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	2016-000756-98
Trial protocol	SK HR BG
Global end of trial date	18 January 2018

Results information

Result version number	v1 (current)
This version publication date	08 February 2019
First version publication date	08 February 2019

Trial information

Trial identification

Sponsor protocol code	RGH-MD-53

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02670538
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	18 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy, safety, and tolerability of cariprazine 1.5 milligrams (mg)/day and 3 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	31 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: 32
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Croatia: 21
Country: Number of subjects enrolled	Serbia: 68
Country: Number of subjects enrolled	Ukraine: 37
Country: Number of subjects enrolled	United States: 313
Worldwide total number of subjects	493
EEA total number of subjects	75

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)	491
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 866 participants were screened, 493 were randomised to receive double-blind treatment (Randomised Population); 490 participants received at least 1 dose of double-blind treatment (Safety Population) and 478 participants had at least 1 postbaseline Montgomery-Åsberg Depression Rating Scale (MADRS) total score assessment (ITT 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	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Following a 7 to 14 day screening/washout period, matching placebo capsule, one per day, orally for 6 weeks.

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

Dosage and administration details:

Matching placebo capsule, one per day, orally for 6 weeks.

Arm title	Cariprazine 1.5 mg

Arm description:

Following a 7 to 14 day screening/washout period, cariprazine 1.5 mg capsule, one per day, orally for 6 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:

Cariprazine 1.5 mg capsule, one per day, orally for 6 weeks.

Arm title	Cariprazine 3.0 mg

Arm description:

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

Cariprazine 1.5 milligrams (mg) capsule, one per day, orally for 2 weeks increased to cariprazine 3.0 mg capsule one per day orally beginning on Day 15 for 4 weeks.

Number of subjects in period 1	Placebo	Cariprazine 1.5 mg	Cariprazine 3.0 mg
Started	167	168	158
Safety Population : Received Study Drug	165	167	158
Intent-to-Treat Population	163	162	153
Completed	135	136	128
Not completed	32	32	30
Withdrawal of Consent	8	6	5
Noncompliance with Study Drug	1	3	2
Adverse event	5	5	11
Lost to follow-up	8	12	7
Other Miscellaneous Reasons	-	1	2
Lack of efficacy	7	1	2
Protocol deviation	3	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Following a 7 to 14 day screening/washout period, matching placebo capsule, one per day, orally for 6 weeks.	
Reporting group title	Cariprazine 1.5 mg
Reporting group description:	
Following a 7 to 14 day screening/washout period, cariprazine 1.5 mg capsule, one per day, orally for 6 weeks.	
Reporting group title	Cariprazine 3.0 mg
Reporting group description:	
Following a 7 to 14 day screening/washout period, cariprazine 1.5 mg capsule, one per day, orally for 2 weeks increased to 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	167	168	158
Age categorical Units: Subjects			
18 - 64 years	165	168	158
65 - 84 years	2	0	0
Age Continuous Units: years			
arithmetic mean	44.4	42.2	43.9
standard deviation	± 11.6	± 12.0	± 11.8
Sex: Female, Male Units: Subjects			
Female	99	107	103
Male	68	61	55
Race/Ethnicity, Customized Units: Subjects			
White	121	121	117
Black or African American	46	41	39
Asian	0	3	2
Multiple Races	0	3	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	18	22	15
Not Hispanic or Latino	149	146	143
Montgomery-Åsberg Depression Rating Scale (MADRS)			
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). ITT population: n=163,162,153.			
Units: score on a scale			
arithmetic mean	31.4	31.5	31.5
standard deviation	± 4.5	± 4.3	± 4.8

Reporting group values	Total		
Number of subjects	493		
Age categorical Units: Subjects			
18 - 64 years	491		
65 - 84 years	2		
Age Continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Subjects			
Female	309		
Male	184		
Race/Ethnicity, Customized Units: Subjects			
White	359		
Black or African American	126		
Asian	5		
Multiple Races	3		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	55		
Not Hispanic or Latino	438		
Montgomery-Åsberg Depression Rating Scale (MADRS)			
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). ITT population: n=163,162,153.			
Units: score on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

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

Primary: Change from Baseline in Montgomery-Åsberg Depression Rating Scale (MADRS)

End point title	Change from Baseline in Montgomery-Åsberg Depression Rating Scale (MADRS)
End point description:	
MADRS is a 10-item, clinician-rated scale that evaluates the participants 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. Mixed-effects Model for Repeated Measures (MMRM) with fixed factors (treatment group, pooled study center, and visit), baseline (a covariate), and interactions (treatment group by visit, baseline by visit). Intent-to-treat (ITT) population consisted of all participants in Safety Population who had at least 1 postbaseline assessment of MADRS total score.	
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	163	162	153	
Units: score on a scale				
least squares mean (standard error)	-12.4 (± 0.75)	-14.8 (± 0.76)	-14.1 (± 0.78)	

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	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0417 [1]
Method	Contrast t-test
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	-0.4

Notes:

[1] - Adjusted p-value: adjustment was performed using matched parallel gatekeeping procedure to control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6.

Statistical analysis title	Cariprazine 3.0 mg vs Placebo
Comparison groups	Placebo v Cariprazine 3.0 mg
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1051 [2]
Method	Contrast t-test
Parameter estimate	LS Mean Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	0.4

Notes:

[2] - Adjusted p-value: adjustment was performed using matched parallel gatekeeping procedure to control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6.

Secondary: Change from Baseline in Clinical Global Impressions–Severity (CGI-S) Score

End point title	Change from Baseline in Clinical Global Impressions–Severity (CGI-S) Score

End point description:

CGI-S is a clinician-rated scale that measures the overall severity of a participant's illness in comparison with the severity of other patients 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 patients". A negative change from Baseline indicates improvement. MMRM with fixed factors (treatment group, pooled study center, and visit), baseline (a covariate), and interactions (treatment group by visit, baseline by visit). ITT population consisted of all participants in Safety Population who had at least 1 postbaseline assessment of MADRS total score.

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	163	162	153	
Units: score on a scale				
least squares mean (standard error)	-1.2 (± 0.09)	-1.5 (± 0.09)	-1.4 (± 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	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0417 [3]
Method	Contrast t-test
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	-0.1

Notes:

[3] - Adjusted p-value: adjustment was performed using matched parallel gatekeeping procedure to control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6.

Statistical analysis title	Cariprazine 3.0 mg vs Placebo
Comparison groups	Placebo v Cariprazine 3.0 mg
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.137 [4]
Method	Contrast t-test
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

Notes:

[4] - Adjusted p-value: adjustment was performed using matched parallel gatekeeping procedure to control the overall type I error rate for multiple comparisons of 2 active doses versus placebo at Week 6.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug up to Day 50

Adverse event reporting additional description:

Safety Population included all participants in the Randomized Population who took at least 1 dose of double-blind investigational drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Following a 7 to 14 day screening/washout period, matching placebo capsule, one per day, orally for 6 weeks.

Reporting group title	Cariprazine 3.0 mg

Reporting group description:

Following a 7 to 14 day screening/washout period, cariprazine 1.5 mg capsule, one per day, orally for 2 weeks increased to cariprazine 3.0 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 day screening/washout period, cariprazine 1.5 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	5 / 165 (3.03%)	1 / 158 (0.63%)	1 / 167 (0.60%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 165 (0.61%)	0 / 158 (0.00%)	0 / 167 (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
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed[1]	0 / 97 (0.00%)	1 / 103 (0.97%)	0 / 107 (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
General disorders and administration			

site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 158 (0.00%)	0 / 167 (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			
Bipolar disorder			
subjects affected / exposed	1 / 165 (0.61%)	0 / 158 (0.00%)	0 / 167 (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
Depression			
subjects affected / exposed	0 / 165 (0.00%)	0 / 158 (0.00%)	1 / 167 (0.60%)
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	1 / 165 (0.61%)	0 / 158 (0.00%)	0 / 167 (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
Substance abuse			
subjects affected / exposed	1 / 165 (0.61%)	0 / 158 (0.00%)	0 / 167 (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

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number of participants exposed for Abortion is based on the number of females in the Safety Population.

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	36 / 165 (21.82%)	45 / 158 (28.48%)	45 / 167 (26.95%)
Nervous system disorders			
Akathisia			
subjects affected / exposed	3 / 165 (1.82%)	15 / 158 (9.49%)	9 / 167 (5.39%)
occurrences (all)	3	17	9
Headache			

subjects affected / exposed	14 / 165 (8.48%)	14 / 158 (8.86%)	14 / 167 (8.38%)
occurrences (all)	14	15	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 165 (1.21%)	5 / 158 (3.16%)	9 / 167 (5.39%)
occurrences (all)	2	6	10
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 165 (3.03%)	8 / 158 (5.06%)	13 / 167 (7.78%)
occurrences (all)	5	10	14
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 165 (4.24%)	11 / 158 (6.96%)	8 / 167 (4.79%)
occurrences (all)	10	18	13
Restlessness			
subjects affected / exposed	5 / 165 (3.03%)	11 / 158 (6.96%)	4 / 167 (2.40%)
occurrences (all)	6	12	4
Agitation			
subjects affected / exposed	10 / 165 (6.06%)	7 / 158 (4.43%)	3 / 167 (1.80%)
occurrences (all)	14	10	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	•Use of the clinician-rated 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	Revised the wording of exclusion criterion #18 to correct an error (i.e., the omission of the word "no" in the sub-bullet pertaining to the 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