



## Clinical trial results:

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

#### Summary

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

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1                |
| This version publication date  | 13 September 2023 |
| First version publication date | 13 September 2023 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | RGH-MD-25 |
|-----------------------|-----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Allergan Limited  |
| Sponsor organisation address | Marlow International The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL   |
| Public contact               | AbbVie, Global Medical Services, 001 8006339110, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a> |
| Scientific contact           | AbbVie, Global Medical Services, 001 8006339110, <a href="mailto:abbvieclinicaltrials@abbvie.com">abbvieclinicaltrials@abbvie.com</a> |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 05 September 2022 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 05 September 2022 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 15 June 2018 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

|          |   |
|----------|---|
| In utero | 0 |
|----------|---|

|   |     |
|---|-----|
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 899 |
| From 65 to 84 years                       | 2   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details: -

### Pre-assignment period milestones

|                            |     |
|----------------------------|-----|
| Number of subjects started | 901 |
|----------------------------|-----|

|                              |     |
|------------------------------|-----|
| Number of subjects completed | 896 |
|------------------------------|-----|

### Pre-assignment subject non-completion reasons

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

### Period 1

|                |                             |
|----------------|-----------------------------|
| Period 1 title | Open Label Treatment Period |
|----------------|-----------------------------|

|                              |     |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

|                   |                |
|-------------------|----------------|
| Allocation method | Not applicable |
|-------------------|----------------|

|               |             |
|---------------|-------------|
| Blinding used | Not blinded |
|---------------|-------------|

### Arms

|           |                             |
|-----------|-----------------------------|
| Arm title | Open Label Treatment Period |
|-----------|-----------------------------|

Arm description:

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

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |             |
|--|-------------|
| Investigational medicinal product name | Cariprazine |
|--|-------------|

|  |  |
|--|--|
| Investigational medicinal product code |  |
|--|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |         |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

once daily

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

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 901 participants were enrolled; 5 participants did not enter the open label treatment period.

## Period 2

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

Blinding implementation details:

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

## Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | Double-Blind Placebo QD |

Arm description:

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

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

Dosage and administration details:

once daily

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Double-Blind Cariprazine 1.5 mg QD |
|------------------|------------------------------------|

Arm description:

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

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

Dosage and administration details:

once daily

|                  |                                    |
|------------------|------------------------------------|
| <b>Arm title</b> | Double-Blind Cariprazine 3.0 mg QD |
|------------------|------------------------------------|

Arm description:

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

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

once daily

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

## Baseline characteristics

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Open Label Treatment Period |
|-----------------------|-----------------------------|

Reporting group description:

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

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

## End points

### End points reporting groups

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

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

|                 |  |
|-----------------|--|
| End point title | Time to First Relapse of Any Mood Episode During the Double-blind Treatment Period |
|-----------------|--|

End point description:

Relapse was defined as the occurrence of any 1 of the following:  
Young Mania Rating Score (YMRS) total score  $\geq 17$  (range 0-60; higher score indicates a worse outcome);  
Montgomery Asberg Depression Rating Scale; (MADRS) total score  $\geq 20$  (range 0-60; higher score indicates more depressive symptoms);  
Clinical Global Impression-Improvement scale (CGI-S)  $\geq 4$  (range from 1 [normal, not at all ill] to 7 [extremely ill]);  
Initiation of additional psychiatric medication;  
Psychiatric hospitalization;  
Exacerbation of illness as judged by clinical impression of the Investigator.

Time to first relapse (days) was calculated as the date of the first relapse - the date of randomization + 1. Participants who did not meet the relapse criteria were considered censored at the time of completion or discontinuation from the Double-Blind Treatment Period (DBTP) of the study. Percentiles (95% Confidence Intervals [CI]) are based on Kaplan-Meier estimates.



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

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

Notes:

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

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

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

## Statistical analyses

| Statistical analysis title   | Statistical Analysis 1  |
|--|---|
| Statistical analysis description:  |   |
| Hazard ratio (Cariprazine 1.5 or 3.0 mg/day vs. Placebo) is based on Cox proportional hazards regression model, with treatment group as an explanatory variable, stratified by modified index episode (manic or depressive) and region (US, non-US). |   |
| Comparison groups  | Double-Blind ITT Population: Double-Blind Placebo v Double-Blind ITT Population: Double-Blind Cariprazine 1.5 mg QD |
| Number of subjects included in analysis  | 285   |
| Analysis specification   | Pre-specified   |
| Analysis type  | superiority <sup>[4]</sup>  |
| P-value  | = 0.5745 <sup>[5]</sup>   |
| Method   | Logrank   |
| Parameter estimate   | Hazard ratio (HR)   |
| Point estimate   | 0.83  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.48  |
| upper limit  | 1.43  |

Notes:

[4] - Superiority of Drug vs Placebo

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

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

---

**Statistical analysis description:**

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

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

**Notes:**

[6] - Superiority of Drug vs Placebo

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

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

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

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 25.1   |

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Open Label Treatment Period |
|-----------------------|-----------------------------|

Reporting group description:

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

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Double-Blind Cariprazine 3.0 mg QD |
|-----------------------|------------------------------------|

Reporting group description:

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

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Double-Blind Cariprazine 1.5 mg QD |
|-----------------------|------------------------------------|

Reporting group description:

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

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Double-Blind Placebo QD |
|-----------------------|-------------------------|

Reporting group description:

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

| Serious adverse events  | Open Label Treatment Period | Double-Blind Cariprazine 3.0 mg QD | Double-Blind Cariprazine 1.5 mg QD |
|---|-----------------------------|------------------------------------|------------------------------------|
| Total subjects affected by serious adverse events                   |                             |                                    |                                    |
| subjects affected / exposed   | 19 / 896 (2.12%)            | 3 / 147 (2.04%)                    | 7 / 144 (4.86%)                    |
| number of deaths (all causes)                                       | 1                           | 0                                  | 0                                  |
| number of deaths resulting from adverse events                      |                             |                                    |                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                             |                                    |                                    |
| CERVIX CARCINOMA  |                             |                                    |                                    |
| subjects affected / exposed   | 0 / 896 (0.00%)             | 0 / 147 (0.00%)                    | 0 / 144 (0.00%)                    |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 0                              | 0 / 0                              |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0                              | 0 / 0                              |
| Injury, poisoning and procedural complications                      |                             |                                    |                                    |
| SPINAL COMPRESSION FRACTURE   |                             |                                    |                                    |
| subjects affected / exposed   | 0 / 896 (0.00%)             | 0 / 147 (0.00%)                    | 0 / 144 (0.00%)                    |
| occurrences causally related to treatment / all                     | 0 / 0                       | 0 / 0                              | 0 / 0                              |
| deaths causally related to treatment / all                          | 0 / 0                       | 0 / 0                              | 0 / 0                              |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| OVERDOSE  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| FALL  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| PALPITATIONS                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| HYPOAESTHESIA                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| PARAESTHESIA                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SACRAL RADICULOPATHY                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| PULMONARY EMBOLISM                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| ASTHMA  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| STEVENS-JOHNSON SYNDROME                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| BIPOLAR DISORDER                                |                 |                 |                 |
| subjects affected / exposed                     | 3 / 896 (0.33%) | 1 / 147 (0.68%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| BIPOLAR I DISORDER                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 1 / 147 (0.68%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| DEPRESSION                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| HALLUCINATION, AUDITORY                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| MAJOR DEPRESSION                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SUICIDAL IDEATION                               |                 |                 |                 |
| subjects affected / exposed                     | 5 / 896 (0.56%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| MANIA   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 896 (0.33%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SUICIDE ATTEMPT                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 1 / 147 (0.68%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| MUSCULAR WEAKNESS                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| CORONAVIRUS PNEUMONIA                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| APPENDICITIS PERFORATED                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| APPENDICEAL ABSCESS                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 896 (0.00%) | 0 / 147 (0.00%) | 1 / 144 (0.69%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| GASTROENTERITIS VIRAL                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| SEPSIS  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 896 (0.11%) | 0 / 147 (0.00%) | 0 / 144 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                                       | Double-Blind<br>Placebo QD |  |  |
|---|----------------------------|--|--|
| Total subjects affected by serious adverse events                   |                            |  |  |
| subjects affected / exposed   | 5 / 145 (3.45%)            |  |  |
| number of deaths (all causes)                                       | 1                          |  |  |
| number of deaths resulting from adverse events                      |                            |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                            |  |  |
| CERVIX CARCINOMA  |                            |  |  |
| subjects affected / exposed   | 1 / 145 (0.69%)            |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                      |  |  |
| deaths causally related to treatment / all                          | 0 / 1                      |  |  |
| Injury, poisoning and procedural complications                      |                            |  |  |
| SPINAL COMPRESSION FRACTURE   |                            |  |  |
| subjects affected / exposed   | 1 / 145 (0.69%)            |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                      |  |  |
| deaths causally related to treatment / all                          | 0 / 0                      |  |  |
| OVERDOSE  |                            |  |  |
| subjects affected / exposed   | 1 / 145 (0.69%)            |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                      |  |  |
| deaths causally related to treatment / all                          | 0 / 0                      |  |  |
| FALL  |                            |  |  |
| subjects affected / exposed   | 1 / 145 (0.69%)            |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                      |  |  |
| deaths causally related to treatment / all                          | 0 / 0                      |  |  |
| Cardiac disorders   |                            |  |  |
| PALPITATIONS  |                            |  |  |
| subjects affected / exposed   | 0 / 145 (0.00%)            |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                      |  |  |
| deaths causally related to treatment / all                          | 0 / 0                      |  |  |
| Nervous system disorders  |                            |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| HYPOAESTHESIA                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| PARAESTHESIA                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SACRAL RADICULOPATHY                            |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| PULMONARY EMBOLISM                              |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| ASTHMA  |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| STEVENS-JOHNSON SYNDROME                        |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| BIPOLAR DISORDER                                |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| BIPOLAR I DISORDER                              |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 2 / 145 (1.38%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| DEPRESSION                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| HALLUCINATION, AUDITORY                         |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| MAJOR DEPRESSION                                |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SUICIDAL IDEATION                               |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| MANIA   |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SUICIDE ATTEMPT                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| MUSCULAR WEAKNESS                               |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| CORONAVIRUS PNEUMONIA                           |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| APPENDICITIS PERFORATED                         |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| APPENDICEAL ABSCESS                             |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| GASTROENTERITIS VIRAL                           |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| COVID-19  |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SEPSIS  |                 |  |  |
| subjects affected / exposed                     | 0 / 145 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Open Label<br>Treatment Period | Double-Blind<br>Cariprazine 3.0 mg<br>QD | Double-Blind<br>Cariprazine 1.5 mg<br>QD |
|---|--------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                |  |  |
| subjects affected / exposed                           | 256 / 896 (28.57%)             | 34 / 147 (23.13%)                        | 34 / 144 (23.61%)                        |
| Investigations  |                                |  |  |
| WEIGHT INCREASED                                      |                                |  |  |

|   |                           |                        |                        |
|---|---------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 40 / 896 (4.46%)<br>40    | 13 / 147 (8.84%)<br>17 | 11 / 144 (7.64%)<br>12 |
| Nervous system disorders<br>AKATHISIA<br>subjects affected / exposed<br>occurrences (all)                               | 105 / 896 (11.72%)<br>117 | 2 / 147 (1.36%)<br>2   | 6 / 144 (4.17%)<br>7   |
| HEADACHE<br>subjects affected / exposed<br>occurrences (all)  | 79 / 896 (8.82%)<br>90    | 10 / 147 (6.80%)<br>13 | 14 / 144 (9.72%)<br>23 |
| Gastrointestinal disorders<br>NAUSEA<br>subjects affected / exposed<br>occurrences (all)                                | 62 / 896 (6.92%)<br>64    | 0 / 147 (0.00%)<br>0   | 2 / 144 (1.39%)<br>2   |
| Psychiatric disorders<br>INSOMNIA<br>subjects affected / exposed<br>occurrences (all)                                   | 77 / 896 (8.59%)<br>85    | 6 / 147 (4.08%)<br>7   | 9 / 144 (6.25%)<br>12  |
| Infections and infestations<br>UPPER RESPIRATORY TRACT<br>INFECTION<br>subjects affected / exposed<br>occurrences (all) | 8 / 896 (0.89%)<br>8      | 10 / 147 (6.80%)<br>10 | 3 / 144 (2.08%)<br>3   |

|   |                            |  |  |
|---|----------------------------|--|--|
| <b>Non-serious adverse events</b>   | Double-Blind<br>Placebo QD |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed   | 27 / 145 (18.62%)          |  |  |
| Investigations<br>WEIGHT INCREASED<br>subjects affected / exposed<br>occurrences (all)    | 7 / 145 (4.83%)<br>7       |  |  |
| Nervous system disorders<br>AKATHISIA<br>subjects affected / exposed<br>occurrences (all) | 2 / 145 (1.38%)<br>2       |  |  |
| HEADACHE<br>subjects affected / exposed<br>occurrences (all)                              | 15 / 145 (10.34%)<br>22    |  |  |
| Gastrointestinal disorders  |                            |  |  |

|   |                      |  |  |
|---|----------------------|--|--|
| NAUSEA<br>subjects affected / exposed<br>occurrences (all)  | 1 / 145 (0.69%)<br>1 |  |  |
| Psychiatric disorders<br>INSOMNIA<br>subjects affected / exposed<br>occurrences (all)                                   | 5 / 145 (3.45%)<br>7 |  |  |
| Infections and infestations<br>UPPER RESPIRATORY TRACT<br>INFECTION<br>subjects affected / exposed<br>occurrences (all) | 4 / 145 (2.76%)<br>6 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 25 August 2017 | <ol style="list-style-type: none"><li>1. Update the serious adverse event (SAE) and pregnancy reporting information (Title page and Section 9.4).</li><li>2. Add detail to the process of washout of prior psychiatric medications (Protocol Summary and Sections 3 and 8.2).</li><li>3. Increase the length of the safety follow-up period from 1 week to 4 weeks, adding an additional follow-up visit (throughout the document).</li><li>4. Add assessment of remission as a separate row in the Schedule of Visits and Procedures.</li><li>5. Clarify the timing of the pharmacogenetic consent and sampling (Table 1 and Section 6.4).</li><li>6. Decrease the suicidality-related MADRS score for exclusion at Screening or Baseline from 5 to 4 (exclusion criterion #9).</li><li>7. Add exclusion criterion and prohibitions for patients who are taking concomitant cytochrome P450 3A4 (CYP3A4) inducers/inhibitors (exclusion criterion #13 and Section 4.8.2).</li><li>8. Clarify the definitions for remission and stability criteria (Section 4.5).</li><li>9. Modify the relapse criterion related to initiation of psychiatric medication (Protocol Summary and Sections 3 and 4.7)</li><li>10. Clarify use of the 1.5 mg dose of cariprazine (Section 5.1)</li><li>11. Clarify treatment compliance evaluation (Section 5.6).</li><li>12. Add an additional efficacy parameter to the study (PSP) (Section 6.2.2.3 and Attachment 12.9)</li><li>13. Add a quality-of-life measure to the study: Work Productivity and Activity Impairment-Bipolar Disorder (WPAI-BD) (Sections 6.5 and Attachment 12.12).</li></ol> |
| 25 August 2017 | <ol style="list-style-type: none"><li>14. Clarify planned analyses for additional efficacy parameters (Sections 7.2.3 and 7.3.3)</li><li>15. Clarify planned safety analyses (Sections 7.3.4)</li><li>16. Clarify the timing and details of visits and associated procedures (Sections 8.4 and 8.7)</li><li>17. Add details about the Safety Follow-up (SFU) Visits (Section 8.4.7).</li><li>18. Modify the discontinuation reason for disallowed medications; add a new reason for discontinuation: postbaseline finding of cataracts; and to delete the discontinuation reason for consecutively missed doses; (Section 8.9).</li></ol>  |

|                  |   |
|------------------|---|
| 28 March 2018    | <ol style="list-style-type: none"> <li>1. Depressed episode to depressive episode. (Global change for clarity)</li> <li>2. Removed patients with a postbaseline cataracts was to be discontinued from the study. (Global change)</li> <li>3. Replaced the scale used to make the diagnostic assessment from Mini International Neuropsychiatric Interview (MINI) to Structured Clinical Interview for DSM-5 (SCID-5). (Operational Change)</li> <li>4. Changed doses (Open-Label Period – Changed from 4.5 mg to 3.0 mg; DB Period: 2 Cariprazine Dose arms are now: 3.0 mg and 1.5 mg). (applicable sections of protocol)</li> <li>5. Inclusion of depressed patients was added in addition to manic patients. manic or depressed patients may either be “with or without mixed features” (related inclusion criterion incorporated). (applicable sections of protocol)</li> <li>6. Sample size was changed.</li> <li>7. Day 4 and Day 10 study visits were deleted and a Day 22 visit was added. Study Visits have been renumbered throughout entire amendment 2. Study days have been renumbered to allow 1 full week of dosing before Visit 3. (applicable sections of protocol)</li> <li>8. Exclusion criteria around urine drug screen has been clarified.</li> <li>9. Removal of Symbol Digit Coding (SDC) – additional efficacy assessment. (applicable sections of protocol)</li> <li>10. MADRS total score was changed from MADRS total score <math>\geq 17</math> to <math>\geq 20</math>. (applicable sections of protocol)</li> <li>11. Added open-label safety-follow-up (OL SFU) population will consist of patients in the OL safety population who were not randomized.</li> <li>12. The primary analysis was updated to use stratified log-rank test instead of unstratified log-rank test and updated the first sensitivity analyses.</li> <li>13. Changed period for reporting of pregnancies during the study from 30 days after last dose to 3 months following last dose. (Section 9.4)</li> <li>14. Deleted the words “formerly” and “popular” when describing Snellen (Appendix 12.10)</li> </ol>  |
| 20 November 2018 | <ol style="list-style-type: none"> <li>1. Corrected Backup Serious Adverse Event Reporting Fax Number. (global change)</li> <li>2. Changed Forest Laboratories to AbbVie Sales. (global change)</li> <li>3. Added text to clarify the location of the Emergency Telephone Numbers. (Title page)</li> <li>4. Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated. (Protocol Summary, Screening/Washout period)</li> <li>5. Added text to clarify that Day 8 is Visit 3. (Protocol Summary, Screening/Washout period)</li> <li>6. Added visit windows of +3 days for Visit 2/Baseline and <math>\pm 3</math> days for Visits 3 through 33 to the table header. (Protocol Summary, Table 1)</li> <li>7. Changed “Blood Alcohol Level” to “Blood Alcohol Concentration by Breathalyzer”. (Protocol Summary, Table 1)</li> <li>8. Added serum pregnancy test at Visits 7, 18, 24, and 33. (Protocol Summary, Table 1)</li> <li>9. Added text to clarify the timing of visits. (Protocol Summary, Table 1)</li> <li>10. Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated. (Section 3. Study Design)</li> <li>11. Added text to clarify that Day 8 is Visit 3. (Section 3. Study Design)</li> <li>12. Added text to clarify that the patient must meet the same criterion at both the screening and baseline visits. (Section 4.3 Inclusion Criteria)</li> <li>13. Added text to clarify the need to use birth control for 12 weeks after the last dose of investigational product. (Section 4.3 Inclusion Criteria)</li> <li>14. Added text to clarify that the serum pregnancy test is qualitative. (Section 4.3 Inclusion Criteria)</li> <li>15. Added text to clarify use disorders. (Section 4.4 Exclusion Criteria)</li> <li>16. Added text to clarify that a positive urine drug screen (UDS) is not exclusionary if the drug was used as rescue medication during washout. (Section 4.4 Exclusion Criteria)</li> <li>17. Added text to exclude moderate CYP3A4 inhibitors. (Section 4.4 Exclusion Criteria)</li> <li>18. Changed example of endocrinological disease. (Section 4.4 Exclusion Criteria)</li> </ol> |

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

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

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported