# 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<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 46.4 | 43.3 | 44.8 |
| standard deviation | ± 11.89 | ± 13.59 | ± 13.33 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 184 | 191 | 180 |
| Male | 69 | 61 | 72 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 25 | 24 | 19 |
| Not Hispanic or Latino | 228 | 228 | 233 |
| Race<br>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<br>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<br>arithmetic mean<br>standard deviation | -<br>- | | |
| 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<br>arithmetic mean<br>standard deviation | -<br>- | | |

**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<br>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<br>Units: years | | | |
| arithmetic mean | 44.8 | | |
| standard deviation | ± 13.03 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 551 | | |
| Male | 200 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 68 | | |
| Not Hispanic or Latino | 683 | | |
| Race<br>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:<br>Added the EudraCT number.<br>Added text to extend the safety follow-up period from 1 to 4 weeks.<br>Blood alcohol at Visit 1 as measured by Breathalyzer was added to expedite turnaround time for blood alcohol concentration results.<br>Included a 12-month lookback to the Columbia–Suicide Severity Rating Scale (C-SSRS) completed at Visit 1 (Screening).<br>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.<br>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: