



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	2018-003164-31
Trial protocol	CZ SK PL FI
Global end of trial date	06 September 2021

Results information

Result version number	v1 (current)
This version publication date	11 September 2022
First version publication date	11 September 2022

Trial information

Trial identification

Sponsor protocol code	3111-302-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03739203
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	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	06 September 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the efficacy, safety and tolerability of cariprazine as an adjunctive treatment to antidepressant therapy (ADT) in patients with 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	10 November 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	United States: 382
Country: Number of subjects enrolled	Czechia: 63
Country: Number of subjects enrolled	Finland: 20
Country: Number of subjects enrolled	Poland: 125
Country: Number of subjects enrolled	Serbia: 88
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Slovakia: 65
Worldwide total number of subjects	752
EEA total number of subjects	273

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)	743
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 752 enrolled subjects, 751 took ≥ 1 dose of double-blind investigational product and comprised the Safety Population. 1 subject was randomised but did not receive treatment & was excluded from study analyses. At end of treatment in Double-blind Period, subjects continued on their background antidepressant therapy (ADT) & entered Safety Follow-up Period.

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

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

Dosage and administration details:

Placebo 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 1.5 mg/day + ADT
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Arm 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.

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
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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^[1]	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Started	250	250	251
Modified Intent-to Treat(mITT)Population	249	250	251
Completed	235	233	226
Not completed	15	17	25
Adverse Event	6	9	13
Non-compliance With Study Drug	1	3	1
Lost to follow-up	1	1	2
Reason not Specified	1	-	1
Withdrawal by subject	4	4	6
Protocol deviation	1	-	1
Lack of efficacy	1	-	1

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: One participant was randomised but did not receive treatment and was excluded from the

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

Dosage and administration details:

Placebo 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 1.5 mg/day + ADT
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Arm 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. 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
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Dosage and administration details:

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

Arm title	Cariprazine 3 mg/day + ADT
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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	235	233	226
Completed	240	240	238
Not completed	2	2	4
Death	1	-	-
Lost to follow-up	-	-	2
Reason not Specified	-	-	2
Withdrawal by subject	1	2	-
Joined	7	9	16
Discontinued DB Period, Followed up in Safety Period	7	9	16

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 1.5 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.	

Reporting group values	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Number of subjects	250	250	251
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	46.2 ± 12.12	45.0 ± 12.95	45.8 ± 12.45
Gender categorical Units: Subjects			
Female	191	185	197
Male	59	65	54
Ethnicity Units: Subjects			
Hispanic or Latino	30	38	34
Not Hispanic or Latino	220	212	217
Race Units: Subjects			
American Indian or Alaska Native	0	0	2
Asian	4	0	5
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	29	32	22
White	217	216	221
More than one race	0	1	1
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 randomised participants who had ≥1 postbaseline assessment of the MADRS total			

Units: score on a scale			
arithmetic mean		32.00	32.25
standard deviation	±	± 4.246	± 4.688
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 randomised participants who had ≥1 postbaseline assessment of the MADRS total score.			
Units: score on a scale			
arithmetic mean		4.61	4.65
standard deviation	±	± 0.586	± 0.654

Reporting group values	Total		
Number of subjects	751		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	573		
Male	178		
Ethnicity			
Units: Subjects			
Hispanic or Latino	102		
Not Hispanic or Latino	649		
Race			
Units: Subjects			
American Indian or Alaska Native	2		
Asian	9		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	83		
White	654		
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 randomised 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 randomised 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	Placebo + ADT
Subject analysis set type	Modified intention-to-treat

Subject analysis set 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 values	Placebo + ADT		
Number of subjects	249		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	\pm		
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Race			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
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 randomised participants who had ≥ 1 postbaseline assessment of the MADRS total			
Units: score on a scale			
arithmetic mean	32.99		
standard deviation	± 4.789		
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 randomised participants who had ≥ 1 postbaseline assessment of the MADRS total score.

Units: score on a scale			
arithmetic mean	4.67		
standard deviation	± 0.599		

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 1.5 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.	
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 1.5 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. 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	Placebo + ADT
Subject analysis set type	Modified intention-to-treat
Subject analysis set 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.	

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

End point title	Change From Baseline to Week 6 in the MADRS (Montgomery-Åsberg Depression Rating Scale) Total Score
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 randomised participants who had ≥1 postbaseline assessment of the MADRS total score. Number of subjects analysed 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	236	237	231	
Units: score on a scale				
least squares mean (standard error)	-13.4 (± 0.70)	-13.8 (± 0.69)	-14.8 (± 0.70)	

Statistical analyses

Statistical analysis title	Cariprazine 1.5 mg/day Versus Placebo
Comparison groups	Placebo + ADT v Cariprazine 1.5 mg/day + ADT
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6798 ^[1]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.37
Variability estimate	Standard error of the mean
Dispersion value	0.88

Notes:

[1] - MMRM=Fixed effects:treatment group,ADT failure category,visit,treatment group-by-visit interaction,countries;Covariates:Baseline value& Baseline by-visit interaction.Unstructured covariance matrix models covariance of within-participant scores.

Statistical analysis title	Cariprazine 3 mg/day Versus Placebo
Comparison groups	Placebo + ADT v Cariprazine 3 mg/day + ADT
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1245 ^[2]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	0.38

Variability estimate	Standard error of the mean
Dispersion value	0.89

Notes:

[2] - MMRM=Fixed effects:treatment group,ADT failure category,visit,treatment group-by-visit interaction,countries;Covariates:Baseline value& Baseline by-visit interaction.Unstructured covariance matrix models covariance of within-participant scores.

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
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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 randomised participants who had ≥1 postbaseline assessment of the MADRS total score. Number of subjects analysed are the number of participants with data available for analyses.

End point type	Secondary
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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	236	237	231	
Units: score on a scale				
least squares mean (standard error)	-1.4 (± 0.09)	-1.4 (± 0.09)	-1.6 (± 0.09)	

Statistical analyses

Statistical analysis title	Cariprazine 1.5 mg/day Versus Placebo
Comparison groups	Placebo + ADT v Cariprazine 1.5 mg/day + ADT
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5152 ^[3]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[3] - MMRM=Fixed effects:treatment group,ADT failure category,visit,treatment group-by-visit interaction,countries;Covariates:Baseline value& Baseline by-visit interaction.Unstructured covariance matrix models covariance of within-participant scores.

Statistical analysis title	Cariprazine 3 mg/day Versus Placebo
Comparison groups	Placebo + ADT v Cariprazine 3 mg/day + ADT
Number of subjects included in analysis	467
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0573 ^[4]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[4] - MMRM=Fixed effects:treatment group,ADT failure category,visit,treatment group-by-visit interaction,countries;Covariates:Baseline value& Baseline by-visit interaction.Unstructured covariance matrix models covariance of within-participant scores.

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 randomised population who took ≥ 1 dose of double-blind investigational product.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Placebo + ADT
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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
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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
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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 / 250 (0.80%)	3 / 250 (1.20%)	1 / 251 (0.40%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Injury, poisoning and procedural complications			
ANIMAL BITE			
subjects affected / exposed	0 / 250 (0.00%)	1 / 250 (0.40%)	0 / 251 (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 / 250 (0.00%)	1 / 250 (0.40%)	0 / 251 (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 / 250 (0.00%)	1 / 250 (0.40%)	0 / 251 (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
LIGAMENT SPRAIN			
subjects affected / exposed	0 / 250 (0.00%)	1 / 250 (0.40%)	0 / 251 (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			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 250 (0.00%)	0 / 250 (0.00%)	1 / 251 (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
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	1 / 250 (0.40%)	0 / 250 (0.00%)	0 / 251 (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
Gastrointestinal disorders			
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 250 (0.40%)	0 / 250 (0.00%)	0 / 251 (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			
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 250 (0.00%)	1 / 250 (0.40%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo + ADT	Cariprazine 1.5 mg/day + ADT	Cariprazine 3 mg/day + ADT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 250 (21.60%)	70 / 250 (28.00%)	85 / 251 (33.86%)

Nervous system disorders	AKATHISIA			
	subjects affected / exposed	9 / 250 (3.60%)	19 / 250 (7.60%)	29 / 251 (11.55%)
	occurrences (all)	10	19	34
	SOMNOLENCE			
	subjects affected / exposed	11 / 250 (4.40%)	12 / 250 (4.80%)	17 / 251 (6.77%)
	occurrences (all)	11	13	17
	HEADACHE			
	subjects affected / exposed	27 / 250 (10.80%)	24 / 250 (9.60%)	27 / 251 (10.76%)
	occurrences (all)	33	32	40
Gastrointestinal disorders				
	NAUSEA			
	subjects affected / exposed	10 / 250 (4.00%)	14 / 250 (5.60%)	16 / 251 (6.37%)
	occurrences (all)	15	16	21
Psychiatric disorders				
	INSOMNIA			
	subjects affected / exposed	9 / 250 (3.60%)	16 / 250 (6.40%)	25 / 251 (9.96%)
	occurrences (all)	12	18	29

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”. Added protocol modifications for Coronavirus disease 2019 (COVID-19).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported