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Protocol for Study M22-509

Schizophrenia: Cariprazine in the Acute Exacerbation of Schizophrenia

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FULL TITLE: A 6-Week, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Cariprazine in the Acute Exacerbation of Schizophrenia, with an Additional 18-Week Blinded Extension Period

Incorporating Versions 1.0, 2.0, and 3.0

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted] MD
AbbVie GK
3-1-21 Shibaura, Minato-ku
Tokyo 108-0023, Japan

Mobile: [redacted]
Fax:
Email:

EMERGENCY 24-hour Number: +1 973-784-6402

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix F).

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1 SYNOPSIS

Title: A 6-Week, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Cariprazine in the Acute Exacerbation of Schizophrenia, with an Additional 18-Week Blinded Extension Period	
Background and Rationale:	Cariprazine is an orally active and potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors and partial agonist at serotonin 5-HT1A receptors. Cariprazine may be useful for the treatment of schizophrenia in subjects from Japan and Taiwan, as demonstrated in other populations. For treatment of schizophrenia, cariprazine was approved in the United States (US), European Union (EU), and other countries, at doses of 1.5 to 6 mg/day.
Objectives and Endpoints:	Primary objective: To assess the efficacy, safety, and tolerability of cariprazine in comparison to placebo in subjects from Japan and Taiwan with acute exacerbation of schizophrenia. Primary efficacy endpoint: Change in Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) total score from baseline to double-blind period (DBP) Week 6. Key secondary efficacy endpoint for DBP: Change in Clinical Global Impression-Severity (CGI-S) score from baseline to Week 6. Additional secondary endpoints for DBP: Change in the following from baseline to Week 6: SCI-PANSS positive symptom score, 16-Item Negative Symptom Assessment (NSA-16) total score, SCI-PANSS negative symptom score, and SCI-PANSS negative factor score. Secondary objective: To assess the maintenance of efficacy, safety, and tolerability of cariprazine in an 18-week blinded extension period (BEP) in subjects who completed the DBP of this study. Efficacy endpoints for BEP: Change in the following from baseline and Week 6 to Week 24: SCI-PANSS total score, CGI-S score, SCI-PANSS positive score, NSA-16 total score, SCI-PANSS negative symptom score, and SCI-PANSS negative factor score.
Investigators:	Multicenter
Study Sites:	Planned sites for Japan: Approximately 40 sites Planned sites for Taiwan: Approximately 15 sites
Study Population and Number of Subjects to be Enrolled:	The study population will be male and female subjects experiencing an acute exacerbation of schizophrenia. Approximately 125 subjects per arm (total of approximately 250 subjects) are intended to be enrolled.

Investigational Plan:	This is a randomized, double-blind, placebo-controlled, 6-week Phase 3 study to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of cariprazine in subjects with acute exacerbation of schizophrenia, followed by an 18-week BEP and an 8-week safety follow-up period. Subjects will be randomized in a 1:1 ratio to placebo or cariprazine 6 mg/day for the DBP. Subjects who complete the DBP will have the option to enter the BEP, during which subjects who received placebo during the DBP will be switched to cariprazine 1.5 mg/day, and subjects who received cariprazine 6 mg/day during the DBP will receive cariprazine 3 mg/day in a blinded manner in the BEP.
Key Eligibility Criteria:	To be eligible for this study, subjects must be aged between 18 and 65 years of age, inclusive at the time of screening and must have been diagnosed with schizophrenia at least 1 year before informed consent. Subjects must have experienced a persistent psychotic episode within 2 months prior to informed consent requiring treatment modifications as judged by the investigator or sub-investigator.
Study Drug and Duration of Treatment:	Cariprazine 1.5, 3, or 6 mg once per day Approximately 24 weeks (6-week DBP; 18-week BEP)
Date of Protocol Synopsis:	25 July 2023

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Cariprazine has been approved for the treatment of schizophrenia in the United States (US), the European Union (EU), and other countries at doses of 1.5 to 6 mg/day. Cariprazine is an orally active and potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors and partial agonist at serotonin 5-HT1A receptors. Given cariprazine's efficacy in various global populations, it may be a promising approach for the treatment of acute exacerbation of schizophrenia in subjects from Japan and Taiwan.

The intention of the randomized, double-blind, placebo-controlled, 6-week double-blind period (DBP) in this Phase 3 study is to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of cariprazine in comparison to placebo in subjects from Japan and Taiwan with acute exacerbation of schizophrenia. Subjects who complete the 6-week DBP are eligible to participate in the 18-week blinded extension period (BEP).

2.2 Benefits and Risks to Subjects

In global clinical studies, cariprazine 1.5 to 9 mg/day has been shown to be effective in the treatment of schizophrenia. While the drug has been shown to be effective in this dose range, the benefit-risk profile in the treatment of schizophrenia is maximized in the cariprazine 1.5 to 6 mg/day dose range. Cariprazine 1.5 to 6 mg/day is approved globally for the treatment of schizophrenia, including the US and EU; see the Investigator's Brochure for further details.

Taken together, the safety and efficacy data from previous clinical studies and the global approval of schizophrenia support further development of cariprazine 1.5 to 6 mg/day in subjects from Japan and Taiwan with acute exacerbation of schizophrenia.

For further details, please see findings from completed studies, including safety data in the current cariprazine Investigator's Brochure.

COVID-19 vaccination and assessment of risk for participants in cariprazine clinical trials

Based on the current understanding of available Coronavirus Disease-2019 (COVID-19) vaccines and mechanisms used to produce an immune response (via messenger ribonucleic acid [mRNA], viral vector, or protein subunit), vaccination for COVID-19 does not pose a risk to subjects in cariprazine clinical trials.

- The known safety profile of cariprazine does not confer increased risks for individuals receiving vaccination of any type and subjects in cariprazine trials can receive all recommended vaccinations.
- There is a risk of leukopenia or neutropenia with cariprazine use; however, immunocompromised patients can receive any currently authorized COVID-19 vaccine per current guidance from the World Health Organization

(https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice). Further, cariprazine trials include monitoring of the complete blood count, and subjects with leukopenia or neutropenia will be discontinued from the trial.

- General risks of vaccination such as local site reactions or systemic reactions including anaphylaxis are not increased with cariprazine use.
- Finally, the known safety profile of cariprazine does not predispose patients to certain reported adverse events (AEs) specific to COVID-19 vaccination, namely myocarditis, pericarditis, and thrombosis.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective is to assess the efficacy, safety, and tolerability of cariprazine in comparison to placebo in subjects from Japan and Taiwan with acute exacerbation of schizophrenia.

The primary efficacy objective is to determine if cariprazine (6 mg/day) improves the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) total score compared to placebo in subjects from Japan and Taiwan with acute exacerbation of schizophrenia.

The hypothesis corresponding to the primary efficacy objective is that decrease in SCI-PANSS total score with cariprazine (6 mg/day) is greater than that with placebo.

The attributes of the primary estimand corresponding to the primary efficacy objective are as follows:

- Population: The modified intent-to-treat (mITT) population, which consists of all randomized subjects who receive at least 1 dose of study drug and have both baseline and at least 1 postbaseline value of SCI-PANSS total score during the DBP.
- Variable: The primary efficacy endpoint, change from baseline to Week 6 of the DBP in SCI-PANSS total score.
- Accounting for intercurrent events: regardless of whether rescue medications are used, data are included in the analysis. Data after discontinuation of study drug will not be included in the primary analysis and will be assumed missing at random.
- Population-level summary: The difference in means between cariprazine 6 mg/day and placebo.

Secondary

The secondary objective is to assess the maintenance of efficacy, safety, and tolerability of cariprazine in an 18-week BEP in subjects who completed the DBP of this study.

3.2 Primary Endpoint

The primary endpoint is the change in SCI-PANSS total score from baseline to DBP Week 6.

3.3 Secondary Endpoint

Key Secondary Endpoint for DBP:

- Change in Clinical Global Impression-Severity (CGI-S) score from baseline to Week 6

Additional Secondary Endpoints for DBP:

- Change in SCI-PANSS positive symptom score from baseline to Week 6
- Change in 16-Item Negative Symptom Assessment (NSA-16) total score to baseline to Week 6
- Change in SCI-PANSS negative symptom score from baseline to Week 6
- Change in SCI-PANSS negative factor score from baseline to Week 6

Efficacy Endpoints for BEP:

- Change in SCI-PANSS total score from baseline and Week 6 to Week 24
- Change in CGI-S score from baseline and Week 6 to Week 24
- Change in SCI-PANSS positive score from baseline and Week 6 to Week 24
- Change in NSA-16 total score from baseline and Week 6 to Week 24
- Change in SCI-PANSS negative symptom score from baseline and Week 6 to Week 24
- Change in SCI-PANSS negative factor score from baseline and Week 6 to Week 24

3.4 Safety Endpoints

The safety endpoints are as follows:

- AEs
- Clinical laboratory tests
- Vital signs
- Electrocardiogram (ECG)
- Suicide severity rating (Columbia-Suicide Severity Rating Scale [C-SSRS])
- Extrapyramidal symptom (EPS) assessment:
  - Simpson-Angus Scale (SAS)
  - Abnormal Involuntary Movement Scale (AIMS)

- Barnes Akathisia Rating Scale (BARS)

3.5 Pharmacokinetic Endpoints

Plasma cariprazine concentrations will be obtained at the visits indicated in Appendix D. Plasma samples will be analyzed for the concentrations of cariprazine and its metabolites desmethyl cariprazine and didesmethyl cariprazine using a validated bioanalytical method. A population PK approach will be used to estimate individual-level drug-exposure parameters (e.g., steady-state area under the concentration versus time curve, steady-state maximum concentration, steady-state minimum concentration) for each of the 3 analytes. This will be performed via the use of appropriate nonlinear mixed-effects modeling software. The relationship, if any, between effectiveness and drug-exposure parameters will be explored. These analyses will be reported separately.

4 INVESTIGATIONAL PLAN

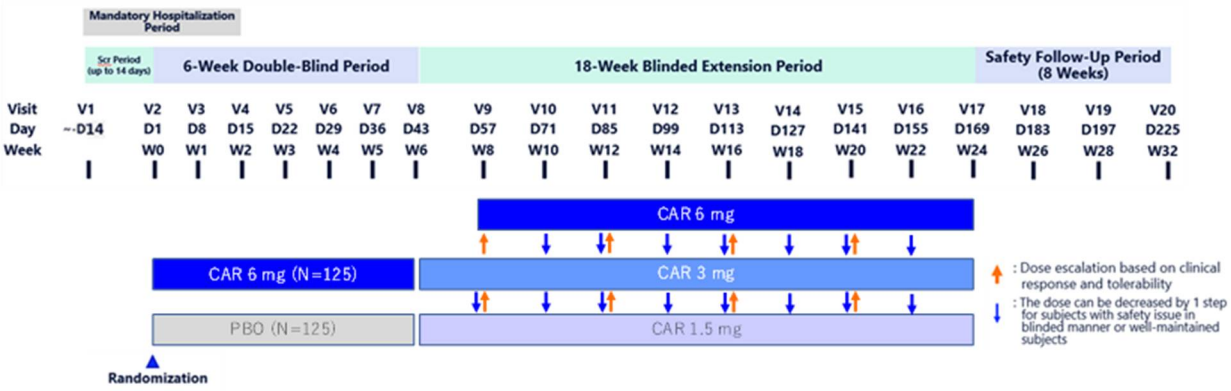
4.1 Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled Phase 3 study consisting of a 6-week DBP to assess the safety, tolerability, PK, and efficacy of cariprazine in subjects from Japan and Taiwan with acute exacerbation of schizophrenia, followed by an 18-week BEP.

This study consists of a screening period, a 6-week DBP, an 18-week BEP, and an 8-week safety follow-up period. The study has a planned enrollment of approximately 250 subjects (125 subjects per arm), randomized on Day 1 (Visit 2) in a 1:1 ratio to placebo or cariprazine 6 mg/day. Subjects who complete the DBP will have the option to enter the 18-week BEP, during which subjects who received placebo during the DBP will be switched to cariprazine 1.5 mg/day and subjects who received cariprazine 6 mg/day during the DBP will receive cariprazine 3 mg/day in a blinded manner in the BEP. Study sites and subjects will remain blinded to treatment assignment for the duration of the study.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual. See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schematic

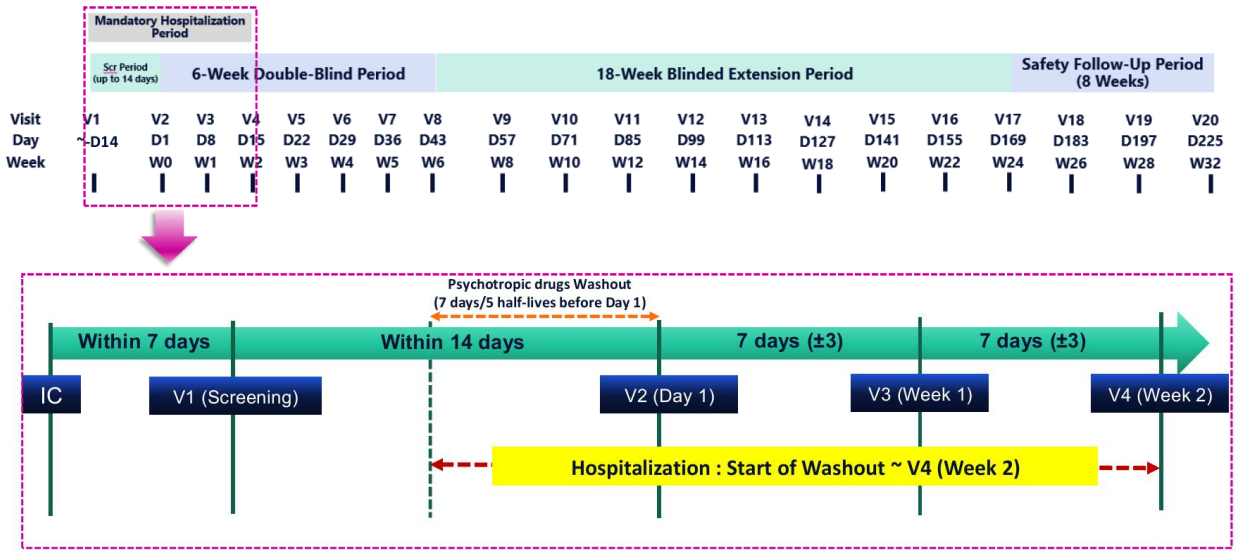


Note: The up-titration schedule for the DBP is specified in Table 1.

Screening Period

Subjects who consent to participate in the study will be admitted to the hospital for washout of all prohibited medications (see Section 5.1) during the screening period and begin screening tests within 7 days after obtaining consent (Visit 1). Ophthalmologic examinations may be started at any time during the screening period but prior to eligibility assessment at baseline (Visit 2).

Figure 2. Study Procedure: Informed Consent, Screening, Day 1 and Week 2



6-Week Double-Blind Period

Subjects will be randomly assigned to receive placebo or cariprazine 6 mg/day for the 6-week DBP. Subjects in the placebo group will receive placebo throughout the 6-week DBP. Subjects in the cariprazine 6 mg/day arm will be dosed based on the dosing schedule in Table 1 in a blinded manner.

Subjects will remain hospitalized at least until Week 2 (Visit 4) to ensure their safety.

Study drug interruption for 1 to 3 days due to study drug tolerability as judged by the investigator (or subinvestigator) is allowed.

Table 1. Dosing Regimen in DBP

	Day 1	Day 2	Day 3	Day 4 – Day 42
Placebo	Placebo	Placebo	Placebo	Placebo
Cariprazine 6 mg/day	1.5 mg	3 mg	4.5 mg	6 mg

18-Week Blinded Extension Period

Subjects who completed the 6-week DBP are likely to comply with the study protocol and are suitable for participation in BEP as judged by the investigator (or subinvestigator) are eligible to participate in the 18-week BEP of this study.

Subjects in the cariprazine 6 mg/day dosing group in the DBP will receive cariprazine 3 mg/day, and subjects from the placebo group in DBP will receive cariprazine 1.5 mg/day in a blinded manner at Week 6 (Visit 8) after completion of scheduled study activities.

At Weeks 8, 12, 16, and 20, the dose can be increased in 1 step (1.5 mg/day to 3 mg/day or 3 mg/day to 6 mg/day) if the subject meets either of the following dose-escalation criteria after treatment of 2 weeks (Week 8) or at least 4 weeks (Weeks 12, 16, and 20) with stable dose and with no tolerability problem judged by the investigator (or subinvestigator) (optional dose escalation):

- Improvement in SCI-PANSS total score from Day 1 (Visit 2) is < 20% and CGI-S score is ≥ 4
- The investigator's (or subinvestigator's) judgment

The maximum dose of cariprazine is 6 mg/day.

An interruption in dosing of up to 3 days is allowed at any time if the investigator (or subinvestigator) has judged that there is a tolerability problem.

Subjects with a tolerability problem or well-maintained subjects judged by the investigator (or subinvestigator) can reduce the dose by 1 step (6 mg/day to 3 mg/day or 3 mg/day to 1.5 mg/day) in a blinded manner at any visit, including unscheduled visits.

Safety Follow-Up Period

Subjects will enter the 8-week safety follow-up period after the last dose of study drug in the study (either DBP or BEP).

Switching to Another Antipsychotic After Completion of Study Treatment

In switching to another antipsychotic after completion of study treatment, the use of antipsychotics should be limited to only 1 atypical antipsychotic, and the dose should be increased according to

symptoms after at least 1 week of treatment with the antipsychotic agent at the initial dose recommended.

The use of a single typical antipsychotic can be permitted at the discretion of the investigator (or subinvestigator) according to the condition and symptoms of the subject. However, another switching procedure and/or other psychotropics use will be allowed at the medical discretion of the investigator (or subinvestigator) in the event of aggravation (including suspected aggravation) of the underlying disease or for any other inevitable reason after the last dose of study drug.

In the clinical studies conducted to date in Japan and overseas, the incidence of AEs was the lowest in patients receiving atypical antipsychotic monotherapy among those confirmed to have used antipsychotics during the safety follow-up period.

4.2 Discussion of Study Design

Choice of Control Group

The 6-week DBP utilizes a placebo control group and a cariprazine 6 mg/day group. The use of placebo control is critical to the study design, allowing for further characterization of the safety profile of cariprazine while also ensuring that results assessing efficacy can be interpreted. In this study, a placebo treatment group is included to comply with worldwide regulatory preferences,[1,2] since placebo-controlled superiority trials have been shown to be conducive to higher quality studies and to provide more reliable outcomes.[1-3] Additionally, from a scientific point of view, randomized double-blind comparisons versus placebo are needed to permit adequate evaluations of efficacy. Comparison to a placebo treatment is also of value for distinguishing disease manifestations from adverse reactions of the investigational product.[4] Participants who are randomized to cariprazine treatment should demonstrate a greater reduction in mean SCI-PANSS total score after 6 weeks compared to those randomized to placebo for the treatment to be considered effective.

The 18-week BEP utilizes 3 dose levels of cariprazine (1.5 mg/day, 3 mg/day, and 6 mg/day) to evaluate the safety, efficacy, PK, and tolerability in subjects from Japan and Taiwan across the dose range approved globally for cariprazine. The investigators and subjects will be blinded throughout the period to keep treatment assignment in DBP blinded.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with schizophrenia. All clinical and laboratory procedures in this study are standard, generally accepted, and consistent with prior cariprazine studies.

Suitability of Subject Population

The eligible population for this study in subjects from Japan and Taiwan reflects the approved population for cariprazine use in the US, EU, and other countries and aligns with the key eligibility criteria used in previous cariprazine clinical studies.

Selection of Doses in the Study

The selected cariprazine dosages for this study are 6 mg/day for the DBP and 1.5, 3, and 6 mg/day for the BEP.

In global clinical studies, a cariprazine dose range of 1.5 to 9 mg/day has been shown to be effective in treatment of schizophrenia. However, the benefit-risk profile in the treatment of schizophrenia is maximized in the cariprazine 1.5 to 6 mg/day dose range. Cariprazine 1.5 to 6 mg/day is approved globally for the treatment of schizophrenia, including the US and EU; see the Investigator's Brochure for further details.

In accordance with previous study results and approved dosage of cariprazine globally, 1.5 to 6 mg/day was selected for this study.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent form**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Male or female between 18 and 65 years of age, inclusive, at the time of screening.
- 3. Body mass index between 17 and 35, inclusive.
- 4. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum alanine transaminase (ALT) < 3 × upper limit of normal (ULN);
  - Serum aspartate aminotransferase (AST) < 3 × ULN;
  - Creatinine < 1.5 x ULN;
  - Glycated hemoglobin (HbA1C) < 6.5%;
  - Total white blood cell (WBC) count > 2,500/µL;
  - Absolute neutrophil count > 1,000/µL;
  - Platelet count > 100,000/µL;
  - Absolute lymphocyte count > 850/µL;
  - Hemoglobin > 10 g/dL.

- 5. Subject must not have active human immunodeficiency virus (HIV), Hepatitis B (HBV), or hepatitis C virus (HCV) infection at Visit 1 (screening visit). Active infection is defined as:
  - HIV: positive test result for HIV antibody;
  - HBV: positive test result for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) except for HBV carrier without active hepatitis judged by investigator (or subinvestigator) and per local guidelines
  - HCV: positive HCV ribonucleic acid (RNA) except for subjects with sustained virologic response treated with direct-acting antivirals.
- 6. Subject must have a negative result from the blood or urine alcohol test and from urine drug screening for narcotics and stimulants, except narcotic analgesics used temporarily (up to 3 days) for acute medical indications. Any positive result from urine drug screening must be assessed for clinical significance.
- 7. Subjects are willing and able to comply with procedures required in this protocol and are not considered unsuitable for participation in this study for any other reason, as judged by the investigator (or subinvestigator).

Disease/Condition Activity

- 8. Diagnosis of schizophrenia at least 1 year before informed consent.
- 9. Subject meets the following disease activity criteria:
  - Subjects diagnosed with schizophrenia according to the diagnostic criteria of the Diagnostic Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5), and Mini International Neuropsychiatric Interview (MINI).
- 10. A history within 2 months before informed consent of a psychotic episode (evidence of schizophrenia exacerbation) requiring treatment modifications (hospitalization or a change or dose increase of antipsychotic drugs) as judged by the investigator (or subinvestigator). The following must be met at the time of the screening visit (Visit 1):
  - Persistence of the psychotic episode stated above
  - SCI-PANSS total score ≥ 80 and ≤ 120
  - At least 2 of the 4 SCI-PANSS positive symptoms (P1. delusions, P2. conceptual disorganization, P3. hallucinatory behavior, and P6. suspiciousness/persecution) rated as 4 (moderate) or higher
  - CGI-S score ≥ 4
  - Physical examination findings, vital signs, clinical laboratory test results, and ECG results that are normal; or some of the results are abnormal but not clinically significant as judged by the investigator (or subinvestigator) and documented as such in the source documents
  - Subjects must agree to start hospitalization for washout of all psychotropics and lemborexant except rescue medications during screening until Week 2 of the treatment period (Visit 4; see Figure 2)
- 11. Subject meets the SCI-PANSS and CGI-S criteria above in Criterion #10 at baseline (Visit 2).

Subject History

- 12. Subjects who do NOT meet any of the following criteria at the time of informed consent:
  - Hospitalization continuing for 3 months or more (except hospitalization for social reasons)
  - Patients during involuntary hospitalization by law except patients who understand clinical study procedures and are willing to follow protocol stipulations
- 13. No current diagnosis of any of the following conditions according to the diagnostic criteria of the DSM-5:
  - Schizoaffective disorder, schizophreniform disorder, and other psychotic disorders within schizophrenia spectrum
  - Bipolar I or II disorder
  - Impaired intellectual ability, mild or major neurocognitive disorder, delirium, and other cognitive disorders
  - Known or suspected borderline or antisocial personality disorder or other personality disorder of sufficient severity to interfere with participation in this study
  - Substance-related disorder (other than tobacco or caffeine) within 6 months before Visit 1 (screening visit)
- 14. Subjects who are NOT in their first episode of psychosis.
- 15. No history of drug hypersensitivity, such as shock and anaphylactoid symptoms.
- 16. Subjects without imminent risk of injuring themselves or others or causing significant property damage, as judged by the investigator (or subinvestigator).
- 17. Subjects without a risk for suicide and without suicidal ideation, as judged by the investigator (or subinvestigator).
  - Subjects must not have had a suicide attempt within the past year before Visit 1 (screening).
  - Subjects must not have significant risk, as judged by the investigator, based on the psychiatric interview or information collected in the C-SSRS at Visit 1 (screening) and Visit 2 (baseline).
- 18. Subjects without any cardiovascular disease that is clinically significant, unstable, or decompensated and any of the following conditions:
  - History of congenital QT interval corrected for heart rate (QTc) prolongation or presence of QTc prolongation (QT interval corrected for heart rate using the Fridericia formula [QTcF] ≥ 450 msec for men and QTcF ≥ 470 msec for women at Visit 1 (screening) or Visit 2 (baseline) in-hospital ECG)
  - Second-degree (Mobitz II) or third-degree atrioventricular block
  - History of ischemic heart disease developed within 6 months before Visit 1 (screening visit), including myocardial infarction and stable or unstable angina
  - Heart rate of ≤ 45 bpm or ≥ 120 bpm on ECG or any heart rate abnormality that is clinically symptomatic

- Premature ventricular contractions associated with clinical symptoms or any complex premature ventricular contractions (multifocal, couplets, triplets [salvos], or the R-on-T phenomenon)
- Atrial fibrillation or flutter that is symptomatic, that is associated with uncontrolled heart rate, that requires anticoagulation, or that has occurred within 1 year before Visit 1 (screening visit)
- Any systolic or diastolic blood pressure abnormality that is symptomatic or requires treatment, unless they are on stable appropriate pharmacotherapy with no change in dosage for at least 3 months before Visit 1 (screening visit)

19. Subjects without hypo- or hyperthyroidism requiring treatment unless they are on stable appropriate pharmacotherapy with no change in dosage for at least 3 months before Visit 1 (screening visit).
20. Subjects without psychiatric symptoms possibly attributable to any other organic condition or abnormal level of vitamin B12 or folate.
21. Subjects without gastric bypass or any condition that is expected to affect drug absorption.
22. No known history or current findings of convulsive disorders such as epilepsy (excluding history of infantile febrile convulsion without epileptiform findings), stroke, significant head injury, tumor of the central nervous system, or any other condition that predisposes the subject to a risk for seizures.
23. Subjects without any of the following conditions:
    - A finding of cataracts (lens opacification[s] which meet Age-Related Eye Disease Study (AREDS) standard photo ≥ #2) at the screening ophthalmological examination
    - Any clinically significant ocular trauma or complications of ocular trauma, or history of retinal detachment, intraocular surgery (with the exception of cataract surgery to remove or replace lenses bilaterally) or laser treatment (except LASIK)
    - History or current findings of ocular disease (e.g., open- or narrow-angle glaucoma, retinopathies, corneal diseases)
    - History of any ocular diseases due to amiodarone or corticosteroid use in the past 3 years
    - Intraocular pressure of > 21 mm Hg in either eye at the screening ophthalmological examination
    - Unable to dilate pupil to at least 5 mm in either eye with the use of dilating eye drops
24. No history of tardive dyskinesia (except for mild cases attributed to use of conventional agents), serotonin syndrome, or neuroleptic malignant syndrome.
25. No history of syndrome of inappropriate antidiuretic hormone secretion.
26. No treatment history of any investigational product during the study or within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug.
27. Subjects with ability to speak and understand the local language sufficiently to understand the nature of the study, to provide written informed consent, or to allow the completion of all study assessments as judged by the investigator (or subinvestigator).

- 28. No history of **any malignancy** within 5 years before randomization, except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix.
- 29. No history of clinically significant (per investigator's [or subinvestigator's] judgment) **drug or alcohol abuse** within the last 6 months.
- 30. No conditions that could **interfere with drug absorption** including but not limited to short bowel syndrome.
- 31. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 32. No known active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., PCR) or 2 negative antigen test results at least 24 hours apart. If a subject was infected and still has symptoms, follow SARS-CoV-2 infection viral clearance criteria below. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations.
  - Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen for the study after they meet the following SARS-CoV-2 infection viral clearance criteria:
    - At least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 33. No history of clinically significant medical conditions or any other reason that the investigator (or subinvestigator) determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 34. No history of any other medical condition not specified above which potentially prevents subjects from completion of the study.

Contraception

- 35. For all females of childbearing potential; a **negative serum pregnancy test** at Visit 1 (screening visit) Serum pregnancy tests will also be performed at end of DBP Visit 8 (Week 6), Visit 13 (Week 16), Visit 17 (Week 24), and Visit 20 (Week 32).
- 36. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control** that is effective from Study Day 1 through 12 weeks after the last dose of study drug. Female subjects of nonchildbearing potential do not need to use birth control.
- 37. Female who is not **pregnant or breastfeeding and is not considering becoming pregnant** or donating eggs during the study.

Concomitant Medications

- 38. Subject is NOT treated with 3 or more antipsychotic drugs concurrently including as-needed use or with antipsychotic drugs whose total doses exceed 900 mg/day chlorpromazine equivalent within 1 month before screening.

- 39. Subject does NOT meet any of the criteria of potential treatment-resistant schizophrenia defined as following:
  - For subjects with treatment history with clozapine:
    - Use of clozapine in the past 6 months before screening
    - Little or no symptomatic response to prior treatment with clozapine
    - Cariprazine/dopamine receptors partial agonists are NOT expected to be beneficial to the subject based on response to prior pharmacological therapies, according to the investigator's (or subinvestigator's) judgment.
  - Little or no symptomatic response to treatment with 3 antipsychotic drugs (monotherapy, attempted at different times) at a therapeutic dose range for an adequate duration (at least 6 weeks) within 1 year before Visit 1 (screening visit)
  - Failure to respond to electroconvulsive therapy in the past
- 40. Subjects who did NOT receive electroconvulsive therapy within 3 months before Visit 1 (screening visit).
- 41. Subjects who can follow the guidance on prohibited medications/therapy while participating in this study.
- 42. Subject **must have discontinued** any prohibited psychotropic drugs (except for rescue medicine listed in Section 5.4) and epinephrine as follows:
  - Oral medicine, patch medicine, intravenous injection, intramuscular injection, or lemborexant at least 7 days or 5 half-lives of the drug, whichever is shorter, prior to the first dose of study drug
  - Depot LAI antipsychotics, at least longer than label-specified dose interval (e.g., aripiprazole LAI: 4 weeks, etc.) prior to the first dose of study drug
- 43. Subject must not be currently enrolled in another clinical study or was previously enrolled in this study.
- 44. Subject must not have systemically used known **strong cytochrome P450** (CYP)3A inhibitors or strong CYP3A inducers from informed consent to the completion of treatment period or premature discontinuation (PD) visit.
- 45. Subjects who have NEVER previously received cariprazine (MP-214/RGH-188).

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Nonchildbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of nonchildbearing potential due to meeting any of the following criteria:

1. Premenopausal female with permanent sterility or permanent infertility due to 1 of the following:
    - Permanent sterility due to a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
    - Nonsurgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
2. Postmenopausal female
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level ≥ 30 IU/L.

- Females, of Childbearing Potential
    - Females of childbearing potential must avoid pregnancy from Study Day 1 through 12 weeks after the last dose of study drug.
    - Females must commit to 1 of the following methods of birth control:
        - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to study Day 1 (baseline).
        - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Day 1 (baseline).
        - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
        - Intrauterine device.
        - Intrauterine hormone-releasing system.
        - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
        - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

          Contraception recommendations related to the use of concomitant therapies prescribed should be based on the local label.
        - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to study Day 1 (baseline).
        - Male or female condom with or without spermicide.
        - Cap, diaphragm, or sponge with spermicide.

- A combination of male condom with cap, diaphragm, or sponge with spermicide (double-barrier method).

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential must agree to use male condoms, even if the male subject has undergone a successful vasectomy, from study Day 1 (baseline) through 12 weeks after the last dose of study drug.

5.3 Prohibited Medications and Therapy

During the study (from informed consent to the completion of double-blind treatment period, blinded extension period, or PD visit, unless otherwise specified), the following medications and therapies are prohibited:

- Psychotropic drugs from the start of washout period to the last dose of study drug except rescue medications listed in Section 5.4
- Drugs, supplements, and foods that inhibit or induce CYP3A4 activity
- Electroconvulsive therapy
- Epinephrine
- Lemborexant from the start of washout period to the last dose of study drug
- Other investigational products

The name, daily dose, administration route, treatment period, and reason for use of antipsychotic drugs prescribed during the 12 weeks before the start of study treatment will be recorded in the case report form (CRF).

For the safety follow-up period, see Section 4.1.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccine, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of Visit 1 (screening) or receives during the study must be recorded from 28 days prior to study drug administration through the post-treatment visit (Safety Follow-Up [SFU] Week 32).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with cariprazine can be located in the current cariprazine Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited psychotropic drugs (except for rescue medicine) and epinephrine as follows:

- Oral medicine, patch medicine, intravenous injection, or intramuscular injection within 7 days or 5 half-lives of the drug, whichever is shorter, prior to the first dose of study drug
- Depot LAI antipsychotics, at least longer than label-specified dose interval (e.g., aripiprazole LAI: 4 weeks, etc.) prior to the first dose of study drug

Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Rescue Medications

Medically appropriate episodic use (up to 3 days) of narcotic analgesics for acute medical indications (e.g., tooth extraction) is allowed during the study. Rescue medication may be changed. The following rescue medications will be allowed from after informed consent to the last dose of study drug according to stipulation for each medication.

For the safety follow-up period, see Section 4.1.

For insomnia, monotherapy of the following will be allowed, but should not be prescribed prophylactically. Two or more concurrent use is not allowed:

- Zolpidem (maximum of 10 mg/day)
- Zolpidem extended release (maximum of 12.5 mg/day)
- Zaleplon (maximum of 20 mg/day)
- Eszopiclone (maximum of 3 mg/day)
- Zopiclone (maximum of 7.5 mg/day)
- Suvorexant (maximum of 20 mg/day)

These medications must be administered before bedtime as recommended in their prescribing information. The medication must be documented on the relevant electronic case report form (eCRF). No such medication is permitted within 8 hours of psychiatric or neurological assessments.

For EPS or akathisia, the following will be allowed but should not be prescribed prophylactically:

For EPS or akathisia that emerge or worsen during the study, use of one or more concurrent rescue medications listed below will be allowed. However, each of the 3 EPS scales (AIMS, BARS, and SAS) should be administered first to support the decision to dispense these rescue medications. The only exception to administering the EPS scales before dispensing rescue medication is medical urgency (e.g., dystonia, severe akathisia, etc).

- Benztropine
- Diphenhydramine
- Propranolol
- Biperiden

- Trihexyphenidyl

The need for continued use of these medications should be regularly assessed by the investigator and documented appropriately.

Injectable agents are not allowed, except for the treatment of an acute dystonic reaction if deemed necessary.

Rescue medications for agitation, restlessness, and hostility:

Episodic use of lorazepam up to 2 mg/day (or equivalent benzodiazepine; one or more concurrent use and either orals or injectables also allowed) and for up to 3 consecutive days at a time is allowed for agitation, restlessness, and hostility. The medication use and the agitation, restlessness, or hostility must be documented on the relevant eCRF pages.

Efficacy assessments should not be performed within 8 hours of administration of lorazepam or equivalent benzodiazepine or within 24 hours of administration of diazepam.

Abrupt discontinuation of benzodiazepines is not advised.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, nonreplicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during Visit 1 (screening), the treatment periods, or the safety follow-up period, as long as components of the vaccine are not contraindicated. The first dose of study drug cariprazine, when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration. Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with schizophrenia and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study drug at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the sponsor.
- The investigator believes it is in the best interest of the subject.

- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Subject misses ≥ 4 consecutive days of study treatment.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the AbbVie Therapeutic Area Medical Director (TA MD) before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Subjects who discontinue study treatment during the DBP or the BEP of the study will undertake the examinations and observations for the PD visit. Allowable time window for scheduled examination is within 3 days from the last administration of study drug (or within 14 days for the ophthalmologic examination). Subjects who discontinued study treatment during the DBP or the BEP will enter the safety follow-up period. For subjects who prematurely discontinue the safety follow-up period, the visit window for the PD visit is within 7 days after discontinuation.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed within 3 days of the last administration of study drug. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. In addition, if a subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs (TEAEs)/serious adverse events (SAEs) have been resolved.

5.7 Study Drug

Cariprazine and/or matching placebo manufactured by AbbVie will be taken orally once daily beginning on Day 1 (baseline; Visit 2) and should be taken at approximately the same time each day. The study drug can be taken with or without food. If subjects should forget to take their study drug at their regularly scheduled dosing time, they should take the next dose at the next scheduled dosing time.

AbbVie will provide study drug for cariprazine and matching placebo. AbbVie provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Cariprazine and matching placebo will be packaged in blister cards with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Table 2. Study Drug Information

	Investigational Product	**Investigational Product Placebo**
Investigational Product Name	Cariprazine	Matching placebo
Mode/Route of Administration (ROA)	Oral administration	Oral administration
Formulation	Capsule	Identically appearing capsule
Dosage Form	1.5 or 3 mg	Identically appearing placebo capsules
Dose and Frequency of Administrations	1.5, 3, or 6 mg once daily	N.A., placebo once daily
Drug Preparation/Packaging	Capsules will be provided in blister cards and labeled per local Regulatory requirements	Capsules will be provided in blister cards and labeled per local Regulatory requirements
Masking	Blinded	Blinded
Storage Conditions	Store between 20°C to 25°C (68°F to 77°F). Excursions permitted to 15° - 30°C (59° - 86°F).	Store between 20°C to 25°C (68°F to 77°F). Excursions permitted to 15° - 30°C (59° - 86°F).
Additional Information	N/A	N/A

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at screening (Visit 1). Subjects will be randomized to either the placebo arm or the cariprazine 6 mg/day arm in a 1:1 ratio on Day 1 (Visit 2). The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment until the database lock after DBP. The investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the cariprazine capsules and placebo capsules provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

5.10 Data Monitoring Committee

A data monitoring committee is not planned for this study. Given that the safety and AE profile of cariprazine has been characterized extensively in studies of both global and Asian populations, the emergence of new AEs affecting subject safety are not anticipated.

A population PK analysis demonstrated about 34% increase in steady-state exposure (area under the concentration time curve from time 0 to 24 hours [AUC_{0-24}]) of total cariprazine in Asian patients (mostly patients from studies that were conducted in India) compared to Caucasian patients. Japanese patients had on average 21% greater steady-state AUC_{0-24} than Caucasian patients (Study RGH-MS-08). These differences are within the observed cariprazine PK variability, are relatively small, and are not clinically relevant. The well characterized safety profile, coupled with data specific to the population of this study, means new safety AEs are not anticipated, and a Data Monitoring Committee is therefore not indicated.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events: Cariprazine

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious AE within 24 hours of the site being made

aware of the serious AE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event.

All AEs reported from the time of study drug administration until 8 weeks after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.

SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets 1 of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study:

- Akathisia and EPS
- The following are considered ocular AEs of special interest, whether serious or nonserious, and are required to be reported within 24 hours of the site being made aware:
  - cataract, lens, or lenticular abnormality or change, opacity, opacification or opalescence
  - blindness, night blindness, visual acuity or vision decrease, abnormality or change, visual acuity test abnormality or change
  - retinal, macular, or optic nerve degeneration, abnormality or change; retinal pigment epithelium detachment, abnormality or change

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe using the following definitions:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

An AE is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours after the site is made aware of the SAE:

- Led to death, injury, or permanent impairment to a body structure of body function
- Led to a serious deterioration in the health of a subject that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - inpatient hospitalization or prolongation of existing hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness
  - chronic disease
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A planned hospitalization for a preexisting condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered an SAE.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 12 weeks following the last dose of study drug. After all study visits, pregnancy should be followed up as spontaneously reported by the subject.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

Potential Hy's Law Cases

Criteria for potential Hy's Law cases are as follows:

- ALT or AST ≥ 3 × ULN AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period.

A laboratory alert for potential Hy's Law cases will be in place, and will notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's Law case must be consulted with the AbbVie TA MD as soon as possible (within 24 hours of learning of the potential Hy's Law).

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The primary analysis for the DBP will be conducted after all subjects have taken their last dose of DBP study drug and a database lock has occurred to evaluate if the primary objective has been met. Data from subjects who were randomized to cariprazine 3 mg/day prior to removal of this dose arm from the DBP will not be included in analyses of the DBP.

7.2 Definition for Analysis Populations

The mITT population will consist of all randomized subjects who receive at least 1 dose of study drug and have both baseline and at least 1 postbaseline value of SCI-PANSS total score during the DBP. Subjects will be included in the treatment group they are randomized to in the mITT population. The mITT population will be used for all efficacy analyses for the DBP.

The safety population will consist of all randomized subjects who receive at least 1 dose of study drug. Subjects will be included in the treatment group corresponding to the double-blind treatment they actually receive in the safety population. The safety population will be used for demographic and safety analyses for the DBP.

The BEP population will consist of all subjects who complete the 6-week DBP and take at least 1 dose of study drug during the BEP. Subjects will be grouped according to their modal (most frequent) daily dose during the BEP.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Regardless of whether rescue medications are used, data are included in the analysis. The clinical objective is to assess the efficacy of treatment regardless of rescue medication use.

Data following discontinuation from the study drug due to any reason will not be included in the primary analysis. These data points will be assumed as missing at random.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

Analysis of the primary endpoint (change from baseline to DBP Week 6 in SCI-PANSS total score) will be conducted on the mITT population based on treatment as randomized. The primary analysis will be performed using the observed postbaseline change from baseline scores during the DBP through a mixed model for repeated measures (MMRM) with treatment, study center, visit, treatment-by-visit interaction as the fixed effects, and the baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the within-subject covariance. If the models fail to converge, the compound symmetry covariance matrix will be used instead. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Summary and Analysis of Secondary Endpoints

Summary and Analysis of Key Secondary Endpoint

Analysis of the key secondary endpoint, change from baseline to DBP Week 6 in CGI-S, will be analyzed using the same MMRM model as the primary endpoint.

Subgroup Analysis for Efficacy

Subgroup analyses of the primary endpoint will be conducted for the following subgroups:

- Age category (< 40 years or ≥ 40 years)
- Sex (male or female)
- Region (Japan or Taiwan)

7.5 Statistical Analyses for Safety

Safety analyses for the DBP will be carried out using the safety population. The baseline value for safety analysis is the last non-missing measurement value collected on or before the first dosing date of study drug. For continuous safety outcomes, the change from baseline will be analyzed in a descriptive manner by treatment group and by visit. For categorical safety outcomes, the number and percentage of each category will be summarized by treatment group and by visit. Shift of laboratory values from baseline to defined time points will be tabulated. Hypothesis testing will not be performed for safety parameters.

Analysis of Adverse Events

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with TEAEs, treatment-emergent SAEs, AEs with a reasonable possibility of being related to study drug, AEs leading to study drug discontinuation during the DBP will be summarized by treatment group and will be tabulated using the primary MedDRA system organ class and preferred term. TEAEs for the DBP will be defined as all events that begin or worsen on or after the first dose of DBP study drug and before the first dose of BEP study drug for subjects who participate in the BEP or within 30 days after the last dose of DBP study drug for subjects who do not participate in the BEP.

Analysis of Laboratory Data

Changes from baseline to each planned visit and to the minimum, maximum, and final value during the DBP will be summarized by n, mean, standard deviation, minimum value, median, and maximum value for each treatment group for each continuous hematology, chemistry, and urinalysis laboratory parameter.

Changes in laboratory parameters from baseline to the final value will be tabulated using shift tables by categories of low, normal, or high based on the normal ranges of the laboratory that performed the assay.

For each hematology, chemistry, and urinalysis laboratory parameter that potentially clinically significant (PCS) criteria are defined, a summary of the number and percentage of subjects who have at least 1 postbaseline observation that meets the PCS criterion and is more extreme than their baseline value will be provided for each treatment group.

Analysis of Vital Signs

Changes from baseline to each planned visit and to the minimum, maximum, and final value during the DBP will be summarized by n, mean, standard deviation, minimum value, median, and maximum value for each treatment group for each vital sign and weight variable.

For each variable, a summary of the number and percentage of subjects who have at least 1 postbaseline observation that meets the PCS criterion and is more extreme than their baseline value will be provided for each treatment group.

Other Safety Analysis

Further details and safety analyses for the BEP will be specified in the SAP.

7.6 Interim Analysis

No interim analysis of efficacy data for the DBP is planned for this study.

The primary analysis for DBP will be conducted after all subjects have taken their last dose of DBP study drug and a database lock has occurred to evaluate if the primary objective has been met. An interim analysis of BEP data will be conducted at that time.

7.7 Overall Type I Error Control

In order to control the overall type I error at significant alpha level of 0.05 (2-sided) for both the primary endpoint of change from baseline to DBP Week 6 in SCI-PANSS total score and key secondary endpoint of change from baseline to DBP Week 6 in CGI-S score, a fixed sequence method will be used to test the primary endpoint and key secondary endpoint in this order.

7.8 Sample Size Determination

In terms of the change from baseline in the SCI-PANSS total score at Week 6, the sample size of 125 subjects per arm (N = 250) can achieve at least 90% power to detect the statistically significant difference between placebo and cariprazine 6 mg/day based on these assumptions using an MMRM; treatment difference of -8.3 between 6 mg/day and placebo based on full analysis set (FAS) 2 in Studies A002-A4 and RGH-MD-04, and common standard deviation of 20 at Week 6 taking into account dropout rates and correlation matrix based on FAS in Study A002-A4.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

12 REFERENCES

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4. EMA. Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia. 2012.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration-time curve from time 0 to 24 hours
BARS	Barnes Akathisia Rating Scale
BEP	Blinded extension period
CAR	Cariprazine
CGI-S	Clinical Global Impression-Severity
ClinRO	Clinician-reported outcomes
COVID-19	Coronavirus Disease – 2019
CRF	Case report form
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome
DBP	Double-blind period
DSM-5	Diagnostic Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EPS	Extrapyramidal symptom
EU	European Union
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HbA1C	Glycated hemoglobin
HBcAB	Hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IRB	Institutional review board
IRT	Interactive response technology
LASIK	Laser in situ keratomileusis
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	Modified intent-to-treat
MMRM	Mixed model for repeated measures
mRNA	Messenger ribonucleic acid
NCS	Not clinically significant
NSA-16	Negative Symptom Assessment
PBO	Placebo
PCR	Polymerase chain reaction
PCS	Potentially clinically significant
PD	Premature discontinuation
PK	Pharmacokinetic(s)
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Simpson-Angus Scale
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SFU	Safety Follow-Up
SUSAR	Suspected unexpected serious adverse reactions
T3	Triiodothyronine
T4	Thyroxine
TAMD	Therapeutic Area Medical Director
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone

ULN	Upper limit of normal
US	United States
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M22-509: A 6-Week, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Cariprazine in the Acute Exacerbation of Schizophrenia, with an Additional 18-Week Blinded Extension Period

Protocol Date: 25 July 2023

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Neuroscience Clinical Development Japan Statistics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities prior to and across the 8 subject visits in the 6-week DBP. Subjects who do not enter the BEP are required to enter the 8-week safety follow-up period (safety follow-up period includes 3 subject visits) after the last dose of the study drug in the 6-week DBP. Study activities for the safety follow-up period are detailed in the Study Activities Table for the Blinded Extension Period and Safety Follow-Up Period.

The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual.

Study Activities Table for the 6-Week Double-Blind Period

	Informed Consent	Screening	Baseline	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6/PD
Visit #	-	1	2	3	4	5	6	7	8
Visit window (days)				±3					- 1/ + 3
Activity		up to Day -14	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
INTERVIEWS & QUESTIONNAIRES									
Subject information and informed consent	✓								
Eligibility criteria		✓	✓						
DSM-5 and MINI		✓							
Medical/surgical history		✓	✓						
Adverse event assessment		✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy		✓	✓	✓	✓	✓	✓	✓	✓
SCI-PANSS		✓	✓	✓	✓	✓	✓	✓	✓
CGI-S		✓	✓	✓	✓	✓	✓	✓	✓
NSA-16			✓		✓		✓		✓
C-SSRS		✓	✓	✓	✓	✓	✓	✓	✓
LOCAL LABS & EXAMS									
SAS/AIMS/BARS			✓	✓	✓	✓	✓	✓	✓
Vital signs		✓	✓	✓	✓	✓	✓	✓	✓
Physical examination (include height*, weight) *Height at screening only		✓							
12-lead ECG		✓							✓
Ophthalmologic examinations (slit-lamp, BCVA, and intraocular pressure during screening period. Only BCVA at Wk 6/PD permitted +14 days.)		✓							✓

	Informed Consent	Screening	Baseline	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6/PD
Visit #	-	1	2	3	4	5	6	7	8
Visit window (days)				±3					- 1/ + 3
Activity		up to Day –14	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43
CENTRAL LABS									
Serum pregnancy test (for all female subjects of childbearing age)		✓							✓
Hematology		✓			✓		✓		✓
Clinical chemistry, urinalysis, and urine myoglobin (urine myoglobin as necessitated by symptoms/lab values)		✓			✓		✓		✓
HbA1c, prolactin, fasting insulin, TSH/T4/T3, LH, FSH		✓							✓
HIV, HBV, and HCV		✓							
Pharmacokinetic (PK) sample					✓		✓		✓
Blood or urine alcohol level		✓ (blood or urine)							✓ (blood only)
Urine drug screening		✓							✓
TREATMENT									
Randomization/drug assignment			✓						
Administration of study drug/placebo			✓	✓	✓	✓	✓	✓	✓

The following table shows the required activities across the 9 subject visits in the BEP and safety follow-up period. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual.

Study Activities Table for the Blinded Extension Period and Safety Follow-Up Period

	Blinded Extension Period									Safety Follow-Up Period		
	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24/PD	SFU Wk 26	SFU Wk 28	SFU Wk 32/ PD
Visit #	9	10	11	12	13	14	15	16	17	18	19	20
Visit window (days)	±7								-1/+3	±7		
Activity	Day 57	Day 71	Day 85	Day 99	Day 113	Day 127	Day 141	Day 155	Day 169	Day 183	Day 197	Day 225
INTERVIEWS & QUESTIONNAIRES												
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SCI-PANSS	✓		✓		✓		✓		✓			
CGI-S	✓		✓		✓		✓		✓			
NSA-16	✓		✓		✓		✓		✓			
C-SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LOCAL LABS & EXAMS												
SAS/AIMS/BARS	✓		✓		✓		✓		✓			
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination									✓			
12-lead ECG									✓			
Ophthalmologic examinations (BCVA; permitted -7/+14-day window)									✓			✓
CENTRAL LABS												
Serum pregnancy test (for all female subjects of childbearing age)					✓				✓			✓
Hematology	✓		✓		✓		✓		✓			
Clinical chemistry, urinalysis, and urine myoglobin (urine myoglobin as necessitated by symptoms/lab values)	✓		✓		✓		✓		✓			
PK sample	✓		✓		✓		✓		✓			✓
Blood alcohol level	✓		✓		✓		✓		✓			✓

	Blinded Extension Period									Safety Follow-Up Period		
	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24/PD	SFU Wk 26	SFU Wk 28	SFU Wk 32/ PD
Visit #	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Visit window (days)	**±7**								**-1/+3**	**±7**		
Activity	**Day 57**	**Day 71**	**Day 85**	**Day 99**	**Day 113**	**Day 127**	**Day 141**	**Day 155**	**Day 169**	**Day 183**	**Day 197**	**Day 225**
Urine drug screening	✓		✓		✓		✓		✓			✓
℞ TREATMENT												
Administration of study drug	✓	✓	✓	✓	✓	✓	✓	✓				

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	27 January 2022
Version 2.0	15 February 2023

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following necessary protocol modifications:

- To simplify the design of the DBP, the cariprazine 3 mg/day treatment arm was removed from the DBP and the total number of subjects to be randomized to treatment in the DBP was reduced.
  - Section 1 and Section 4.1 – modified to:
    - remove the cariprazine 3 mg/day treatment arm from the DBP
    - update the number of subjects to be enrolled from 402 subjects (134 per treatment arm) to 250 subjects (125 per treatment arm)
    - clarify that subjects will be randomized in a 1:1 ratio to placebo or cariprazine 6 mg/day for the DBP
    - clarify that subjects who complete the DBP and opt to enter the BEP will be switched to the following treatment at Week 6 (Visit 8): subjects who received placebo during the DBP will be switched to cariprazine 1.5 mg/day, and subjects who received cariprazine 6 mg/day during the DBP will receive cariprazine 3 mg/day in a blinded manner
    - revise the approximate number of study sites
  - Figure 1 – modified to remove the cariprazine 3 mg/day treatment arm in the DBP and add a footnote to reference the DBP titration schedule in Table 1, and to clarify that subjects who received cariprazine 6 mg/day during the DBP will receive cariprazine 3 mg/day in a blinded manner at Week 6 (Visit 8)
  - Table 1 – modified to remove the cariprazine 3 mg/day treatment arm from the DBP
  - Section 4.2 – modified to remove mention of the cariprazine 3 mg/day treatment group from the DBP
- Eligibility criterion #6 and Appendix D were modified to allow the alcohol screening test (Visit 1) to be performed using either a blood or urine test.
- Lemborexant was added to eligibility criteria #10 and #42 to clarify washout requirements.
- Eligibility criterion #32 was modified to clarify criteria to follow for a symptomatic subject infected with SARS-CoV-2.
- Section 5.5 and Section 5.7 – removed reference to direct-to-patient shipping of study drug because this service is no longer available.

- Section 6.1 – clarified that all AEs reported from the time of study drug administration until 8 weeks after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject.
- Section 5.8 – modified to state that subjects will be randomized to either the placebo arm or the cariprazine 6 mg/day arm in a 1:1 ratio on Day 1 (Visit 2).
- Section 7.7 – revised overall Type I error control to reflect the reduction from 3 to 2 double-blinded treatment arms (because of the removal of the cariprazine 3 mg/day arm from the DBP).
- Section 7.8 – modified to clarify that the sample size of 125 subjects per arm (N = 250) can achieve at least 90% power to detect the statistically significant difference from placebo and cariprazine 6 mg/day. Updated treatment difference of -8.3 between 6 mg/day and placebo based on full analysis set (FAS) 2 in Studies A002-A4 and RGH-MD-04.

The following modifications were made to the Operations Manual:

- Section 1 and Section 4.2 – the contact information was updated for reporting SAE, pregnancy, or nonserious ocular adverse event of special interest outside of EDC.
- Section 2.1, Section 3.3, Section 3.12 – revised to reflect that the alcohol screen at Visit 1 can be performed either via blood or urine test.
- Section 3.6 – the description of the CGI-S scale was corrected to specify responses ranging from "normal, to at all ill" (1) to "among the most extremely ill patients" (7).
- Section 3.11 and Section 6.1 – removed reference to direct-to-patient shipping of study drug because this service is no longer available.