Clinical trial results:
A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARIPRAZINE AS AN ADJUNCT TO ANTIDEPRESSANTS IN THE TREATMENT OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER WHO HAVE HAD AN INADEQUATE RESPONSE TO ANTIDEPRESSANTS ALONE

Summary

EudraCT number	2018-002782-19
Trial protocol	DE HU BG GB
Global end of trial date	30 September 2021

Results information

Result version number	v1 (current)
This version publication date	15 October 2022
First version publication date	15 October 2022

Trial information

Trial identification

Sponsor protocol code	3111-301-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03738215
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 104,466

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Marlow International The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Global Medical Services, AbbVie, AbbVie Deutschland GmbH &Co. KG, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, AbbVie Deutschland GmbH &Co. KG, 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	30 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety, and tolerability of cariprazine 1.5 mg/day and 3 mg/day compared with placebo as an adjunctive treatment to antidepressant therapy (ADT) in patients with major depressive disorder (MDD) who have had an inadequate response to antidepressants alone.

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	09 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Bulgaria: 103
Country: Number of subjects enrolled	Estonia: 29
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Ukraine: 100
Country: Number of subjects enrolled	United States: 458
Worldwide total number of subjects	757
EEA total number of subjects	190

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)	757
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 759 participants were randomized to double-blind treatment, 757 participants received at least 1 dose of double-blind investigational product (safety population), and 751 treated participants had at least 1 postbaseline assessment of Montgomery-Åsberg Depression Rating Scale (MADRS) total score (modified intent-to-treat population)

Period 1

Period 1 title	Double-blind Treatment Period (6 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + ADT

Arm description:

Cariprazine matching placebo capsules, orally, once daily in addition to their ongoing ADT (same antidepressant and dose of ADT they were on at the Baseline) during the Double-blind Treatment Period, up to Week 6.

Arm type	Placebo
Investigational medicinal product name	Antidepressant Therapy (ADT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ADT as prescribed by the physician per standard of care in clinical practice

Arm title	Cariprazine 1.5 mg/day + ADT

Arm description:

Cariprazine 1.5mg, orally, once daily in addition to their ongoing ADT (Same antidepressant and dose of ADT they were on at baseline) during the Double-blind treatment period, up to week 6.

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

Dosage and administration details:

Cariprazine supplied in capsules

Investigational medicinal product name	Antidepressant Therapy (ADT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ADT as prescribed by the physician per standard of care in clinical practice

Arm title	Cariprazine 3 mg/day + ADT

Arm description:

Cariprazine 1.5 mg capsules, orally, once daily for 2 weeks starting at the Baseline, titrated to 3.0 mg capsules, orally, once daily from Week 2 through Week 6 in addition to their ongoing ADT (same antidepressant and dose of ADT) during the Double-blind Treatment Period, up to Week 6.

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

Dosage and administration details:

Cariprazine supplied in capsules

Investigational medicinal product name	Antidepressant Therapy (ADT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ADT as prescribed by the physician per standard of care in clinical practice

Number of subjects in period 1	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Started	253	252	252
Completed	229	231	219
Not completed	24	21	33
Consent withdrawn by subject	13	11	9
Adverse event, non-fatal	6	3	18
Non-Compliance with study drug	-	1	1
Lost to follow-up	3	3	5
Lack of efficacy	2	2	-
Protocol deviation	-	1	-

Period 2

Period 2 title	Safety Follow Up Period (4 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open Label

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + ADT

Arm description:

Cariprazine matching placebo capsules, orally, once daily in addition to their ongoing ADT (same antidepressant and dose of ADT they were on at the Baseline) during the Double-blind Treatment Period, up to Week 6. Participants continued on their background ADT without placebo during the Safety Follow-up Period. The investigator may have initiated alternative treatment as clinically necessary.

Arm type	Placebo
Investigational medicinal product name	Antidepressant Therapy (ADT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ADT as prescribed by the physician per standard of care in clinical practice

Arm title	Cariprazine 1.5 mg/day + ADT

Arm description:

Cariprazine 1.5mg, orally, once daily in addition to their ongoing ADT (Same antidepressant and dose of ADT they were on at baseline) during the Double-blind treatment period, up to week 6. Participants continued on their background ADT without cariprazine during the Safety Follow-up Period. The investigator may have initiated alternative treatment as clinically necessary.

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

Dosage and administration details:

Cariprazine supplied in capsules

Investigational medicinal product name	Antidepressant Therapy (ADT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ADT as prescribed by the physician per standard of care in clinical practice

Arm title	Cariprazine 3 mg/day + ADT

Arm description:

Cariprazine 1.5 mg capsules, orally, once daily for 2 weeks starting at the Baseline, titrated to 3.0 mg capsules, orally, once daily from Week 2 through Week 6 in addition to their ongoing ADT (same antidepressant and dose of ADT) during the Double-blind Treatment Period, up to Week 6. Participants

continued on their background ADT without cariprazine during the Safety Follow-up Period. The investigator may have initiated alternative treatment as clinically necessary.

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

Dosage and administration details:

Cariprazine supplied in capsules

Investigational medicinal product name	Antidepressant Therapy (ADT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ADT as prescribed by the physician per standard of care in clinical practice

Number of subjects in period 2	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Started	229	231	219
Completed	237	234	230
Not completed	3	5	8
Consent withdrawn by subject	1	1	3
Adverse event, non-fatal	-	-	1
Lost to follow-up	2	2	4
Reason not Specified	-	2	-
Joined	11	8	19
Discontinued DB Period,Followedup in Safety Period	11	8	19

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + ADT

Reporting group description:

Cariprazine matching placebo capsules, orally, once daily in addition to their ongoing ADT (same antidepressant and dose of ADT they were on at the Baseline) during the Double-blind Treatment Period, up to Week 6.

Reporting group title	Cariprazine 1.5 mg/day + ADT

Reporting group description:

Cariprazine 1.5mg, orally, once daily in addition to their ongoing ADT (Same antidepressant and dose of ADT they were on at baseline) during the Double-blind treatment period, up to week 6.

Reporting group title	Cariprazine 3 mg/day + ADT

Reporting group description:

Cariprazine 1.5 mg capsules, orally, once daily for 2 weeks starting at the Baseline, titrated to 3.0 mg capsules, orally, once daily from Week 2 through Week 6 in addition to their ongoing ADT (same antidepressant and dose of ADT) during the Double-blind Treatment Period, up to Week 6.

Reporting group values	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Number of subjects	253	252	252
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	46.4	43.3	44.8
standard deviation	± 11.89	± 13.59	± 13.33
Gender categorical Units: Subjects			
Female	184	191	180
Male	69	61	72
Ethnicity Units: Subjects			
Hispanic or Latino	25	24	19
Not Hispanic or Latino	228	228	233
Race Units: Subjects			
American Indian or Alaska Native	1	1	0
Asian	5	4	7

Native Hawaiian or Other Pacific Islander	1	3	0
Black or African American	43	37	30
White	203	205	215
More than one race	0	2	0
Montgomery-Asberg Depression Rating Scale (MADRS) Total Score			
The MADRS is a 10-item,clinician-rated scale that evaluates the participant's depressive symptomatology during the past week. Participants are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration; lack of interest. Each item is scored on a 7-point scale with a score of 0=no symptoms and score of 6=maximum severity. The total score ranges from 0 to 60 with a higher score=more depression. mITT Population=all randomized participants who had ≥1 postbaseline assessment of the MADRS total			
Units: Score on a Scale			
arithmetic mean	31.90	32.81	32.72
standard deviation	± 5.680	± 32.00	± 4.920
Clinical Global Impression-Severity (CGI-S) Scale Score			
The CGI-S is a clinician-rated scale used to rate the severity of the participant's current state of mental illness compared with MDD population. The participant was rated on a scale from 1 to 7, where 1=normal, not at all ill and 7=among the most extremely ill participants. Higher score indicates worsening of mental illness. mITT Population included all randomized participants who had ≥1 postbaseline assessment of the MADRS total score.			
Units: Score on a Scale			
arithmetic mean	31.90	32.81	32.72
standard deviation	± 5.680	± 4.951	± 4.920

Reporting group values	Total		
Number of subjects	757		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	555		
Male	202		
Ethnicity			
Units: Subjects			
Hispanic or Latino	68		
Not Hispanic or Latino	689		

Race Units: Subjects			
American Indian or Alaska Native	2		
Asian	16		
Native Hawaiian or Other Pacific Islander	4		
Black or African American	110		
White	623		
More than one race	2		
Montgomery-Asberg Depression Rating Scale (MADRS) Total Score			
The MADRS is a 10-item,clinician-rated scale that evaluates the participant's depressive symptomatology during the past week. Participants are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration; lack of interest. Each item is scored on a 7-point scale with a score of 0=no symptoms and score of 6=maximum severity. The total score ranges from 0 to 60 with a higher score=more depression. mITT Population=all randomized participants who had ≥1 postbaseline assessment of the MADRS total			
Units: Score on a Scale arithmetic mean standard deviation	- -		
Clinical Global Impression-Severity (CGI-S) Scale Score			
The CGI-S is a clinician-rated scale used to rate the severity of the participant's current state of mental illness compared with MDD population. The participant was rated on a scale from 1 to 7, where 1=normal, not at all ill and 7=among the most extremely ill participants. Higher score indicates worsening of mental illness. mITT Population included all randomized participants who had ≥1 postbaseline assessment of the MADRS total score.			
Units: Score on a Scale arithmetic mean standard deviation	- -		

Subject analysis sets

Subject analysis set title	Modified Intent-to-Treat Population (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population includes all randomized participants who had ≥1 postbaseline assessment of the MADRS total score.

Reporting group values	Modified Intent-to-Treat Population (mITT)		
Number of subjects	751		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			

85 years and over			

Age continuous Units: years			
arithmetic mean	44.8		
standard deviation	± 13.03		
Gender categorical Units: Subjects			
Female	551		
Male	200		
Ethnicity Units: Subjects			
Hispanic or Latino	68		
Not Hispanic or Latino	683		
Race Units: Subjects			
American Indian or Alaska Native	2		
Asian	16		
Native Hawaiian or Other Pacific Islander	4		
Black or African American	109		
White	618		
More than one race	2		
Montgomery-Asberg Depression Rating Scale (MADRS) Total Score			
The MADRS is a 10-item,clinician-rated scale that evaluates the participant's depressive symptomatology during the past week. Participants are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration; lack of interest. Each item is scored on a 7-point scale with a score of 0=no symptoms and score of 6=maximum severity. The total score ranges from 0 to 60 with a higher score=more depression. mITT Population=all randomized participants who had ≥1 postbaseline assessment of the MADRS total			
Units: Score on a Scale			
arithmetic mean	32.48		
standard deviation	± 5.203		
Clinical Global Impression-Severity (CGI-S) Scale Score			
The CGI-S is a clinician-rated scale used to rate the severity of the participant's current state of mental illness compared with MDD population. The participant was rated on a scale from 1 to 7, where 1=normal, not at all ill and 7=among the most extremely ill participants. Higher score indicates worsening of mental illness. mITT Population included all randomized participants who had ≥1 postbaseline assessment of the MADRS total score.			
Units: Score on a Scale			
arithmetic mean	32.48		
standard deviation	± 5.203		

End points

End points reporting groups

Reporting group title	Placebo + ADT

Reporting group description:

Cariprazine matching placebo capsules, orally, once daily in addition to their ongoing ADT (same antidepressant and dose of ADT they were on at the Baseline) during the Double-blind Treatment Period, up to Week 6.

Reporting group title	Cariprazine 1.5 mg/day + ADT

Reporting group description:

Cariprazine 1.5mg, orally, once daily in addition to their ongoing ADT (Same antidepressant and dose of ADT they were on at baseline) during the Double-blind treatment period, up to week 6.

Reporting group title	Cariprazine 3 mg/day + ADT

Reporting group description:

Cariprazine 1.5 mg capsules, orally, once daily for 2 weeks starting at the Baseline, titrated to 3.0 mg capsules, orally, once daily from Week 2 through Week 6 in addition to their ongoing ADT (same antidepressant and dose of ADT) during the Double-blind Treatment Period, up to Week 6.

Reporting group title	Placebo + ADT

Reporting group description:

Cariprazine matching placebo capsules, orally, once daily in addition to their ongoing ADT (same antidepressant and dose of ADT they were on at the Baseline) during the Double-blind Treatment Period, up to Week 6. Participants continued on their background ADT without placebo during the Safety Follow-up Period. The investigator may have initiated alternative treatment as clinically necessary.

Reporting group title	Cariprazine 1.5 mg/day + ADT

Reporting group description:

Cariprazine 1.5mg, orally, once daily in addition to their ongoing ADT (Same antidepressant and dose of ADT they were on at baseline) during the Double-blind treatment period, up to week 6. Participants continued on their background ADT without cariprazine during the Safety Follow-up Period. The investigator may have initiated alternative treatment as clinically necessary.

Reporting group title	Cariprazine 3 mg/day + ADT

Reporting group description:

Cariprazine 1.5 mg capsules, orally, once daily for 2 weeks starting at the Baseline, titrated to 3.0 mg capsules, orally, once daily from Week 2 through Week 6 in addition to their ongoing ADT (same antidepressant and dose of ADT) during the Double-blind Treatment Period, up to Week 6. Participants continued on their background ADT without cariprazine during the Safety Follow-up Period. The investigator may have initiated alternative treatment as clinically necessary.

Subject analysis set title	Modified Intent-to-Treat Population (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT population includes all randomized participants who had ≥1 postbaseline assessment of the MADRS total score.

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

End point title	Total Score Change From Baseline to Week 6 in the MADRS (Montgomery-Åsberg Depression Rating Scale)

End point description:

The 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 item 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. The total score ranges from 0 to 60 with a higher score indicating more depression. A negative change from Baseline indicates improvement. Mixed-effects Model for Repeated Measures (MMRM) was used for analyses. mITT Population included all randomized participants who had ≥1 postbaseline assessment of the MADRS total score. Number of subjects analyzed are the number of participants with data available for analyses.

End point type	Primary
End point timeframe:	
Baseline and Week 6	

End point values	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	231	223	
Units: Score on a scale				
least squares mean (standard error)	-11.5 (± 0.70)	-14.1 (± 0.70)	-13.1 (± 0.70)	

Statistical analyses

Statistical analysis title	Placebo v/s Cariprazine 1.5 mg/day
Comparison groups	Placebo + ADT v Cariprazine 1.5 mg/day + ADT
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [1]
Method	MMRM
Parameter estimate	Lease Squares Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.17
upper limit	-0.89
Variability estimate	Standard error of the mean
Dispersion value	0.88

Notes:

[1] - Adjusted P-Value (based on truncated Hochberg with parameter=0.9)

Statistical analysis title	Placebo v/s Cariprazine 3 mg/day
Comparison groups	Placebo + ADT v Cariprazine 3 mg/day + ADT
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0727 [2]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.16
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.84

Notes:

[2] - Adjusted P-Value (based on truncated Hochberg with parameter=0.9)

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

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

End point description:

The CGI-S is a clinician-rated scale used to rate the severity of the participant's current state of mental illness compared with MDD population. The participant was rated on a scale from 1 to 7, where 1=normal, not at all ill and 7=among the most extremely ill participants. Higher scores indicate worsening of mental illness. A negative change from Baseline indicates improvement. MMRM was used for analyses. mITT Population included all randomized participants who had ≥1 postbaseline assessment of the MADRS total score. Number of subjects analyzed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 6

End point values	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	231	231	223	
Units: Score on a scale				
least squares mean (standard error)	-1.1 (± 0.09)	-1.4 (± 0.09)	-1.3 (± 0.09)	

Statistical analyses

Statistical analysis title	Placebo v/s Cariprazine 1.5 mg/day
Comparison groups	Cariprazine 1.5 mg/day + ADT v Placebo + ADT
Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0727 [3]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	-0.07
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[3] - Adjusted P-Value (based on Hochberg procedure)

Statistical analysis title	Placebo v/s Cariprazine 3 mg/day
Comparison groups	Placebo + ADT v Cariprazine 3 mg/day + ADT
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0944 [4]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[4] - Adjusted P-Value (based on Hochberg procedure)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug until 30 days after the last dose of study drug (up to 12 weeks)

Adverse event reporting additional description:

Safety Population included all participants in the randomized population who took ≥1 dose of double-blind investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Placebo + ADT

Reporting group description:

Cariprazine matching placebo capsules, orally, once daily in addition to their ongoing ADT (same antidepressant and dose of ADT they were on at the Baseline) during the Double-blind Treatment Period, up to Week 6.

Reporting group title	Cariprazine 1.5 mg/day + ADT

Reporting group description:

Cariprazine 1.5 mg capsules, orally, once daily in addition to their ongoing ADT (same antidepressant and dose of ADT they were on at the Baseline) during the Double-blind Treatment Period, up to Week 6.

Reporting group title	Cariprazine 3 mg/day + ADT

Reporting group description:

Cariprazine 1.5 mg capsules, orally, once daily for 2 weeks starting at the Baseline, titrated to 3.0 mg capsules, orally, once daily from Week 2 through Week 6 in addition to their ongoing ADT (same antidepressant and dose of ADT) during the Double-blind Treatment Period, up to Week 6.

Serious adverse events	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 253 (0.79%)	3 / 252 (1.19%)	3 / 252 (1.19%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	0 / 252 (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
Fibula fracture			

subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	0 / 252 (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
Tibia fracture			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	0 / 252 (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
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	0 / 252 (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 spontaneous			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	0 / 252 (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
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	0 / 253 (0.00%)	1 / 252 (0.40%)	0 / 252 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 253 (0.40%)	0 / 252 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 253 (0.00%)	0 / 252 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			

subjects affected / exposed	0 / 253 (0.00%)	0 / 252 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 253 (15.42%)	68 / 252 (26.98%)	62 / 252 (24.60%)
Nervous system disorders			
Akathisia			
subjects affected / exposed	3 / 253 (1.19%)	13 / 252 (5.16%)	20 / 252 (7.94%)
occurrences (all)	3	14	23
Headache			
subjects affected / exposed	16 / 253 (6.32%)	24 / 252 (9.52%)	11 / 252 (4.37%)
occurrences (all)	19	25	23
Somnolence			
subjects affected / exposed	7 / 253 (2.77%)	13 / 252 (5.16%)	11 / 252 (4.37%)
occurrences (all)	7	13	12
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 253 (2.37%)	20 / 252 (7.94%)	16 / 252 (6.35%)
occurrences (all)	6	21	19
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 253 (4.35%)	18 / 252 (7.14%)	16 / 252 (6.35%)
occurrences (all)	18	18	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2018	The following changes were made in Amendment 1: Added the EudraCT number. Added text to extend the safety follow-up period from 1 to 4 weeks. Blood alcohol at Visit 1 as measured by Breathalyzer was added to expedite turnaround time for blood alcohol concentration results. Included a 12-month lookback to the Columbia–Suicide Severity Rating Scale (C-SSRS) completed at Visit 1 (Screening). Specified primary estimand and alternative covariance structures; added one more sensitivity analysis. The reporting period for pregnancies was changed from 3 months to 12 weeks.
27 July 2020	The following changes were made in Amendment 3: Revised text to clarify expectation around inadequate response to 1-3 ADTs in the current episode. Added text to extend the screening period up to an additional 7 days if needed with Sponsor approval. Extended the maximum duration of current major depressive episode at screening from "not exceeding 18 months" to "less than 24 months".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: