Clinical trial results:
A Double-blind, Placebo-controlled, Randomized Withdrawal, Multicenter Clinical Trial Evaluating the Efficacy, Safety and Tolerability of Cariprazine in a Dose-reduction Paradigm in the Prevention of Relapse in Bipolar I Disorder Patients Whose Current Episode is Manic or Depressive, With or Without Mixed Features

Summary

EudraCT number	2017-000803-25
Trial protocol	BG RO
Global end of trial date	05 September 2022

Results information

Result version number	v2 (current)
This version publication date	15 October 2023
First version publication date	13 September 2023
Version creation reason	• Correction of full data set Editorial change for clarification.

Trial information

Trial identification

Sponsor protocol code	RGH-MD-25

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03573297
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Marlow International The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	AbbVie, Global Medical Services, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	AbbVie, Global Medical Services, 001 8006339110, abbvieclinicaltrials@abbvie.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	05 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To evaluate the efficacy and safety of cariprazine at a target dose of 3.0 mg/d compared with placebo in prevention of relapse in patients with bipolar I disorder whose current episode (i.e. index episode) is manic or depressive, with or without mixed features; 2) To evaluate the efficacy and safety of cariprazine at a target dose of 1.5 mg/d compared with placebo in prevention of relapse in patients with bipolar I disorder whose current episode (i.e. index episode) is manic or depressive, with or without mixed features who were initially stabilized on a target dose of 3.0 mg/d

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2018
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	Malaysia: 2
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	United States: 590
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	Bulgaria: 45
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Russian Federation: 121
Country: Number of subjects enrolled	Ukraine: 86
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Taiwan: 4
Worldwide total number of subjects	901
EEA total number of subjects	61

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)	899
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	901
Number of subjects completed	896

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not enter open label treatment period: 5

Period 1

Period 1 title	Open Label Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open Label Treatment Period

Arm description:

Participants started on cariprazine 1.5 mg QD, with a target dose of 3.0 mg once daily (QD), for up to 16 weeks.

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

Dosage and administration details:

once daily

Number of subjects in period 1[1]	Open Label Treatment Period
Started	896
Completed	440
Not completed	456
Consent withdrawn by subject	104
Failure to meet randomization criteria	143
Other, not specified	7
Pregnancy	1
Adverse event	67

Non-compliance with study drug	25
Study terminated by sponsor	2
Lost to follow-up	55
Lack of efficacy	35
Protocol deviation	17

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: Did not enter open label treatment period: 5 subjects

Period 2

Period 2 title	Double-Blind Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

During the Double-Blind period, all study treatment will be provided in identical blister cards to maintain masking of the study. All patients will be instructed to take 1 capsule of IP once daily at approximately the same time each day.

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Placebo QD

Arm description:

Partcipants randomized to receive placebo QD for up to 39 weeks.

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

Dosage and administration details:

once daily

Arm title	Double-Blind Cariprazine 1.5 mg QD

Arm description:

Participants randomized to receive cariprazine 1.5 mg QD for up to 39 weeks.

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

Dosage and administration details:

once daily

Arm title	Double-Blind Cariprazine 3.0 mg QD

Arm description:

Participants randomized to receive cariprazine 3.0 mg QD for up to 39 weeks.

Arm type	Experimental

Investigational medicinal product name	Cariprazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

once daily

Number of subjects in period 2	Double-Blind Placebo QD	Double-Blind Cariprazine 1.5 mg QD	Double-Blind Cariprazine 3.0 mg QD
Started	145	147	148
Completed	79	82	84
Not completed	66	65	64
Relapse event during double-blind treatment period	29	25	26
Consent withdrawn by subject	23	11	14
Other, not specified	5	8	6
Adverse event	1	5	1
Non-compliance with study drug	-	4	4
Lost to follow-up	4	4	9
Lack of efficacy	1	-	-
Protocol deviation	3	8	4

Baseline characteristics

Reporting groups	
Reporting group title	Open Label Treatment Period
Reporting group description:	
Participants started on cariprazine 1.5 mg QD, with a target dose of 3.0 mg once daily (QD), for up to 16 weeks.	

Reporting group values	Open Label Treatment Period	Total	
Number of subjects	896	896	
Age categorical Units: Subjects			
< 45 years	539	539	
≥ 45 years	357	357	
Gender categorical Units: Subjects			
Female	542	542	
Male	354	354	
Ethnicity Units: Subjects			
Hispanic or Latino	89	89	
Not Hispanic or Latino	806	806	
Unknown or Not Reported	1	1	
Race Units: Subjects			
American Indian or Alaska Native	3	3	
Asian	32	32	
Native Hawaiian or Other Pacific Islander	2	2	
Black or African American	258	258	
White	591	591	
More than one race	10	10	

End points

End points reporting groups

Reporting group title	Open Label Treatment Period
Reporting group description:	
Participants started on cariprazine 1.5 mg QD, with a target dose of 3.0 mg once daily (QD), for up to 16 weeks.	
Reporting group title	Double-Blind Placebo QD
Reporting group description:	
Partcipants randomized to receive placebo QD for up to 39 weeks.	
Reporting group title	Double-Blind Cariprazine 1.5 mg QD
Reporting group description:	
Participants randomized to receive cariprazine 1.5 mg QD for up to 39 weeks.	
Reporting group title	Double-Blind Cariprazine 3.0 mg QD
Reporting group description:	
Participants randomized to receive cariprazine 3.0 mg QD for up to 39 weeks.	
Subject analysis set title	Double-Blind ITT Population: Double-Blind Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants randomized to receive placebo QD for up to 39 weeks who took at least 1 dose of DB IP and had at least 1 post-randomization assessment of the YMRS, MADRS or CGI-S scores during the 39-week DBTP of the study.	
Subject analysis set title	Double-Blind ITT Population:Double-Blind Cariprazine 1.5 mg QD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants randomized to receive cariprazine 1.5 mg QD for up to 39 weeks who took at least 1 dose of DB IP and had at least 1 post-randomization assessment of the YMRS, MADRS or CGI-S scores during the 39-week DBTP of the study.	
Subject analysis set title	Double-Blind ITT Population:Double-Blind Cariprazine 3.0 mg QD
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants randomized to receive cariprazine 3.0 mg QD for up to 39 weeks who took at least 1 dose of DB IP and had at least 1 post-randomization assessment of the YMRS, MADRS or CGI-S scores during the 39-week DBTP of the study.	

Primary: Time to First Relapse of Any Mood Episode During the Double-blind Treatment Period

End point title	Time to First Relapse of Any Mood Episode During the Double-blind Treatment Period
End point description:	
Relapse was defined as the occurrence of any 1 of the following: - Young Mania Rating Score (YMRS) total score ≥ 17 (range 0-60; higher score indicates a worse outcome); - Montgomery Asberg Depression Rating Scale; (MADRS) total score ≥ 20 (range 0-60; higher score indicates more depressive symptoms); - Clinical Global Impression-Improvement scale (CGI-S) ≥ 4 (range from 1 [normal, not at all ill] to 7 [extremely ill]); - Initiation of additional psychiatric medication; - Psychiatric hospitalization; - Exacerbation of illness as judged by clinical impression of the Investigator. Time to first relapse (days) was calculated as the date of the first relapse - the date of randomization + 1. Participants who did not meet the relapse criteria were considered censored at the time of completion or discontinuation from the Double-Blind Treatment Period (DBTP) of the study. Percentiles (95% Confidence Intervals [CI]) are based on Kaplan-Meier estimates.	

End point type	Primary
End point timeframe:	
From Week 16 to Week 55	

End point values	Double-Blind ITT Population: Double-Blind Placebo	Double-Blind ITT Population:Double-Blind Cariprazine 1.5	Double-Blind ITT Population:Double-Blind Cariprazine 3.0	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	142[1]	143[2]	145[3]	
Units: days				
median (confidence interval 95%)				
25% percentile	99999 (156.0 to 99999)	99999 (220.0 to 99999)	99999 (224.0 to 99999)	
50% percentile	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	
75% percentile	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Notes:

[1] - 99999=Not estimable since the 3 treatment curves did not pass through the 25/50/75% percentile mark.
[2] - 99999=Not estimable since the 3 treatment curves did not pass through the 25/50/75% percentile mark.
[3] - 99999=Not estimable since the 3 treatment curves did not pass through the 25/50/75% percentile mark.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio (Cariprazine 1.5 or 3.0 mg/day vs. Placebo) is based on Cox proportional hazards regression model, with treatment group as an explanatory variable, stratified by modified index episode (manic or depressive) and region (US, non-US).

Comparison groups	Double-Blind ITT Population: Double-Blind Placebo v Double-Blind ITT Population:Double-Blind Cariprazine 1.5 mg QD
Number of subjects included in analysis	285
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.5745 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.43

Notes:

[4] - Superiority of Drug vs Placebo

[5] - P-value is based on the log-rank test stratified by modified index episode (manic or depressive) and region (US, non-US).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard ratio (Cariprazine 1.5 or 3.0 mg/day vs. Placebo) is based on Cox proportional hazards regression model, with treatment group as an explanatory variable, stratified by modified index episode (manic or depressive) and region (US, non-US).

Comparison groups	Double-Blind ITT Population: Double-Blind Placebo v Double-Blind ITT Population:Double-Blind Cariprazine 3.0 mg QD
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.6308 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.51

Notes:

[6] - Superiority of Drug vs Placebo

[7] - P-value is based on the log-rank test stratified by modified index episode (manic or depressive) and region (US, non-US).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Open Label Treatment Period: from first dose of study drug (adverse events [AEs]) through Week 16 (Day 113). Double-Blind Treatment Period (ACM/AEs): From first dose of double-blind treatment up to end of study, Week 59 (Day 414).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Open Label Treatment Period

Reporting group description:

Participants started on cariprazine 1.5 mg QD, with a target dose of 3.0 mg QD, for up to 16 weeks.

Reporting group title	Double-Blind Placebo QD

Reporting group description:

Participants randomized to receive placebo QD for up to 39 weeks.

Reporting group title	Double-Blind Cariprazine 1.5 mg QD

Reporting group description:

Participants randomized to receive cariprazine 1.5 mg QD for up to 39 weeks.

Reporting group title	Double-Blind Cariprazine 3.0 mg QD

Reporting group description:

Participants randomized to receive cariprazine 3.0 mg QD for up to 39 weeks.

Serious adverse events	Open Label Treatment Period	Double-Blind Placebo QD	Double-Blind Cariprazine 1.5 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 896 (2.12%)	5 / 145 (3.45%)	7 / 144 (4.86%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CERVIX CARCINOMA			
subjects affected / exposed	0 / 896 (0.00%)	1 / 145 (0.69%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 896 (0.00%)	1 / 145 (0.69%)	0 / 144 (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

OVERDOSE			
subjects affected / exposed	0 / 896 (0.00%)	1 / 145 (0.69%)	0 / 144 (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
FALL			
subjects affected / exposed	0 / 896 (0.00%)	1 / 145 (0.69%)	0 / 144 (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			
PALPITATIONS			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
Nervous system disorders			
HYPOAESTHESIA			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
PARAESTHESIA			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
SACRAL RADICULOPATHY			
subjects affected / exposed	0 / 896 (0.00%)	0 / 145 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 896 (0.00%)	0 / 145 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASTHMA			

subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
Skin and subcutaneous tissue disorders			
STEVENS-JOHNSON SYNDROME			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
Psychiatric disorders			
BIPOLAR DISORDER			
subjects affected / exposed	3 / 896 (0.33%)	0 / 145 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BIPOLAR I DISORDER			
subjects affected / exposed	0 / 896 (0.00%)	2 / 145 (1.38%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEPRESSION			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
HALLUCINATION, AUDITORY			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
MAJOR DEPRESSION			
subjects affected / exposed	0 / 896 (0.00%)	0 / 145 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MANIA			
subjects affected / exposed	3 / 896 (0.33%)	0 / 145 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDAL IDEATION			

subjects affected / exposed	5 / 896 (0.56%)	0 / 145 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 896 (0.00%)	0 / 145 (0.00%)	0 / 144 (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
Musculoskeletal and connective tissue disorders			
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
Infections and infestations			
APPENDICEAL ABSCESS			
subjects affected / exposed	0 / 896 (0.00%)	0 / 145 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONAVIRUS PNEUMONIA			
subjects affected / exposed	0 / 896 (0.00%)	0 / 145 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APPENDICITIS PERFORATED			
subjects affected / exposed	0 / 896 (0.00%)	0 / 145 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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
COVID-19			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

SEPSIS			
subjects affected / exposed	1 / 896 (0.11%)	0 / 145 (0.00%)	0 / 144 (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	Double-Blind Cariprazine 3.0 mg QD		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 147 (2.04%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CERVIX CARCINOMA			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
OVERDOSE			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
FALL			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

HYPOAESTHESIA			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PARAESTHESIA			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SACRAL RADICULOPATHY			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ASTHMA			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
STEVENS-JOHNSON SYNDROME			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
BIPOLAR DISORDER			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BIPOLAR I DISORDER			

subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DEPRESSION			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HALLUCINATION, AUDITORY			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MAJOR DEPRESSION			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MANIA			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUICIDAL IDEATION			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUICIDE ATTEMPT			
subjects affected / exposed	1 / 147 (0.68%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

APPENDICEAL ABSCESS			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CORONAVIRUS PNEUMONIA			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
APPENDICITIS PERFORATED			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	0 / 147 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SEPSIS			
subjects affected / exposed	0 / 147 (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	Open Label Treatment Period	Double-Blind Placebo QD	Double-Blind Cariprazine 1.5 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	256 / 896 (28.57%)	27 / 145 (18.62%)	34 / 144 (23.61%)
Investigations			
WEIGHT INCREASED			

subjects affected / exposed	40 / 896 (4.46%)	7 / 145 (4.83%)	11 / 144 (7.64%)
occurrences (all)	40	7	12
Nervous system disorders			
AKATHISIA			
subjects affected / exposed	105 / 896 (11.72%)	2 / 145 (1.38%)	6 / 144 (4.17%)
occurrences (all)	117	2	7
HEADACHE			
subjects affected / exposed	79 / 896 (8.82%)	15 / 145 (10.34%)	14 / 144 (9.72%)
occurrences (all)	90	22	23
Gastrointestinal disorders			
NAUSEA			
subjects affected / exposed	62 / 896 (6.92%)	1 / 145 (0.69%)	2 / 144 (1.39%)
occurrences (all)	64	1	2
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	77 / 896 (8.59%)	5 / 145 (3.45%)	9 / 144 (6.25%)
occurrences (all)	85	7	12
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 896 (0.89%)	4 / 145 (2.76%)	3 / 144 (2.08%)
occurrences (all)	8	6	3

Non-serious adverse events	Double-Blind Cariprazine 3.0 mg QD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 147 (23.13%)		
Investigations			
WEIGHT INCREASED			
subjects affected / exposed	13 / 147 (8.84%)		
occurrences (all)	17		
Nervous system disorders			
AKATHISIA			
subjects affected / exposed	2 / 147 (1.36%)		
occurrences (all)	2		
HEADACHE			
subjects affected / exposed	10 / 147 (6.80%)		
occurrences (all)	13		
Gastrointestinal disorders			

NAUSEA subjects affected / exposed occurrences (all)	0 / 147 (0.00%) 0		
Psychiatric disorders INSOMNIA subjects affected / exposed occurrences (all)	6 / 147 (4.08%) 7		
Infections and infestations UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	10 / 147 (6.80%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2017	1. Update the serious adverse event (SAE) and pregnancy reporting information (Title page and Section 9.4). 2. Add detail to the process of washout of prior psychiatric medications (Protocol Summary and Sections 3 and 8.2). 3. Increase the length of the safety follow-up period from 1 week to 4 weeks, adding an additional follow-up visit (throughout the document). 4. Add assessment of remission as a separate row in the Schedule of Visits and Procedures. 5. Clarify the timing of the pharmacogenetic consent and sampling (Table 1 and Section 6.4). 6. Decrease the suicidality-related MADRS score for exclusion at Screening or Baseline from 5 to 4 (exclusion criterion #9). 7. Add exclusion criterion and prohibitions for patients who are taking concomitant cytochrome P450 3A4 (CYP3A4) inducers/inhibitors (exclusion criterion #13 and Section 4.8.2). 8. Clarify the definitions for remission and stability criteria (Section 4.5). 9. Modify the relapse criterion related to initiation of psychiatric medication (Protocol Summary and Sections 3 and 4.7) 10. Clarify use of the 1.5 mg dose of cariprazine (Section 5.1) 11. Clarify treatment compliance evaluation (Section 5.6). 12. Add an additional efficacy parameter to the study (PSP) (Section 6.2.2.3 and Attachment 12.9) 13. Add a quality-of-life measure to the study: Work Productivity and Activity Impairment-Bipolar Disorder (WPAI-BD) (Sections 6.5 and Attachment 12.12).
25 August 2017	14. Clarify planned analyses for additional efficacy parameters (Sections 7.2.3 and 7.3.3) 15. Clarify planned safety analyses (Sections 7.3.4) 16. Clarify the timing and details of visits and associated procedures (Sections 8.4 and 8.7) 17. Add details about the Safety Follow-up (SFU) Visits (Section 8.4.7). 18. Modify the discontinuation reason for disallowed medications; add a new reason for discontinuation: postbaseline finding of cataracts; and to delete the discontinuation reason for consecutively missed doses; (Section 8.9).

28 March 2018	1. Depressed episode to depressive episode. (Global change for clarity) 2. Removed patients with a postbaseline cataracts was to be discontinued from the study. (Global change) 3. Replaced the scale used to make the diagnostic assessment from Mini International Neuropsychiatric Interview (MINI) to Structured Clinical Interview for DSM-5 (SCID-5). (Operational Change) 4. Changed doses (Open-Label Period – Changed from 4.5 mg to 3.0 mg; DB Period: 2 Cariprazine Dose arms are now: 3.0 mg and 1.5 mg). (applicable sections of protocol) 5. Inclusion of depressed patients was added in addition to manic patients. manic or depressed patients may either be "with or without mixed features" (related inclusion criterion incorporated). (applicable sections of protocol) 6. Sample size was changed. 7. Day 4 and Day 10 study visits were deleted and a Day 22 visit was added. Study Visits have been renumbered throughout entire amendment 2. Study days have been renumbered to allow 1 full week of dosing before Visit 3. (applicable sections of protocol) 8. Exclusion criteria around urine drug screen has been clarified. 9. Removal of Symbol Digit Coding (SDC) – additional efficacy assessment. (applicable sections of protocol) 10. MADRS total score was changed from MADRS total score ≥ 17 to ≥ 20. (applicable sections of protocol) 11. Added open-label safety-follow-up (OL SFU) population will consist of patients in the OL safety population who were not randomized. 12. The primary analysis was updated to use stratified log-rank test instead of unstratified log-rank test and updated the first sensitivity analyses. 13. Changed period for reporting of pregnancies during the study from 30 days after last dose to 3 months following last dose. (Section 9.4) 14. Deleted the words "formerly" and "popular" when describing Snellen (Appendix 12.10)
20 November 2018	1. Corrected Backup Serious Adverse Event Reporting Fax Number. (global change) 2. Changed Forest Laboratories to AbbVie Sales. (global change) 3. Added text to clarify the location of the Emergency Telephone Numbers. (Title page) 4. Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated. (Protocol Summary, Screening/Washout period) 5. Added text to clarify that Day 8 is Visit 3. (Protocol Summary, Screening/Washout period) 6. Added visit windows of +3 days for Visit 2/Baseline and ± 3 days for Visits 3 through 33 to the table header. (Protocol Summary, Table 1) 7. Changed "Blood Alcohol Level" to "Blood Alcohol Concentration by Breathalyzer". (Protocol Summary, Table 1) 8. Added serum pregnancy test at Visits 7, 18, 24, and 33. (Protocol Summary, Table 1) 9. Added text to clarify the timing of visits. (Protocol Summary, Table 1) 10. Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated. (Section 3. Study Design) 11. Added text to clarify that Day 8 is Visit 3. (Section 3. Study Design) 12. Added text to clarify that the patient must meet the same criterion at both the screening and baseline visits. (Section 4.3 Inclusion Criteria) 13. Added text to clarify the need to use birth control for 12 weeks after the last dose of investigational product. (Section 4.3 Inclusion Criteria) 14. Added text to clarify that the serum pregnancy test is qualitative. (Section 4.3 Inclusion Criteria) 15. Added text to clarify use disorders. (Section 4.4 Exclusion Criteria) 16. Added text to clarify that a positive urine drug screen (UDS) is not exclusionary if the drug was used as rescue medication during washout. (Section 4.4 Exclusion Criteria) 17. Added text to exclude moderate CYP3A4 inhibitors. (Section 4.4 Exclusion Criteria) 18. Changed example of endocrinological disease. (Section 4.4 Exclusion Criteria)

20 November 2018	19. Added: 30. Absolute neutrophil count < 1000 per mm^3 at screening; 31. Hemoglobin A1c (HbA1c) > 7% at screening; 32. Blood alcohol concentration ≥ 0.02 g/dL at Visit 1 as measured by breathalyzer (Section 4.4. Exclusion Criteria) 20. Changed text to clarify that an additional barrier method must be used if hormonal contraception is used by a female patient, and added text to state that contraception must be used for 12 weeks after the last dose of study drug. (Section 4.8.1 Permissible Medications/Treatments) 21. Added phenazepam to list of prohibited psychotropic medications. (Section 4.8.2 Prohibited Medications/Treatments) 22. Added text to clarify that moderate CYP3A4 inhibitors are also prohibited. (Section 4.8.2 Prohibited Medications/Treatments) 23. Added Suvorexant (maximum of 20 mg/d) to the list of allowed medications for insomnia. (Section 4.8.3. Rescue Medications) 24. Added Biperiden to permissible rescue medications for extrapyramidal symptoms (EPS) or akathisia and removed dosing guidance. (Section 4.8.3. Rescue Medications) 25. Added: All investigational products (IPs) will be taken orally as a single daily dose at approximately the same time of day (morning or evening). The dosing time can be switched if there are tolerability problems. Any switch must allow at least 24 hours between 2 consecutive doses and must be documented in the eCRF. (Section 5.5 Treatment Regimen and Dosing) 26. Added text to state that any patient who misses ≥ 4 consecutive doses of IP must be discontinued from the study. (Section 5.6 Treatment Compliance) 27. Changed text to state that the rating scale must be administered by a trained rater. (Section 6.2.1.2 Montgomery-Asberg Depression Rating Scale) 28. Changed text to state that the rating scale must be administered by a trained rater (Section 6.2.1.3 Clinical Global Impressions-Severity)
20 November 2018	29. Changed text to state that the rating scale must be administered by a trained rater (Section 6.2.2.1 Clinical Global Impressions-Improvement) 30. Changed text to state that the rating scale must be administered by a trained rater (Section 6.2.2.2 Personal and Social Performance Scale) 31. Added text to correct the timing of urine myoglobin testing (Section 6.6.3 Clinical Laboratory Determinations, Table 3) 32. Added text to include a serum pregnancy test at Visit 33 (Section 6.6.3 Clinical Laboratory Determinations, Table 3) 33. Replaced “Blood Alcohol Level” with “Blood alcohol concentration as measured by breathalyzer” (Section 6.6.3 Clinical Laboratory Determinations, Table 3) 34. Changed text to state that the rating scale must be performed by a trained rater (Section 6.6.7.2 Columbia-Suicide Severity Rating Scale) 35. Deleted text stating that, for Clinical Global Impressions (CGI)-Improvement Scale (I), the OL baseline CGI-Severity Scale (S) value will be used as the baseline variable (Section 7.3.3 Other Efficacy Analyses) 36. Replaced all text to define how AEs and treatment emergent AEs will be coded and summarized (Section 7.3.4.1 Adverse Events) 37. Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated (Section 8.2 Washout Intervals/Run-in) 38. Added text to clarify that Day 8 is Visit 3 (Section 8.2 Washout Intervals/Run-in) 39. Added text to allow rescreening under certain situations after consultation with the AbbVie medical monitor (Section 8.3 Procedures for Final Study Entry) 40. Added text to clarify that the serum pregnancy test is qualitative (Section 8.3 Procedures for Final Study Entry) 41. Added text to clarify the timing of visits (Section 8.4 Visits and Associated Procedures)

20 November 2018	42. Changed text to clarify how blood alcohol concentration is assessed (Section 8.4.1 Screening/Visit 1) 43. Changed text to clarify how blood alcohol concentration is assessed (Section 8.4.4 End of OL Period/Randomization Visit) 44. Edited text to make serum pregnancy test mandatory at Visit 33. (Section 8.4.7 Safety Follow-up Visits 32 and 33) 45. Added text to clarify the timing of visits (Section 8.7 Compliance with Protocol) 46. Added text to clarify that Day 8 is Visit 3 (Section 8.9. Withdrawal Criteria) 47. Added text to number 6 to clarify that a patient with a positive UDS after enrollment should only be withdrawn if the positive test is confirmed at the next scheduled visit and to cross reference to Section 4.8.3 (Section 8.9. Withdrawal Criteria) 48. Added text to number 9 to clarify the timing of repeat testing and that the patient should be discontinued if his or her neutrophil values are not normalized or are not increasing (Section 8.9. Withdrawal Criteria) 49. Changed 3 months to 12 weeks (Section 9.4 Reporting of Pregnancies Occurring During the Study) 50. Added text to clarify that source documents must follow Attributable, Legible, Contemporaneous, Original, Accurate, and Complete (ALCOA-C) principles (Section 10.4.1 Source Documents) 51. Changed interval 40 – 31 to Severe difficulties in 1 and marked difficulties in at least 1 of areas a-c, or marked difficulties in d (Section 12.9. Personal and Social Performance [PSP] Scale, Guidelines for PSP Total Score)
17 December 2019	1. There is no longer a distinct SAE reporting form and AESI reporting form. It is a combined SAE/AESI form. (Global) 2. Exclusion Criterion #24a revised. (4.4 Exclusion Criteria) 3. Text revised to clarify which pregnancy outcomes or genetic abnormalities are considered SAEs. (9.1.2 Serious Adverse Events)
09 June 2022	1. Sample size calculation updated. (Protocol Summary and Section 7.5) 2. Coronavirus Disease 2019 (COVID-19) addendum was incorporated into Protocol Amendment 5. (Attachment 12.13)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported