Clinical trial results:
A Double-blind, Placebo Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar Depression

Summary

EudraCT number	2011-002334-39
Trial protocol	BG
Global end of trial date	10 January 2014

Results information

Result version number	v1 (current)
This version publication date	18 April 2018
First version publication date	18 April 2018

Trial information

Trial identification

Sponsor protocol code	RGH-MD-56

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01396447
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Laboratories, LLC, an Allergan Affiliate
Sponsor organisation address	5 Giralda Farms, Madison, United States, NJ 07940
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area Head, Allergan plc, 001 862-261-7000, IR-CTRegistration@Allergan.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	10 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine relative to placebo in subjects with bipolar depression.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 65
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Russian Federation: 93
Country: Number of subjects enrolled	Ukraine: 68
Country: Number of subjects enrolled	United States: 340
Worldwide total number of subjects	584
EEA total number of subjects	65

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)	581

From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult subjects with a diagnosis of bipolar I disorder with a current major depressive episode were considered for participation in the study.

Pre-assignment

Screening details:

A total of 1013 subjects were screened for eligibility; 584 subjects were randomized to receive double-blind treatment; 578 subjects received at least 1 dose of double-blind treatment (Safety Population).

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, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo orally once a day for 8 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo nontrade capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo orally once a day for 8 weeks.

Arm title	Cariprazine 0.75 mg

Arm description:

Subjects received cariprazine 0.5 mg orally once on Days 1-2 and cariprazine 0.75 mg orally once a day starting on Day 3 for the remainder of the 8 week treatment period.

Arm type	Experimental
Investigational medicinal product name	Cariprazine nontrade capsules, 0.75 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received cariprazine 0.75 mg orally once a day starting on Day 3 for the remainder of the 8 week treatment period.

Arm title	Cariprazine 1.5 mg

Arm description:

Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, and cariprazine 1.5 mg orally once a day starting on Day 8 for the remainder of the 8 week treatment period.

Arm type	Experimental

Investigational medicinal product name	Cariprazine nontrade capsules, 1.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received cariprazine 1.5 mg orally once a day starting on Day 8 for the remainder of the 8 week treatment period.

Arm title	Cariprazine 3.0 mg

Arm description:

Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, cariprazine 1.5 mg orally on Days 8-14, and cariprazine 3.0 mg orally once a day starting on Day 15 for the remainder of the 8 week treatment period.

Arm type	Experimental
Investigational medicinal product name	Cariprazine nontrade capsules, 3 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received cariprazine 3.0 mg orally once a day starting on Day 15 for the remainder of the 8 week treatment period.

Number of subjects in period 1[1]	Placebo	Cariprazine 0.75 mg	Cariprazine 1.5 mg
Started	145	141	146
Completed	105	103	117
Not completed	40	38	29
Withdrawal of Consent	11	9	4
Adverse event, non-fatal	15	12	12
Lost to follow-up	4	8	7
Other Miscellaneous Reasons	-	2	1
Insufficient Therapeutic Response	5	5	2
Protocol deviation	5	2	3

Number of subjects in period 1[1]	Cariprazine 3.0 mg
Started	146
Completed	94
Not completed	52
Withdrawal of Consent	15
Adverse event, non-fatal	17
Lost to follow-up	9
Other Miscellaneous Reasons	-
Insufficient Therapeutic Response	4

Protocol deviation	7

Notes:

[1] - 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: Baseline Period is based on the Safety Population, that included all randomized participants who received at least 1 dose of investigational product. 6 participants did not receive study drug and are excluded.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo orally once a day for 8 weeks.	
Reporting group title	Cariprazine 0.75 mg
Reporting group description:	
Subjects received cariprazine 0.5 mg orally once on Days 1-2 and cariprazine 0.75 mg orally once a day starting on Day 3 for the remainder of the 8 week treatment period.	
Reporting group title	Cariprazine 1.5 mg
Reporting group description:	
Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, and cariprazine 1.5 mg orally once a day starting on Day 8 for the remainder of the 8 week treatment period.	
Reporting group title	Cariprazine 3.0 mg
Reporting group description:	
Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, cariprazine 1.5 mg orally on Days 8-14, and cariprazine 3.0 mg orally once a day starting on Day 15 for the remainder of the 8 week treatment period.	

Reporting group values	Placebo	Cariprazine 0.75 mg	Cariprazine 1.5 mg
Number of subjects	145	141	146
Age categorical Units: Subjects			
Adults (18-64 years)	144	141	145
From 65-84 years	1	0	1
Age Continuous Units: years			
arithmetic mean	43.6	40.1	40.9
standard deviation	± 12.0	± 11.2	± 11.4
Gender, Male/Female Units: Subjects			
Female	89	91	92
Male	56	50	54
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	13	11
Not Hispanic or Latino	133	128	135
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	1	1
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	30	26	30
White	110	111	109
More than one race	0	0	0
Other	2	2	4

Weight			
Units: kg			
arithmetic mean	79.98	80.81	81.43
standard deviation	± 17.08	± 18.36	± 16.79
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	27.81	28.42	28.44
standard deviation	± 5.27	± 5.71	± 5.39
Waist circumference			
Units: cm			
arithmetic mean	91.40	93.32	93.38
standard deviation	± 14.24	± 15.45	± 14.55

Reporting group values	Cariprazine 3.0 mg	Total	
Number of subjects	146	578	
Age categorical			
Units: Subjects			
Adults (18-64 years)	145	575	
From 65-84 years	1	3	
Age Continuous			
Units: years			
arithmetic mean	42.8		
standard deviation	± 10.8	-	
Gender, Male/Female			
Units: Subjects			
Female	88	360	
Male	58	218	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	12	48	
Not Hispanic or Latino	134	530	
Unknown or Not Reported	0	0	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	3	7	
Asian	0	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	26	112	
White	113	443	
More than one race	0	0	
Other	4	12	
Weight			
Units: kg			
arithmetic mean	81.45		
standard deviation	± 17.86	-	
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	28.28		
standard deviation	± 5.64	-	
Waist circumference			
Units: cm			

arithmetic mean	93.24		
standard deviation	± 15.40	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo orally once a day for 8 weeks.	
Reporting group title	Cariprazine 0.75 mg
Reporting group description:	
Subjects received cariprazine 0.5 mg orally once on Days 1-2 and cariprazine 0.75 mg orally once a day starting on Day 3 for the remainder of the 8 week treatment period.	
Reporting group title	Cariprazine 1.5 mg
Reporting group description:	
Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, and cariprazine 1.5 mg orally once a day starting on Day 8 for the remainder of the 8 week treatment period.	
Reporting group title	Cariprazine 3.0 mg
Reporting group description:	
Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, cariprazine 1.5 mg orally on Days 8-14, and cariprazine 3.0 mg orally once a day starting on Day 15 for the remainder of the 8 week treatment period.	

Primary: Change From Baseline in the Montgomery-Åsberg Depression Rating Scale Total Score at Week 6

End point title	Change From Baseline in the Montgomery-Åsberg Depression Rating Scale Total Score at Week 6
End point description:	
The Montgomery-Åsberg Depression Rating Scale is a 10-item, clinician-rated scale that evaluates the subject's depressive symptomatology during the past week. Subjects are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each item is scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity. The scores on the 10 items are summed for a total score that can range from 0 to 60. A higher score indicates greater depression. A negative change score indicates improvement. Intent-to-treat population: All randomized subjects who took at least 1 dose of investigational product and had at least 1 post-baseline assessment of the Montgomery-Åsberg Depression Rating Scale.	
End point type	Primary
End point timeframe:	
Baseline to Week 6	

End point values	Placebo	Cariprazine 0.75 mg	Cariprazine 1.5 mg	Cariprazine 3.0 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	141	140	145	145
Units: units on a scale				
least squares mean (standard error)	-11.1 (± 0.9)	-13.0 (± 0.9)	-15.1 (± 0.8)	-13.7 (± 0.9)

Statistical analyses

Statistical analysis title	Cariprazine 0.75 mg vs Placebo
Comparison groups	Placebo v Cariprazine 0.75 mg
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1292 [1]
Method	Repeated measures mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	0.5

Notes:

[1] - The analysis included treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Statistical analysis title	Cariprazine 1.5 mg vs Placebo
Comparison groups	Placebo v Cariprazine 1.5 mg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [2]
Method	Repeated measures mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-1.6

Notes:

[2] - The analysis included treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Statistical analysis title	Cariprazine 3.0 mg vs Placebo
Comparison groups	Placebo v Cariprazine 3.0 mg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0374 [3]
Method	Repeated measures mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	-0.1

Notes:

[3] - The analysis included treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Secondary: Change From Baseline in the Clinical Global Impressions-Severity Total Score at Week 6

End point title	Change From Baseline in the Clinical Global Impressions-Severity Total Score at Week 6

End point description:

The Clinical Global Impressions-Severity scale is a clinician-rated scale that measures the overall severity of a subject's illness in comparison with the severity of illness in other subjects the physician has observed. The subject is rated on a scale from 1 to 7 with 1 indicating a "normal state" and 7 indicating "among the most extremely ill subjects." A higher score indicates greater illness. A negative change score indicates improvement. Intent-to-treat population: All randomized subjects who took at least 1 dose of investigational product and had at least 1 post-Baseline assessment of the Montgomery-Åsberg Depression Rating Scale.

End point type	Secondary

End point timeframe:

Baseline to Week 6

End point values	Placebo	Cariprazine 0.75 mg	Cariprazine 1.5 mg	Cariprazine 3.0 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	141	140	145	145
Units: units on a scale				
least squares mean (standard error)	-1.0 (± 0.1)	-1.1 (± 0.1)	-1.4 (± 0.1)	-1.3 (± 0.1)

Statistical analyses

Statistical analysis title	Cariprazine 0.75 mg vs Placebo

Statistical analysis description:

The analysis included treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Comparison groups	Placebo v Cariprazine 0.75 mg
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3025
Method	Repeated measures mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

Statistical analysis title	Cariprazine 1.5 mg vs Placebo

Statistical analysis description:

The analysis included treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Comparison groups	Placebo v Cariprazine 1.5 mg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044
Method	Repeated measures mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.2

Statistical analysis title	Cariprazine 3.0 mg vs Placebo

Statistical analysis description:

The analysis included treatment group, pooled study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline value-by-visit interaction as covariates.

Comparison groups	Placebo v Cariprazine 3.0 mg
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0489
Method	Repeated measures mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected and recorded from the time the subject signs the informed consent form until 30 days after the last dose of treatment.

Adverse event reporting additional description:

Safety population: All randomized subjects who took at least 1 dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo orally once a day for 8 weeks.

Reporting group title	Cariprazine 0.75 mg

Reporting group description:

Subjects received cariprazine 0.5 mg orally once on Days 1-2 and cariprazine 0.75 mg orally once a day starting on Day 3 for the remainder of the 8 week treatment period.

Reporting group title	Cariprazine 1.5 mg

Reporting group description:

Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, and cariprazine 1.5 mg orally once a day starting on Day 8 for the remainder of the 8 week treatment period.

Reporting group title	Cariprazine 3.0 mg

Reporting group description:

Subjects received cariprazine 0.5 mg orally once on Days 1-2, cariprazine 0.75 mg orally once on Days 3-4, cariprazine 1.0 mg orally once on Days 5-7, cariprazine 1.5 mg orally on Days 8-14, and cariprazine 3.0 mg orally once a day starting on Day 15 for the remainder of the 8 week treatment period.

Serious adverse events	Placebo	Cariprazine 0.75 mg	Cariprazine 1.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 145 (3.45%)	1 / 141 (0.71%)	2 / 146 (1.37%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 145 (0.00%)	0 / 141 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			

subjects affected / exposed	0 / 145 (0.00%)	0 / 141 (0.00%)	0 / 146 (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
Injury			
subjects affected / exposed	0 / 145 (0.00%)	0 / 141 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Vertigo CNS origin			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	0 / 145 (0.00%)	0 / 141 (0.00%)	0 / 146 (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
Hemiparesis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	0 / 146 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	0 / 146 (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			
Depression			
subjects affected / exposed	1 / 145 (0.69%)	1 / 141 (0.71%)	0 / 146 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomania			
subjects affected / exposed	0 / 145 (0.00%)	0 / 141 (0.00%)	1 / 146 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			

subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	0 / 146 (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
Suicidal ideation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	0 / 146 (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

Serious adverse events	Cariprazine 3.0 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 146 (1.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury			
subjects affected / exposed	0 / 146 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Vertigo CNS origin			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	1 / 146 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			

subjects affected / exposed	0 / 146 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 146 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 146 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomania			
subjects affected / exposed	0 / 146 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mania			
subjects affected / exposed	0 / 146 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 146 (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	Placebo	Cariprazine 0.75 mg	Cariprazine 1.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 145 (28.97%)	43 / 141 (30.50%)	51 / 146 (34.93%)
Nervous system disorders			

Akathisia			
subjects affected / exposed	2 / 145 (1.38%)	4 / 141 (2.84%)	7 / 146 (4.79%)
occurrences (all)	2	4	7
Headache			
subjects affected / exposed	17 / 145 (11.72%)	11 / 141 (7.80%)	11 / 146 (7.53%)
occurrences (all)	20	12	12
Somnolence			
subjects affected / exposed	7 / 145 (4.83%)	6 / 141 (4.26%)	10 / 146 (6.85%)
occurrences (all)	7	6	10
Gastrointestinal disorders			
Nausea			
alternative dictionary used: MedDRA 16.1			
subjects affected / exposed	7 / 145 (4.83%)	12 / 141 (8.51%)	12 / 146 (8.22%)
occurrences (all)	10	13	15
Diarrhoea			
subjects affected / exposed	10 / 145 (6.90%)	2 / 141 (1.42%)	9 / 146 (6.16%)
occurrences (all)	11	2	9
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 145 (8.28%)	16 / 141 (11.35%)	10 / 146 (6.85%)
occurrences (all)	13	18	11
Restlessness			
subjects affected / exposed	5 / 145 (3.45%)	4 / 141 (2.84%)	4 / 146 (2.74%)
occurrences (all)	5	4	5

Non-serious adverse events	Cariprazine 3.0 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 146 (38.36%)		
Nervous system disorders			
Akathisia			
subjects affected / exposed	21 / 146 (14.38%)		
occurrences (all)	24		
Headache			
subjects affected / exposed	10 / 146 (6.85%)		
occurrences (all)	10		
Somnolence			

subjects affected / exposed occurrences (all)	10 / 146 (6.85%) 11		
Gastrointestinal disorders Nausea alternative dictionary used: MedDRA 16.1 subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 12 / 146 (8.22%) 13 3 / 146 (2.05%) 3		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Restlessness subjects affected / exposed occurrences (all)	 17 / 146 (11.64%) 19 9 / 146 (6.16%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2011	• Add the cariprazine 3 mg/day treatment group, which increased the number of treatment groups from 3 to 4 and increased the number of study centers • Increase the screening period from up to 7 days to up to 14 days and decrease the safety follow-up period from 2 weeks to 1 week • Allow hospitalization of study subjects per local clinical practice • Modify inclusion criteria #2, #3 (duration of current depressive episode), #4 (verification of previous manic or mixed episode), and #10 (body mass index [BMI]) • Modify exclusion criteria #7 (urine drug screen), #9 (prior treatment trials with antidepressants or mood stabilizers), #15 (prior treatment with clozapine), #16 (concomitant medications), #18 (vagus nerve stimulation and experimental treatments), and #30 (hepatitis C) • Revise the cariprazine starting dose from 0.25 mg/day to 0.50 mg/day and change investigational product form from tablets to capsules • Clarify the start of dosing on the evening of Visit 2 or the morning after Visit 2 • Clarify noncompliance due to missed doses • Remove Clinical Global Impressions–Improvement (CGI-I) assessment at all visits and Functioning Assessment Short Test (FAST) assessment at Visit 5 • Remove hepatitis C virus Recombinant ImmunoBlot Assay (HCV RIBA), propoxyphene, tricyclic antidepressants, folate and vitamin B testing and change hemoglobin A1c testing from reflex to required at Visits 1 and 7 • Revise the primary efficacy analysis section and sample size estimate to account for the additional treatment group and update endpoint to Week 6 and Week 8
29 September 2011	•Revise the efficacy analyses section to change the multiplicity strategy from a serial gatekeeping procedure to a matched parallel gatekeeping procedure • Update the power to reflect the new multiplicity strategy • Modify the study center pooling algorithm to require at least 2 intent-to-treat (ITT) subjects per treatment group at each study center • Specify the range of shift parameter values for the pattern-mixture model (PMM) sensitivity analysis • Modify inclusion criterion #4 to provide additional guidance on verifying previous manic episodes • Modify exclusion #9 to clarify and provide additional guidance on the definition of an adequate trial and exclusion #21b to clarify the contraceptive requirements • Update the concomitant medication section to clarify the use of allowed and disallowed medications • Clarify the order of assessing procedures at Visit 2 • Modify the collection of BP and pulse measurements.
09 November 2012	• Specify Week 6 as the primary endpoint for primary and secondary analysis, per FDA Feedback • Clarify inclusion criterion # 4; revise exclusion criterion #30 for consistency with other cariprazine studies • Update the sample size calculation section to reflect changes in the endpoint of primary and secondary parameters •Modify the analysis model for the imputed data with the PMM approach from mixed-effects model for repeated measures (MMRM) to analysis of covariance (ANCOVA).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported