Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Fixed-dose Clinical Trial Evaluating the Efficacy, Safety and Tolerability of Cariprazine in Patients with Bipolar I Depression

Summary

EudraCT number	2016-000757-13
Trial protocol	EE LT PL BG
Global end of trial date	19 July 2017

Results information

Result version number	v1 (current)
This version publication date	24 November 2018
First version publication date	24 November 2018

Trial information

Trial identification

Sponsor protocol code	RGH-MD-54

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02670551
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	19 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine 1.5 milligram (mg)/day and 3.0 mg/day relative to placebo in participants with bipolar I depression.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2016
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: 116
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Poland: 63
Country: Number of subjects enrolled	United States: 290
Worldwide total number of subjects	488
EEA total number of subjects	198

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)	485
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 782 participants were screened for eligibility; 488 participants randomised to receive double-blind treatment; 480 participants received at least 1 dose of double-blind treatment (Safety Population) and 474 participants had at least 1 postbaseline Montgomery-Åsberg Depression Rating Scale total score assessment (Intent-to-Treat 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:

Following a 7 to 14 days screening/washout period, placebo-matching cariprazine capsule, one per day, orally for 6 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:

Participants received placebo-matching cariprazine capsule, orally, once a day for 6 weeks.

Arm title	Cariprazine 1.5 mg

Arm description:

Following a 7 to 14 days screening/washout period, cariprazine 1.5 milligram (mg) capsule, one per day, orally for 6 weeks.

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:

Participants received cariprazine 1.5 mg capsule, orally, once a day for 6 weeks.

Arm title	Cariprazine 3.0 mg

Arm description:

Following a 7 to 14 days screening/washout period, cariprazine 1.5 mg capsule, one per day for 2 weeks followed by cariprazine 3.0 mg capsule, one per day, orally beginning on Day 15 for 4 weeks.

Arm type	Experimental

Investigational medicinal product name	Cariprazine nontrade capsules, 3.0 mg
Investigational medicinal product code	RGH-188
Other name	VRAYLAR®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received cariprazine 3.0 mg capsule, orally, once a day beginning on Day 15 for 4 weeks.

Number of subjects in period 1	Placebo	Cariprazine 1.5 mg	Cariprazine 3.0 mg
Started	163	160	165
Received Treatment (Safety Population)	158	157	165
Completed	135	134	134
Not completed	28	26	31
Withdrawal of Consent	6	3	8
Adverse event, non-fatal	4	7	9
Noncompliance with study drug	3	3	2
Lost to follow-up	5	7	6
Other Miscellaneous Reasons	2	3	3
Did Not Receive Treatment	5	3	-
Lack of efficacy	2	-	3
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Following a 7 to 14 days screening/washout period, placebo-matching cariprazine capsule, one per day, orally for 6 weeks.	
Reporting group title	Cariprazine 1.5 mg
Reporting group description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 milligram (mg) capsule, one per day, orally for 6 weeks.	
Reporting group title	Cariprazine 3.0 mg
Reporting group description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 mg capsule, one per day for 2 weeks followed by cariprazine 3.0 mg capsule, one per day, orally beginning on Day 15 for 4 weeks.	

Reporting group values	Placebo	Cariprazine 1.5 mg	Cariprazine 3.0 mg
Number of subjects	163	160	165
Age categorical Units: Subjects			
18 - 64 years	161	159	165
65 - 84 years	2	1	0
>= 85 Years	0	0	0
Age Continuous Units: years			
arithmetic mean	43.9	42.6	41.9
full range (min-max)	18 to 65	18 to 65	19 to 64
Sex: Female, Male Units: Subjects			
Female	94	101	94
Male	69	59	71
Race/Ethnicity, Customized Units: Subjects			
White	118	126	126
Black or African American	39	29	37
Asian	3	2	0
American Indian or Alaska Native	1	1	1
Native Hawaiian or Other Pacific Islander	2	0	0
Multiple	0	2	1
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	13	15	14
Not Hispanic or Latino	150	145	151
Montgomery-Åsberg Depression Rating Scale (MADRS) Score at Baseline			
The Montgomery-Åsberg Depression Rating Scale is a 10-item, clinician-rated scale that evaluates the participant's depressive symptomatology during the past week. Participants were rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each of the 10 items was scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity for a total possible score of 0 (best) to 60 (worst).			

Units: score on a scale arithmetic mean standard deviation	±	±	±
Clinical Global Impressions-Severity (CGI-S) Score at Baseline			
The Clinical Global Impressions-Severity (CGI-S) is a clinician-rated scale that measures the overall severity of a participant's illness in comparison with the severity of other participants the physician has observed. The participant was rated on a scale from 1 to 7, with 1 indicating a "normal state" and 7 indicating "among the most extremely ill participants."			
Units: score on a scale arithmetic mean standard deviation	±	±	±

Reporting group values	Total		
Number of subjects	488		
Age categorical Units: Subjects			
18 - 64 years	485		
65 - 84 years	3		
>= 85 Years	0		
Age Continuous Units: years arithmetic mean full range (min-max)	--		
Sex: Female, Male Units: Subjects			
Female	289		
Male	199		
Race/Ethnicity, Customized Units: Subjects			
White	370		
Black or African American	105		
Asian	5		
American Indian or Alaska Native	3		
Native Hawaiian or Other Pacific Islander	2		
Multiple	3		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	42		
Not Hispanic or Latino	446		
Montgomery-Åsberg Depression Rating Scale (MADRS) Score at Baseline			
The Montgomery-Åsberg Depression Rating Scale is a 10-item, clinician-rated scale that evaluates the participant's depressive symptomatology during the past week. Participants were rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each of the 10 items was scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity for a total possible score of 0 (best) to 60 (worst).			
Units: score on a scale arithmetic mean standard deviation	--		
Clinical Global Impressions-Severity (CGI-S) Score at Baseline			
The Clinical Global Impressions-Severity (CGI-S) is a clinician-rated scale that measures the overall			

severity of a participant's illness in comparison with the severity of other participants the physician has observed. The participant was rated on a scale from 1 to 7, with 1 indicating a "normal state" and 7 indicating "among the most extremely ill participants."			
Units: score on a scale			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Following a 7 to 14 days screening/washout period, placebo-matching cariprazine capsule, one per day, orally for 6 weeks.	
Subject analysis set title	Cariprazine 1.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 milligram (mg) capsule, one per day, orally for 6 weeks.	
Subject analysis set title	Cariprazine 3.0 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 mg capsule, one per day for 2 weeks followed by cariprazine 3.0 milligram (mg) capsule, one per day, orally beginning on Day 15 for 4 weeks.	

Reporting group values	Placebo	Cariprazine 1.5 mg	Cariprazine 3.0 mg
Number of subjects	156	154	164
Age categorical			
Units: Subjects			
18 - 64 years			
65 - 84 years			
>= 85 Years			
Age Continuous			
Units: years			
arithmetic mean			
full range (min-max)			
Sex: Female, Male			
Units: Subjects			
Female			
Male			
Race/Ethnicity, Customized			
Units: Subjects			
White			
Black or African American			
Asian			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Multiple			
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino			

Not Hispanic or Latino			

Montgomery-Åsberg Depression Rating Scale (MADRS) Score at Baseline			
The Montgomery-Åsberg Depression Rating Scale is a 10-item, clinician-rated scale that evaluates the participant's depressive symptomatology during the past week. Participants were rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each of the 10 items was scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity for a total possible score of 0 (best) to 60 (worst).			
Units: score on a scale			
arithmetic mean	30.3	30.6	31.1
standard deviation	± 4.5	± 4.2	± 4.8
Clinical Global Impressions-Severity (CGI-S) Score at Baseline			
The Clinical Global Impressions-Severity (CGI-S) is a clinician-rated scale that measures the overall severity of a participant's illness in comparison with the severity of other participants the physician has observed. The participant was rated on a scale from 1 to 7, with 1 indicating a "normal state" and 7 indicating "among the most extremely ill participants."			
Units: score on a scale			
arithmetic mean	4.5	4.5	4.5
standard deviation	± 0.5	± 0.5	± 0.5

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Following a 7 to 14 days screening/washout period, placebo-matching cariprazine capsule, one per day, orally for 6 weeks.	
Reporting group title	Cariprazine 1.5 mg
Reporting group description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 milligram (mg) capsule, one per day, orally for 6 weeks.	
Reporting group title	Cariprazine 3.0 mg
Reporting group description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 mg capsule, one per day for 2 weeks followed by cariprazine 3.0 mg capsule, one per day, orally beginning on Day 15 for 4 weeks.	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Following a 7 to 14 days screening/washout period, placebo-matching cariprazine capsule, one per day, orally for 6 weeks.	
Subject analysis set title	Cariprazine 1.5 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 milligram (mg) capsule, one per day, orally for 6 weeks.	
Subject analysis set title	Cariprazine 3.0 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 mg capsule, one per day for 2 weeks followed by cariprazine 3.0 milligram (mg) capsule, one per day, orally beginning on Day 15 for 4 weeks.	

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

End point title	Change From Baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) Score at Week 6
End point description:	
The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item, clinician-rated scale that evaluates the participant's depressive symptomatology during the past week. Participants were rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each of the 10 items was scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity for a total possible score of 0 (best) to 60 (worst). A negative change from Baseline indicates improvement. The Intent-to-Treat (ITT) Population included all participants from the safety population who had at least 1 postbaseline assessment of the MADRS total score. Overall number of participants analysed is the number of participants with data available for analysis at the given time-point.	
End point type	Primary
End point timeframe:	
Baseline (Week 0) to Week 6	

End point values	Placebo	Cariprazine 1.5 mg	Cariprazine 3.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	135	136	
Units: score on a scale				
least squares mean (standard error)	-12.6 (± 0.76)	-15.1 (± 0.77)	-15.6 (± 0.76)	

Statistical analyses

Statistical analysis title	Cariprazine 1.5 mg vs Placebo
Comparison groups	Placebo v Cariprazine 1.5 mg
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0331 [2]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	-0.4

Notes:

[1] - To control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6 for the primary and secondary efficacy parameters, the parallel gatekeeping procedure was implemented.

[2] - MMRM analysis was used. Fixed factors: treatment group, pooled study centre, visit, treatment-group-by-visit interaction. Covariates: Baseline value, baseline value-by-visit interaction. P-value was adjusted by matched parallel gatekeeping procedure.

Statistical analysis title	Cariprazine 3.0 mg vs Placebo
Comparison groups	Placebo v Cariprazine 3.0 mg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0103 [4]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Least Squares Mean Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	-0.9

Notes:

[3] - To control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6 for the primary and secondary efficacy parameters, the parallel gatekeeping procedure was implemented.

[4] - MMRM analysis was used. Fixed factors: treatment group, pooled study centre, visit, treatment-group-by-visit interaction. Covariates: Baseline value, baseline value-by-visit interaction. P-value was adjusted by matched parallel gatekeeping procedure.

Secondary: Change From Baseline in Clinical Global Impressions-Severity (CGI-S) Score at Week 6

End point title	Change From Baseline in Clinical Global Impressions-Severity (CGI-S) Score at Week 6

End point description:

The Clinical Global Impressions-Severity is a clinician-rated scale that measures the overall severity of a participant's illness in comparison with the severity of other participants the physician has observed. The participant was rated on a scale from 1 to 7, with 1 indicating a "normal state" and 7 indicating "among the most extremely ill participants." A negative change from Baseline indicates improvement. ITT Population included all participants from the safety population who had at least 1 postbaseline assessment of the MADRS total score. Overall number of participants analysed is the number of participants with data available for analysis at the given time-point.

End point type	Secondary

End point timeframe:

Baseline (Week 0) to Week 6

End point values	Placebo	Cariprazine 1.5 mg	Cariprazine 3.0 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	135	136	
Units: score on a scale				
least squares mean (standard error)	-1.3 (± 0.09)	-1.6 (± 0.10)	-1.6 (± 0.09)	

Statistical analyses

Statistical analysis title	Cariprazine 1.5 mg vs Placebo
Comparison groups	Placebo v Cariprazine 1.5 mg
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0714 [6]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0

Notes:

[5] - To control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6 for the primary and secondary efficacy parameters, the parallel gatekeeping procedure was implemented.

[6] - MMRM analysis was used. Fixed factors: treatment group, pooled study centre, visit, treatment-group-by-visit interaction. Covariates: Baseline value, baseline value-by-visit interaction. P-value was adjusted by matched parallel gatekeeping procedure.

Statistical analysis title	Cariprazine 3.0 mg vs Placebo
Comparison groups	Placebo v Cariprazine 3.0 mg

Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0662 [8]
Method	Mixed Model Repeated Measures (MMRM)
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0

Notes:

[7] - To control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6 for the primary and secondary efficacy parameters, the parallel gatekeeping procedure was implemented.

[8] - MMRM analysis was used. Fixed factors: treatment group, pooled study centre, visit, treatment-group-by-visit interaction. Covariates: Baseline value, baseline value-by-visit interaction. P-value was adjusted by matched parallel gatekeeping procedure.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First dose to 30 days past last dose (Up to 80 Days)	
Adverse event reporting additional description:	
Safety Population included all randomised participants who took at least 1 dose of double-blind investigational product.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Following a 7 to 14 days screening/washout period, placebo-matching cariprazine capsule, one per day, orally for 6 weeks.	
Reporting group title	Cariprazine 3.0 mg
Reporting group description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 mg capsule, one per day for 2 weeks followed by cariprazine 3.0 milligram (mg) capsule, one per day, orally beginning on Day 15 for 4 weeks.	
Reporting group title	Cariprazine 1.5 mg
Reporting group description:	
Following a 7 to 14 days screening/washout period, cariprazine 1.5 milligram (mg) capsule, one per day, orally for 6 weeks.	

Serious adverse events	Placebo	Cariprazine 3.0 mg	Cariprazine 1.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 158 (1.27%)	2 / 165 (1.21%)	2 / 157 (1.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 165 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 158 (0.63%)	0 / 165 (0.00%)	0 / 157 (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			
Asthma			
subjects affected / exposed	0 / 158 (0.00%)	0 / 165 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 158 (0.00%)	1 / 165 (0.61%)	0 / 157 (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
Suicidal ideation			
subjects affected / exposed	0 / 158 (0.00%)	1 / 165 (0.61%)	0 / 157 (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			
Chronic tonsillitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 165 (0.00%)	0 / 157 (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

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

Non-serious adverse events	Placebo	Cariprazine 3.0 mg	Cariprazine 1.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 158 (27.22%)	62 / 165 (37.58%)	48 / 157 (30.57%)
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 158 (8.23%)	12 / 165 (7.27%)	7 / 157 (4.46%)
occurrences (all)	17	15	7
Akathisia			
subjects affected / exposed	5 / 158 (3.16%)	9 / 165 (5.45%)	10 / 157 (6.37%)
occurrences (all)	5	9	12
Dizziness			
subjects affected / exposed	3 / 158 (1.90%)	6 / 165 (3.64%)	8 / 157 (5.10%)
occurrences (all)	3	7	8
Somnolence			

subjects affected / exposed	3 / 158 (1.90%)	6 / 165 (3.64%)	8 / 157 (5.10%)
occurrences (all)	3	6	8
Sedation			
subjects affected / exposed	2 / 158 (1.27%)	5 / 165 (3.03%)	8 / 157 (5.10%)
occurrences (all)	2	5	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 158 (0.63%)	15 / 165 (9.09%)	6 / 157 (3.82%)
occurrences (all)	1	16	6
Dry mouth			
subjects affected / exposed	9 / 158 (5.70%)	3 / 165 (1.82%)	6 / 157 (3.82%)
occurrences (all)	9	3	6
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 158 (6.96%)	12 / 165 (7.27%)	7 / 157 (4.46%)
occurrences (all)	11	12	7
Restlessness			
subjects affected / exposed	6 / 158 (3.80%)	12 / 165 (7.27%)	2 / 157 (1.27%)
occurrences (all)	6	14	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	The following changes were implemented with Amendment 1: • Used the clinician-rated Columbia–Suicide Severity Rating Scale (C-SSRS), rather than the patient-rated scale, in order to provide greater clinical oversight • Clarification of the following exclusion criteria: - 6: was modified to reflect the classification of substance-related disorders - 16: was modified to clarify the allowed duration and to ensure consistency of bipolar disorder diagnosis - 18: was revised to clarify and limit the doses and allowances for benzodiazepines • Deletion of exclusion criterion 19: because cariprazine had been approved for prescription use (in the United States), there was no clinical rationale for excluding participants with prior participation in a cariprazine study. • Addition of an exclusion criterion (23) addressing use of contraception for male participants; and amendment of exclusion 24 to clarify allowable contraception methods Clarification of Table 9.4.5-1 (blister card configuration and dosing regimen); • Clarification on the use of lorazepam (or equivalent benzodiazepine) as rescue medication for agitation, restlessness, and hostility, and removal of the restriction on injectable benzodiazepine agents for use as rescue medication for agitation, restlessness, and hostility.
17 February 2016	The following changes were implemented with Amendment 2: Revised the wording of exclusion criterion 18 to correct an error (ie, the omission of the word "no" in the sub-bullet pertaining to use of benzodiazepines, which caused this exception to exclusion criterion 18 to convey the reverse of what was intended).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported