance Phase.

End point type	Primary
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End point timeframe:

At baseline and Phase C trial week 52/ET

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was specified for this endpoint.

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	464			
Units: Number				
number (not applicable)				
Fasting cholesterol	53			
Fasting glucose	39			
Fasting low-density lipoprotein cholesterol	32			
Fasting triglycerides	124			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Abnormal Vital Signs

End point title	Number of Participants With Clinically Significant Abnormal Vital Signs ^[4]
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End point description:

Vital sign measurements included body temperature, systolic and diastolic blood pressure, and heart rate.

Analysis Population Description:

IM Depot Maintenance Phase Safety Sample: All participants who received at least 1 dose of aripiprazole IM depot in the IM Depot Maintenance Phase.

End point type	Primary
End point timeframe:	
At baseline, Phase C trial weeks 1 to 52/early termination (ET) and post-treatment follow-up	

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was specified for this endpoint.

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	464			
Units: Number				
number (not applicable)				
Weight gain of $\geq 7\%$ (n= 454)	93			
Weight loss of $\geq 7\%$ (n= 454)	66			
Blood pressure increased	4			
Heart rate increased	3			
Blood pressure decreased	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Abnormal Electrocardiogram (ECGs)

End point title	Number of Participants With Clinically Significant Abnormal Electrocardiogram (ECGs) ^[5]
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End point description:

Twelve-lead ECGs were recorded at specified visits. For each time point, three 12-lead ECG recordings were obtained approximately 5 minutes apart. Additional 12-lead ECGs were permitted to be obtained at the investigator's discretion and were always obtained in the event of an early termination. The ECGs were evaluated at the investigational site to determine the participant's eligibility and to monitor safety during the trial.

End point type	Primary
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End point timeframe:

At baseline and Phase C trial week 52/ET

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was specified for this endpoint.

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	412			
Units: Number				
number (not applicable)				
Symmetrical T-wave inversion	9			
Supraventricular premature beat	8			
Ventricular premature beat	4			
Myocardial ischemia	2			

Statistical analyses

No statistical analyses for this end point

Primary: Extrapyramidal Symptoms (EPS) assessed by Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS Used only in Japan), and Barnes Akathisia Rating Scale (BARS)

End point title	Extrapyramidal Symptoms (EPS) assessed by Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Scale (SAS), Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS Used only in Japan), and Barnes Akathisia Rating Scale (BARS) ^[6]
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End point description:

Extrapyramidal symptoms were evaluated by calculating mean change from baseline in the following: AIMS assessment consisted of 10 items describing symptoms of dyskinesia. Each item was rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness/severe distress). The SAS consisted of a list of 10 symptoms of parkinsonism. Each item was rated on a 5-point scale, with a score of 1 representing absence of symptoms, and a score of 5 representing a severe condition. The SAS Total Score is the sum of the scores for all 10 items. The DIEPSS was a rating scale for assessing extrapyramidal symptoms that consisted of 8 items for assessing individual symptoms and 1 item for assessing general severity—9 items in all. Each item was assessed on a scale of 0 (no symptoms, normal) to 4 (severe). The BARS consisted of 4 items related to akathisia.

End point type	Primary
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End point timeframe:

At baseline and Phase C trial weeks 4, 8, 12 to 52/ET

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was specified for this endpoint.

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	464			
Units: Number				
arithmetic mean (standard deviation)				

AIMS, Week 28 (n= 457)	0.07 (± 1)			
AIMS, Week 52 (n= 457)	0.05 (± 0.97)			
SAS, Week 28 (n= 377)	0.21 (± 1.59)			
SAS, Week 52 (n= 377)	0.2 (± 1.58)			
DIEPSS, Week 28 (n= 75)	0.32 (± 1.29)			
DIEPSS, Week 52 (n= 75)	0.21 (± 1.11)			
BARS, Week 28 (n= 457)	0.05 (± 0.61)			
BARS, Week 52 (n= 457)	0.04 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Assessment of Risk of Suicidal Events and Classification by Completion of Columbia Suicide Severity Rating Scale (C-SSRS)

End point title	Assessment of Risk of Suicidal Events and Classification by Completion of Columbia Suicide Severity Rating Scale (C-SSRS) ^[7]
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End point description:

Suicidality was monitored by using the C-SSRS at every visit. The C-SSRS scale consisted of a screening/baseline evaluation that assessed the participant's lifetime experience and experience over the last 90 days with suicide events and suicidal ideation and a postbaseline/ "Since Last Visit" evaluation that focused on suicidality since the last trial visit.

Analysis Population Description:

All participants who received at least 1 dose of aripiprazole IM depot. Total = Participants with multiple ratings within the same category were counted towards the total (used in result table).

End point type	Primary
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End point timeframe:

At baseline and Phase C trial weeks 1 to 52/ET

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was specified for this endpoint.

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	461			
Units: Participants				
number (not applicable)				
Total	46			
Completed Suicide	0			
Suicide Attempt	3			
Preparatory action toward imminent suicide	4			
Suicidal ideation	46			
Non-suicidal self-injurious behaviour	4			

Statistical analyses

No statistical analyses for this end point

Primary: Injection Site Evaluations (Pain, Redness, Swelling, Induration) by Investigator Rating

End point title	Injection Site Evaluations (Pain, Redness, Swelling, Induration) by Investigator Rating ^[8]
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End point description:

Participants were followed for 1 hour post-injection and the investigator (or qualified designee) re-assessed localized pain, redness, swelling, and induration at the injection site at 1 hour (\pm 15 minutes) post-injection with focus on the most recent injection site. Injection evaluations were completed on the same day that the injection was administered. Investigators rated localized pain, redness, swelling, and induration at the most recent injection site using a 4-point categorical scale ranging from absent to severe. The participant indicated the degree of pain at the most recent injection site using a VAS. Ratings ranged from 0 (no pain) to 100 (unbearably painful).

Analysis Population Description:

All participants who received at least 1 dose of aripiprazole IM depot in the IM Depot Maintenance Phase

End point type	Primary
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End point timeframe:

At baseline and Phase C trial weeks 4, 8, 12 to 48

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was specified for this endpoint.

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	464			
Units: Participants				
number (not applicable)				
Participant with any injection-site TEAE	42			
Injection Site Bruising	2			
Injection Site Erythema	1			
Injection Site Induration	1			
Injection Site Mass	2			
Injection Site Pain	34			
Injection Site Swelling	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Remained Stable at End of Treatment in Phase C

End point title	Percentage of Participants Who Remained Stable at End of Treatment in Phase C
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End point description:

To evaluate the efficacy, as measured by the percentage of stable participants at baseline who remained stable at the end of treatment in the IM depot maintenance phase C, of aripiprazole IM depot administered every 4 weeks for up to 52 weeks to participants with bipolar I disorder.

Analysis Population Description

IM Depot Maintenance Phase Efficacy Sample: All participants who entered the IM Depot Maintenance Phase, received at least 1 dose of aripiprazole IM depot, and had at least 1 post-baseline efficacy evaluation in the IM Depot Maintenance Phase. Number analyzed (n) is the number of participants evaluated at the specified trial week.

End point type	Secondary
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End point timeframe:

At baseline, and phase C trial weeks 2, 4, 8, 12 to 52/ET

End point values	Phase C: Open-label IM Depot Maintenance Phase			
Subject group type	Reporting group			
Number of subjects analysed	464			
Units: Percentage of participants				
number (not applicable)				
Baseline (n= 463)	100			
Week 2 (n= 430)	96.98			
Week 4 (n= 432)	97.22			
Week 8 (n= 413)	95.64			
Week 12 (n= 406)	96.31			
Week 16 (n= 396)	96.46			
Week 20 (n= 381)	95.54			
Week 24 (n= 361)	96.4			
Week 28 (n= 346)	95.09			
Week 32 (n= 287)	97.91			
Week 36 (n= 271)	95.94			
Week 40 (n= 255)	98.04			
Week 44 (n= 249)	97.59			
Week 48 (n= 243)	97.53			
Week 52 (n=237)	95.78			
Last Visit (n= 460)	88.91			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse events (AEs) were recorded from the signing of informed consent onward.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Phase C: Open-label IM Depot Maintenance Phase
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Reporting group description:

All De novo participants received open-label aripiprazole 400/300 mg IM depot and the participants who completed Trial 31-08-250 entered phase C on aripiprazole IM depot 400 mg, regardless of their last dose of IM depot. De novo participants also received daily supplemental oral aripiprazole (10 to 20 mg daily for non-Japanese sites; 6 to 18 mg for Japanese sites) for the first 2 weeks to maintain therapeutic plasma concentrations. For participants who completed Trial 31-08-250 (some of whom had received double-blind placebo), the use of supplemental oral aripiprazole for the first ≤ 2 weeks was at the investigator's discretion based on the clinical status of the participant. Administration of rescue therapy was recommended for participants who did not meet stability criteria during the IM Depot Maintenance Phase, unless in the investigator's judgment withdrawal from the trial was considered more appropriate.

Serious adverse events	Phase C: Open-label IM Depot Maintenance Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 464 (6.47%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Myocardial Infarction			

subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prinzmetal angina			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tardive dyskinesia			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 464 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bipolar disorder			
subjects affected / exposed	2 / 464 (0.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bipolar I disorder			
subjects affected / exposed	4 / 464 (0.86%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	3 / 464 (0.65%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Social avoidant behaviour			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	4 / 464 (0.86%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Suicide attempt			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperprolactinaemia			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Kidney infection			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obesity			
subjects affected / exposed	1 / 464 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase C: Open-label IM Depot Maintenance Phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	367 / 464 (79.09%)		
Investigations			

Weight increased subjects affected / exposed occurrences (all)	62 / 464 (13.36%) 66		
Nervous system disorders Akathisia subjects affected / exposed occurrences (all)	68 / 464 (14.66%) 79		
Headache subjects affected / exposed occurrences (all)	29 / 464 (6.25%) 37		
Tremor subjects affected / exposed occurrences (all)	28 / 464 (6.03%) 38		
General disorders and administration site conditions Injection site pain subjects affected / exposed occurrences (all)	34 / 464 (7.33%) 50		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	46 / 464 (9.91%) 60		
Depression subjects affected / exposed occurrences (all)	26 / 464 (5.60%) 35		
Insomnia subjects affected / exposed occurrences (all)	51 / 464 (10.99%) 54		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	56 / 464 (12.07%) 87		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	24 / 464 (5.17%) 27		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2013	Amendment 1- Clarifications and additions to trial procedures and inclusion/exclusion criteria intended to enhance subject safety and accuracy of data.
04 February 2015	Amendment 2- Due to a well-established safety profile in the completed aripiprazole IM depot trials, as well as sufficient collection of safety data within this trial, the duration of the IM Depot Maintenance Phase of the trial was reduced from 52 weeks to 28 weeks for rollover subjects (but not for de novo subjects or subjects at sites in Japan). The reduction of the IM Depot Maintenance Phase is described in detail in CSR Section 9.1.4 and in protocol Amendment 2 (Section 16.1.1, Appendix 23).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported