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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 PATIENTS WITH SCHIZOPHRENIA

Protocol Number:	RGH-MD-24
Phase:	3B
Name of Investigational Product:	Cariprazine
Sponsor:	Allergan Sales, LLC 5 Giralda Farms Madison, NJ 07940 USA Allergan Ltd. 1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire SL7 1YL United Kingdom
Emergency Telephone Number(s):	Refer to the Study Contacts List in the Investigator Site File or Trial Master File.
Serious Adverse Event Reporting Fax Number/ Back-up Fax Number: Email:	+1-714-796-9504/ +1-714-246-5295 IR-Clinical-SAE@allergan.com
Medical Safety Physician Contact Information:	Refer to the Study Contacts List.
Allergan Signatory:	[redacted] [redacted] [redacted] Clinical Development, CNS Global Branded Research and Development
Protocol Date:	28 June 2017

Protocol Amendment 1 Date:	21 December 2017
Protocol Amendment 2 Date:	16 April 2018
Protocol Amendment 3 Date:	28 November 2018
Protocol Amendment 4 Date:	17 December 2019

The following information can be found on FDA Form 1572 (US) and/or study contacts list and/or Trial Master File: Name and contact information of Allergan study personnel and emergency telephone numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: Cariprazine

Phase: 3B

Study Objectives: 1) To evaluate the efficacy and safety of cariprazine at a target dose of 4.5 mg/d compared with placebo in prevention of relapse in patients with schizophrenia; 2) 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 schizophrenia who were initially stabilized on a target dose of 4.5 mg/d

Clinical Hypotheses: 1) In patients with schizophrenia, cariprazine at 4.5 mg/d is safe and effective in preventing relapse when compared to placebo; 2) In patients with schizophrenia who were initially stabilized on a target dose of 4.5 mg/d, cariprazine at 3.0 mg/d is safe and effective in preventing relapse when compared to placebo.

Study Design

Structure: This is a multicenter, multinational, double-blind (DB), placebo-controlled, randomized-withdrawal study evaluating the safety and efficacy of cariprazine compared with placebo in the prevention of relapse in patients with schizophrenia. The study schematic is presented in Figure 1.

Duration:

Screening/Washout Period: Patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for schizophrenia will undergo a Screening/washout period up to 7 days, during which consent, assessment of eligibility, and withdrawal of prior psychiatric and prohibited medications will occur. The length and timing of the washout of prior psychiatric medications during the 7 days allotted for the Screening period is at the discretion of the investigator. Prior medications should be gradually withdrawn such that the washout is completed by Visit 2/Baseline. Please note that during the screening/washout period, psychotropic medications, other than those listed as rescue (Section 4.8.3), may not be newly initiated or reinstated. In order to ensure the safe transition of patients into the study, based upon the clinical judgment of the investigator, patients may be hospitalized during initiation of the study. This hospitalization can be for up to 14 days during the Screening and Open-label (OL) periods (with the end of hospitalization no later than Visit 3 [Day 8] of the OL treatment period). This 14-day allowance for hospitalization may include all or part of the Screening period. Hospitalization beyond the initial 14 days allowed will require consultation with the medical monitor. Following the protocol-allowed 14 days of hospitalization (and any sponsor-allowed extension), patients should be treated as outpatients.

Open-label Treatment Period: Patients who continue to meet eligibility criteria at Visit 2/Baseline will enter an OL treatment period for up to 18 weeks. Patients will receive OL cariprazine dosed as 1.5 mg/d beginning at Visit 2; titrated to 3.0 mg/d at Visit 3 and then titrated to 4.5 mg/d at Visit 4. Following the dose increase to 4.5 mg/d, if there are significant tolerability issues, the investigator should utilize rescue medications as clinically appropriate. If further tolerability issues arise, a temporary drug holiday up to 3 days, will be allowed. The date and reason for any holiday will be recorded on the appropriate page of the electronic case report form. Patients who are unable to tolerate the 4.5 mg/d dose will be discontinued. Patients, who are able to tolerate the dose will continue on the 4.5 mg/d dose for the remainder of the OL treatment period.

Beginning at Week 4 (Visit 6), patients will be assessed for response to the initial treatment with cariprazine. For the purposes of this protocol, *response threshold* will be defined as meeting all of the following criteria on or after Week 4 (Visit 6):

- Positive and Negative Syndrome Scale (PANSS) total score ≤ 60, and
- ≥ 20% decrease in PANSS total score from Visit 2/Baseline, and
- Score of ≤ 4 on each of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control; and

- Clinical Global Impression-Severity (CGI-S) ≤ 4, and
- No significant tolerability issues as judged by the investigator

Once a patient achieves the response threshold criteria, he/she will be evaluated at the subsequent visit to determine if the response criteria will be met again. Reconfirmation of response threshold criteria at either the visit following first attainment of response threshold or, in the event of an excursion, at the second visit following first attainment, will be defined as *stability*. One clinical excursion outside of the response threshold range is allowed between the first attainment of response threshold criteria and the subsequent confirmation of it (ie, stability). Following the excursion, patients not meeting response threshold criteria must be discontinued.

Once stability has been achieved, patients must continue to meet the response threshold criteria for an additional 8 weeks (ie, maintenance of stability) to qualify for randomization. During the maintenance of stability period, one excursion outside the response threshold criteria will be allowed. The excursion may occur at any time during the 8-week period with the exception of Visit 13/End of OL, but must be followed by a return to response threshold at the next visit. In the event the excursion occurs in a patient's 8th week of stability, but prior to Visit 13/End of OL, the patient should be assessed at the following scheduled visit to confirm whether randomization criteria have been met.

Patients who do not meet the response threshold criteria by Week 8 (Visit 8) or stability criteria by Week 10 (Visit 9) will be discontinued and undergo early termination (ET) procedures and subsequently complete the safety follow-up (SFU) period. Additionally, patients who at any time require either hospitalization (excluding protocol-allowed hospitalization during Screening/OL periods for the purpose of washout of prior psychiatric medications) or initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator will be discontinued.

During the 8-week maintenance of stability period, patients who meet any of the following will be discontinued and will subsequently enter the SFU period:

- PANSS total score increases by ≥ 30% relative to Visit 2/Baseline, or
- Score > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control, or
- Have an increase in CGI-S score by 2 or more points relative to Visit 2/Baseline

Double-blind Treatment Period: OL patients who are able to maintain the response threshold criteria for 8 weeks with no more than 1 excursion of response threshold criteria will be randomized 1:1:1 to receive cariprazine at the same dose (4.5 mg/d), a reduced dose (3.0 mg/d), or placebo for up to 26 weeks. Patients will continue to receive study treatment until a relapse event occurs or until completion of the 26 weeks of randomized treatment.

Relapse is defined as the occurrence of any 1 of the following:

- Increase in PANSS total score by ≥ 30% for patients who had a PANSS total score of ≥ 50 at Randomization/Visit 13 or a ≥ 10-point increase in PANSS total score for patients who had a PANSS total score < 50 at Randomization/Visit 13
- Increase in CGI-S score by 2 or more points relative to Randomization/Visit 13
- Score of > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control
- Deliberate self-injury or aggressive/violent behavior
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator
- Psychiatric hospitalization due to worsening of the patient's underlying condition

- Exacerbation of psychiatric illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

Safety Follow-up Period: Patients who complete the study, or who prematurely discontinue from either the OL or DB treatment periods will be followed for 4 more weeks and will have 2 evaluations for safety assessments at Visits 27 and 28 during the SFU period. During the SFU period, patients will continue as outpatients and will receive treatment as usual at the discretion of the investigator or designee. Patients will not receive investigational product (IP) during the SFU period.

Study Treatment Groups: cariprazine 4.5 mg/d and 3.0 mg/d

Controls: Matching placebo

Dosage/Dose Regimen: IP in the form of capsules packaged in blister packs will be provided by the sponsor. No IP will be administered during the Screening/washout period or the SFU period. During the OL treatment period (up to 18 weeks), patients will take 1 capsule daily. Patients will begin with 1.5 mg/d at Visit 2; will be titrated to 3.0 mg/d at Visit 3 and then titrated to 4.5 mg/d at Visit 4. For the 26-week DB treatment period, patients will be supplied with identically appearing capsules of either cariprazine 4.5 mg/d, cariprazine 3.0 mg/d, or placebo.

Randomization: After completing the OL treatment period, eligible patients will be randomized in a 1:1:1 ratio to cariprazine 4.5 mg/d, cariprazine 3.0 mg/d, or placebo.

Visit Schedule: There are a total of up to 28 visits that comprise the Screening/washout and the OL treatment periods (Table 1) and the DB treatment and the SFU periods (Table 2).

Patients completing the maintenance of stability period with no more than one excursion outside the remission threshold range will be eligible for early randomization beginning at Week 14 (Visit 11) and will move forward to the DB treatment period without requiring all visits in the OL treatment period.

If no tolerability issues arise, all patients will receive at least 8 weeks of OL treatment. Some patients will be discontinued after 8 or 10 weeks if response threshold criteria or stability criteria, respectively, have not been achieved.

Study Population Characteristics

Number of Patients: Approximately 345 patients are planned to be randomized (115 per treatment arm). It is anticipated that approximately 1569 patients will be screened and 1035 patients will enter the OL treatment period. In the event that screening or randomization failure rates are higher than projected, enrollment will continue until approximately 115 patients per treatment arm are randomized.

Condition/Disease: Patients with schizophrenia

Key Inclusion Criteria: Male or female 18 to 64 years of age, inclusive; meeting DSM-5 criteria for schizophrenia, whose current psychotic episode is < 4 weeks in duration at Visit 1; and having a PANSS total score ≥ 70 and ≤ 120 at Visits 1 and 2, and a rating of at least 4 (moderate) on at least 2 of the following 4 PANSS positive symptoms; P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior, and P6: suspiciousness/persecution at Visits 1 and 2.

Key Exclusion Criteria: Patients currently meeting DSM-5 criteria for schizoaffective disorder, schizophreniform disorder, and other psychotic disorders; bipolar I and II disorder; autism spectrum disorder, intellectual development disorder, delirium, major/minor neurocognitive disorder.

Efficacy Measures

Primary efficacy parameter: Time to first relapse during the DB treatment period. Time to first relapse is defined as number of days from randomization to the first relapse.

Relapse is defined as the occurrence of any 1 of the following:

- Increase in PANSS total score by ≥ 30% for patients who had a PANSS total score of ≥ 50 at Randomization/Visit 13 or a ≥ 10-point increase in PANSS total score for patients who had a PANSS total score < 50 at Randomization/Visit 13
- Increase in CGI-S score by 2 or more points relative to Randomization/Visit 13

- Score of > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control
- Deliberate self-injury or aggressive/violent behavior
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator
- Psychiatric hospitalization due to worsening of the patient's underlying condition
- Exacerbation of psychiatric illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

Pharmacokinetics: Not Applicable

Pharmacogenetic Sampling: Blood samples will be collected at any timepoint between Visit 2/ Baseline and Visit 8/Week 8 to determine individual genotype status and for pharmacogenetic bio banking. Patient participation is optional.

Safety Assessments: Adverse events recording, clinical laboratory parameters (hematology, chemistry, urinalysis, prolactin), vital sign parameters (including orthostatic blood pressure, pulse rate), body mass index, weight, waist circumference, physical examinations, electrocardiograms, ophthalmological examinations, Columbia–Suicide Severity Rating Scale (C-SSRS), measures of extrapyramidal symptoms (EPS): Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and Simpson-Angus Scale (SAS).

General Statistical Methods and Types of Analyses:

The DB safety population will consist of all randomized patients who took at least 1 dose of DB IP. The DB intent-to-treat (DB ITT) population will consist of all patients in the DB safety population who had at least 1 post-randomization assessment of the PANSS or CGI-S scores during the DB treatment period of the study.

The primary efficacy analysis will compare the time to first relapse between each cariprazine group and the placebo group using the log-rank test for the DB ITT population. Estimates of the hazard ratio and 95% CIs will be based on the Cox proportional hazards model. The Kaplan-Meier estimates for cumulative distribution function of relapse rate for each treatment group will be provided.

The fixed-sequence testing procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. The comparison of cariprazine 4.5 mg/d versus placebo will be tested first at a 0.05 significance level, only when the testing is significant, the comparison of cariprazine 3.0 mg/d versus placebo will be tested.

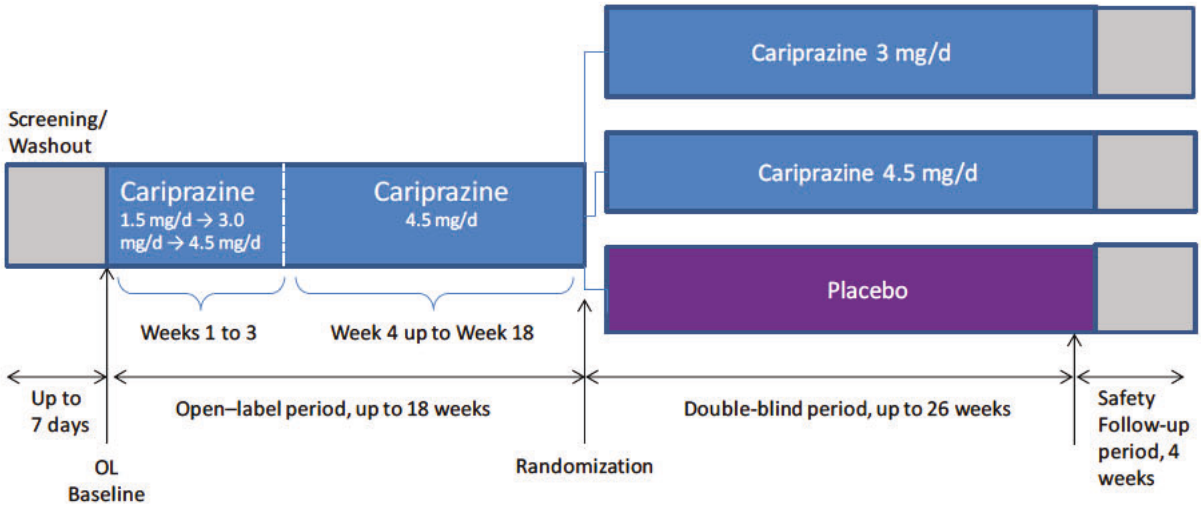
All safety parameters will be analyzed descriptively.

Sample Size Calculation:

The sample size and power calculations are based on the analysis of time to relapse in the DB treatment period to compare each cariprazine dose group versus placebo based on a log-rank test.

Based on the first 26 weeks' data from RGH-MD-06, the relapse hazard ratio is assumed to be 0.50, and cumulative relapse rate at Week 26 for the placebo group is 46%. In addition, the cumulative dropout rate due to reasons other than relapse at 26 weeks is assumed to be 20.0%. A total of approximately 103 in the DB treatment period need to be observed in order to have 85% power to detect a statistically significant difference between each cariprazine and placebo group, using two-tailed, log-rank tests at a 5% level of significance. The study should randomize approximately 345 patients, 115 patients each arm, to provide the required number of relapse events. Given the fixed-sequence testing strategy, the higher dose of 4.5 mg/d has 85% statistical power to show significance versus placebo, and the 3.0 mg/d dose, would also have an 85% power provided that testing for cariprazine 4.5 mg/d group is statistically significant. EAST 6.0 was used for power and sample size calculation.

Figure 1: Study Schematic



Note: Patients will receive open-label cariprazine dosed as 1.5 mg/d beginning at Visit 2 (Baseline); titrated to 3.0 mg/d at Visit 3 (end of Week 1), and then titrated to 4.5 mg/d at Visit 4 (end of Week 2). Patients will continue on the 4.5 mg/d dose for the remainder of the open-label treatment period.

Table 1: Schedule of Visits and Procedures—Screening/Washout and Open-label Treatment Periods

Study Period	Screening/Washout Period		Open-label Treatment Period										
Visit Number/Visit Title	**1/ Screening**	**2/ Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/End of OL**
End of Study Week (Day)	**Up to 7 days (Days -7 to -1)**	**0 (1)**	**1 (8)**	**2 (15)**	**3 (22)**	**4 (29)**	**6 (43)**	**8 (57)**	**10 (71)**	**12 (85)**	**14 (99)**	**16 (113)**	**18 (127)**
Visit Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Informed Consent	X												
Verified Clinical Trials check[a]	X												
Inclusion/Exclusion criteria	X	X											
Medical and psychiatric history	X												
SCID-5	X												
Hepatitis screen	X												
Urine drug screen/blood alcohol concentration by Breathalyzer	X												X
Serum pregnancy test[b]	X							X					X
Clinical laboratory tests	X							X					X
Hemoglobin A1c	X							X					X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
SCI-PANSS	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X	X	X
PSP		X						X					X
BACS		X											X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X
EPS assessment (AIMS/BARS/SAS)		X	X				X		X		X		X
Vital signs (including weight)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Screening/Washout Period**		**Open-label Treatment Period**										
Visit Number/Visit Title	**1/ Screening**	**2/ Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13/End of OL**
End of Study Week (Day)	**Up to 7 days (Days -7 to -1)**	**0 (1)**	**1 (8)**	**2 (15)**	**3 (22)**	**4 (29)**	**6 (43)**	**8 (57)**	**10 (71)**	**12 (85)**	**14 (99)**	**16 (113)**	**18 (127)**
Visit Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Waist circumference	X								X				X
Height	X												
Physical examination	X												
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X												X
Ophthalmological examination[d]	X												X[e]
Assessment of response threshold criteria[f]						X	X	X					
Assessment of stability criteria[g]							X	X	X				
Maintenance of stability[h]								X	X	X	X	X	X
Randomization criteria[i]											X	X	X
Randomization													X
Access IWRS for IP dispensing		X	X	X	X	X	X	X	X	X	X	X	X
IP Return: Compliance and Accountability			X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetic consent[j]	X	X	X	X	X	X	X	X					
Pharmacogenetic sampling[k]		X	X	X	X	X	X	X					

Note: Visit 2/Baseline is expected to occur within 7 days of Visit 1; if required, it may be conducted up to 3 days after the scheduled visit. If necessary, Visits 3 to 13 may be conducted up to 3 days before or after the scheduled visits. The visit windows for each scheduled visit are relative to Visit 2 for Visits 3 through 13.
AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BACS = Brief Assessment of Cognition in Schizophrenia; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression-Improvement scale; CGI-S = Clinical Global Impression-Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptoms; IP = investigational product; IWRS = interactive web response system; OL = Open-label; SCI-PANSS = Structured Clinical Interview for the Positive and Negative Syndrome Scale; PSP = Personal and Social Performance scale; SAE = serious adverse event; SAS = Simpson-Angus Scale; SCID-5 = Structured Clinical Interview for DSM-5.

[a] Verified Clinical Trials database check to be performed where applicable.

[b] For women of childbearing potential only.

[c] Blood pressure and pulse rate will be measured both standing and supine.

[d] The Screening ophthalmological examination must be completed prior to Visit 2/Baseline and the start of OL IP.

[e] For patients eligible for randomization, every attempt should be made to complete the Visit 13/End of OL ophthalmological examination on the same day as all other Visit 13/End of OL procedures. If the examination cannot be accommodated, it must occur within 7 days after randomization.

[f] Assess response threshold criteria beginning at Visit 6/Week 4 (per Section 4.5). Patients who do not meet response threshold criteria by Visit 8/Week 8 must be discontinued and will undergo procedures for Visit 26/early termination (ET) and subsequently complete the Safety follow-up (SFU) period.

[g] Assess patient for attainment of stability criteria (per Section 4.5). If response threshold criteria are met but are not confirmed at the subsequent visit (ie, stability is not attained), reassess patient for attainment of stability (reconfirmation of response threshold criteria) at the next visit. Patients not meeting the response threshold criteria following the excursion, must be discontinued. Patients who do not otherwise meet stability of response threshold criteria by Visit 9/Week 10 must be discontinued and will undergo procedures for Visit 26/ET and subsequently complete the SFU period.

[h] Assess PANSS and CGI-S during the 8-week period following achievement of stability to ensure that response threshold criteria continue to be met. During the 8 weeks, 1 excursion is allowed (see Section 4.5).

[i] Patients who have met stability of maintenance criteria (per Section 4.5) should be assessed for fulfillment of randomization criteria (per Section 4.6). Patients who meet randomization criteria should undergo Visit 13/End of OL procedures and be randomized to DB treatment. Patients eligible for early randomization will skip any remaining visits in the OL treatment period.

[j] Pharmacogenetic consent may be obtained at any time between Visit 1/Screening and Visit 8/Week 8.

[k] Pharmacogenetic sampling (one sample) may be obtained at any time between Visit 2/Baseline and Visit 8/Week 8.

Table 2: Schedule of Visits and Procedures—Double-blind Treatment Period

Study Period	Double-blind Treatment Period													Safety Follow-up	
Visit Number/ Visit Title	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26/ET**	**27**	**28[c]**
End of Study Week (Day)	**20 (141)**	**22 (155)**	**24 (169)**	**26 (183)**	**28 (197)**	**30 (211)**	**32 (225)**	**34 (239)**	**36 (253)**	**38 (267)**	**40 (281)**	**42 (295)**	**44 (309)**	**46 (323)**	**48 (337)**
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Serum pregnancy test[a]					X				X				X		X
Clinical laboratory tests					X				X				X		
Hemoglobin A1c					X				X				X		
IP dispensing	X	X	X	X	X	X	X	X	X	X	X	X			
IP Return: Compliance and Accountability	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SCI-PANSS	X	X	X	X	X	X	X	X	X	X	X	X	X		
BACS			X										X		
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-I	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSP			X				X						X		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X		
EPS assessment (AIMS/BARS/SAS)		X		X		X		X		X			X		
Assess relapse criteria	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital signs (including weight)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference						X							X		
Physical examination													X		

Study Period	Double-blind Treatment Period													Safety Follow-up	
Visit Number/ Visit Title	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26/ET**	**27**	**28[c]**
End of Study Week (Day)	**20 (141)**	**22 (155)**	**24 (169)**	**26 (183)**	**28 (197)**	**30 (211)**	**32 (225)**	**34 (239)**	**36 (253)**	**38 (267)**	**40 (281)**	**42 (295)**	**44 (309)**	**46 (323)**	**48 (337)**
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
ECG													X		
Ophthalmological examination[c]													X		(X)
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: If necessary, Visits 14 to 28 may be conducted up to 3 days before or after the scheduled visits. The visit windows for each scheduled visit are relative to Visit 13 for Visits 14 through 26/ET, and relative to Visit 26/ET for Visits 27 and 28.

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BACS = Brief Assessment of Cognition in Schizophrenia scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression-Improvement scale; CGI-S = Clinical Global Impression-Severity scale; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptoms; ET = early termination; IP = investigational product; SCI-PANSS = Structured Clinical Interview for the Positive and Negative Syndrome Scale; PSP = Personal and Social Performance scale; SAE = serious adverse event; SAS = Simpson-Angus Scale.

[a] For women of childbearing potential only.

[b] Blood pressure and pulse rate will be measured both standing and supine.

[c] Every attempt should be made to complete the Visit 26/ET ophthalmological examination on the same day as all other Visit 26 procedures. Any patients with a finding of cataracts at Visit 26/ET must be scheduled for a follow-up ophthalmological examination at Visit 28. The Visit 28 ophthalmological examination is only applicable to patients with a postbaseline finding of cataracts.

1 Background and Clinical Rationale

Schizophrenia is a common and severe, often disabling psychiatric illness of unknown etiology that is characterized by extreme disturbances of cognition and thought, affecting language, perception and sense of self. It is a chronic disorder typified by a life-long pattern of acute psychotic episodes superimposed upon chronically poor psychosocial adjustment (Silveira 2012; Owen 2016).

Symptoms of schizophrenia fall into 3 domains: positive symptoms (auditory hallucinations, disorganized or bizarre thoughts, delusions and irrational fears); negative symptoms (affective blunting, emotional withdrawal, anhedonia, poverty of speech and apathy); and cognitive dysfunction (symptoms ranging from impaired attention to abnormal executive function, as well as memory impairment, depression and/or anxiety) (Nuechterlein 2012). Positive symptoms appear to reflect an excess or distortion of normal functions, while negative symptoms reflect a diminution or loss of normal functions. All schizophrenic individuals experience positive symptoms, although not continuously. Negative symptoms are present in approximately one-third of all patients, with an especially high rate during first-episode psychosis (Miyamoto 2012; Foussias 2014). Cognitive dysfunction may present prior to positive and negative symptoms, and can change over time. These cardinal symptoms lead to social and occupational dysfunction, which inevitably have a profound effect on the family and the place of the affected individual in wider society.

Symptoms typically emerge in late adolescence or early adulthood and often persist throughout the rest of the patient's lifetime, resulting in significant disruption of the patients' life, as well as those of family members and friends (Schultz 2007). According to data from the World Health Organization's (WHO) Global Burden of Disease (GBD) study 2010, schizophrenia is the fifth most disabling mental/behavioral disorder, accounting for nearly 15,000 (0.6%) of a total of 2,490 billion disability-adjusted life years worldwide in that year (Murray 2013).

This disorder knows no ethnic, economic or cultural boundaries. According to the National Institute of Mental Health in the United States, approximately 1% of Americans have schizophrenia (Mental health information: Schizophrenia [National Institute of Mental Health 2015]). In the 2015 GBD study, there were approximately 23.4 million prevalent cases of schizophrenia worldwide (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016).

In addition to their psychiatric symptoms, patients with schizophrenia are at greater risk for medical comorbidities than is the general population. As a result, the mortality rate for

schizophrenia patients is 2 to 3 times higher than in the general population (Auquier 2007). According to the WHO 2010 GBD study, schizophrenia was the cause of 19,800 (range 16,600 to 25,000) deaths worldwide in 2010 (Lozano 2012).

Suicide is a major contributor to morbidity and mortality in patients with schizophrenia. It is estimated that approximately 10% to 15% of all schizophrenia patients eventually commit suicide, and up to 50% will attempt suicide at some point in their lifetime. In the United States, the suicide rate in patients with schizophrenia is about 8 to 13 times greater than that of the general population (Meltzer 2002).

Cariprazine is an orally active and potent dopamine (DA) D_3/D_2 receptor functional antagonist developed by Gedeon Richter Plc., and Allergan Sales, LLC. It is approved in the United States for the treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder. For schizophrenia, the starting dose is 1.5 mg/d with a recommended dose of 1.5 mg/d to 6 mg/d.

The chemical name of the hydrochloride salt of cariprazine is trans-N-{4-[2-[4- (2,3-dichlorophenyl)-piperazine-1-yl]-ethyl]-cyclohexyl}-N',N'-dimethylurea hydrochloride. Its molecular formula is $C_{21}H_{32}Cl_2N_4O$ HCl; its molecular weight is 463.87. Desmethyl and didesmethyl cariprazine have been identified as circulating plasma metabolites. The receptor-binding profile of these 2 metabolites is similar to that of cariprazine.

Cariprazine also has considerable affinity for, and is a partial agonist and antagonist at, the serotonin 5-HT1A and 5-HT2B receptors, respectively. Antidepressant- and/or anxiolytic-like effects of cariprazine may also be mediated through these receptors.

Cariprazine has low potency at other receptor sites, such as the 5-HT2C, histamine H1, and adrenergic receptor sites, suggesting a lower potential for side effects such as extrapyramidal symptoms (EPS) and body weight gain. Cariprazine displays potent in vivo oral activity in various animal models of psychosis and mania and shows antidepressant- and anxiolytic-like activity as well as procognitive-like effects.

Discussion of Study Design, Including the Choice of Control Groups

In a previously conducted randomized withdrawal trial (RGH-MD-06), cariprazine 3 to 9 mg/d was shown to reduce time to relapse when compared to placebo. In RGH-MD-06, patients were initially treated with cariprazine 3 to 9 mg/d during a 20-week open-label period and then randomized to continue cariprazine (3 to 9 mg/d) or placebo, for up to 72 additional weeks or until relapse. The purpose of this study is to evaluate the efficacy and

safety of cariprazine at a target dose of 4.5 mg/d compared with placebo in prevention of relapse in patients with schizophrenia. Additionally, the study will 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 schizophrenia who were initially stabilized on a target dose of 4.5 mg/d.

The placebo-controlled, randomized withdrawal design is considered standard to demonstrate effectiveness of long-term maintenance treatment.

Up to 18 weeks of open-label (OL) treatment are included to allow patients to have enough time to achieve and maintain stability of symptoms following continuation of treatment at the established dose.

Another feature of this study design is to evaluate if a dose-reduction paradigm can be utilized in the maintenance treatment of schizophrenia. The common clinical management of schizophrenia is to treat a patient with an established dose until stability of symptoms is achieved. Once stability has been achieved, the same dose that was used to achieve stability is typically continued during the maintenance treatment of the illness. This study will attempt to address the question of whether a dose lower than the one used to achieve stability of symptoms can be used to maintain a therapeutic response and prevent relapse.

The double-blind (DB) design is included to minimize systematic bias resulting from the scale raters, patients, or investigator knowing the treatment being administered. Randomization at the beginning of the DB treatment period is expected to minimize patient selection bias and increase Baseline comparability of the 2 treatment groups.

The use of placebo control is critical to the study design both to understand the safety findings of the drug and to ensure that efficacy results can be interpreted. In this study, the placebo control is used during the DB treatment period to demonstrate the reemergence of symptoms of schizophrenia upon withdrawal of cariprazine compared with patients who continue cariprazine treatment. Patients who continue cariprazine treatment should maintain improvement in their schizophrenia symptoms for a longer period of time when compared to those switched to placebo. Patients switched to placebo should have an earlier return of symptoms of schizophrenia.

The fixed-dose design during the DB treatment period was selected to maintain patients at the cariprazine dose level at which their symptoms of schizophrenia had responded. The dose selected, 4.5 mg/d, represents a dose that has been proven to be efficacious in schizophrenia while minimizing side effects. The lower dose during the DB treatment period was

determined following an FDA request to include doses lower than those used to achieve a response in the acute phase, while maintaining a dose within the approved range for that indication (1.5 to 6.0 mg/d). If both doses prove to be effective in preventing relapse, an evaluation will be made to see if a lower dose also achieves better tolerability during the maintenance phase of treatment.

The duration of the DB treatment period, with a maximum of 26 weeks, was selected to provide sufficient time to demonstrate schizophrenia relapse upon withdrawal of cariprazine. The 4-week safety follow-up (SFU) period allows continued patient monitoring after investigational product (IP) has been discontinued.

2 Study Objectives and Clinical Hypotheses

2.1 Study Objectives

1) To evaluate the efficacy and safety of cariprazine at a target dose of 4.5 mg/d compared with placebo in prevention of relapse in patients with schizophrenia; 2) 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 schizophrenia who were initially stabilized on a target dose of 4.5 mg/d.

2.2 Clinical Hypotheses

1) In patients with schizophrenia, cariprazine at 4.5 mg/d is safe and effective in preventing relapse when compared to placebo;

2) In patients with schizophrenia who were initially stabilized on a target dose of 4.5 mg/d, cariprazine at 3.0 mg/d is safe and effective in preventing relapse when compared to placebo.

3 Study Design

Structure: This is a multicenter, multinational, DB, placebo-controlled, randomized-withdrawal study evaluating the safety and efficacy of cariprazine compared with placebo in the prevention of relapse in patients with schizophrenia. The study schematic is presented in Figure 1.

3.1 Screening/Washout Period

Patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for schizophrenia will undergo a Screening/washout period of up to 7 days,

during which consent, assessment of eligibility, and withdrawal of prior psychiatric and prohibited medications will occur. The length and timing of the washout of prior psychiatric medications during the 7 days allotted for the Screening period is at the discretion of the investigator. Prior medications should be gradually withdrawn such that the washout is completed by Visit 2/Baseline. Please note that during the screening/washout period, psychotropic medications, other than those listed as rescue (Section 4.8.3), may not be newly initiated or reinstated. In order to ensure the safe transition of patients into the study, based upon the clinical judgment of the investigator, patients may be hospitalized during initiation of the study. This hospitalization can be for up to 14 days during the Screening and OL periods (with the end of hospitalization no later than Visit 3 [Day 8] of the OL treatment period). This 14-day allowance for hospitalization may include all or part of the Screening period. Hospitalization beyond the initial 14 days allowed will require consultation with the medical monitor. Following the protocol-allowed 14 days of hospitalization (and any sponsor-allowed extension), patients should be treated as outpatients.

3.2 Open-label Treatment Period

Patients who continue to meet eligibility criteria at Visit 2/Baseline will enter an OL treatment period for up to 18 weeks. Patients will receive OL cariprazine dosed as 1.5 mg/d beginning at Visit 2; titrated to 3.0 mg/d at Visit 3 and then titrated to 4.5 mg/d at Visit 4. Following the dose increase to 4.5 mg/d, if there are significant tolerability issues, the investigator should utilize rescue medications as clinically appropriate. If further tolerability issues arise, a temporary drug holiday up to 3 days, will be allowed. The date and reason for any holiday will be recorded on the appropriate page of the electronic case report form (eCRF). Patients who are unable to tolerate the 4.5 mg/d dose will be discontinued. Patients, who are able to tolerate the dose will continue on the 4.5 mg/d dose for the remainder of the OL treatment period.

Beginning at Week 4 (Visit 6), patients will be assessed for response to the initial treatment with cariprazine. For the purposes of this protocol, response threshold will be defined as meeting all of the following criteria on or after Week 4 (Visit 6):

- Positive and Negative Syndrome Scale (PANSS) total score ≤ 60, and
- ≥ 20% decrease in PANSS total score from Visit 2/Baseline, and

- Score of ≤ 4 on each of the following 7 PANSS items:
    - P1: delusions
    - P2: conceptual disorganization
    - P3: hallucinatory behavior
    - P6: suspiciousness/persecution
    - P7: hostility
    - G8: uncooperativeness
    - G14: poor impulse control; and
- Clinical Global Impression-Severity (CGI-S) ≤ 4, and
- No significant tolerability issues as judged by the investigator

Once a patient achieves the response threshold criteria, he/she will be evaluated at the subsequent visit to determine if the response criteria will be met again. Reconfirmation of response threshold criteria at either the visit following first attainment of response threshold or, in the event of an excursion, at the second visit following first attainment, will be defined as *stability*. One clinical excursion outside of the response threshold range is allowed between the first attainment of response threshold criteria and the subsequent confirmation of it (ie, stability). Following the excursion, patients not meeting response threshold criteria must be discontinued.

Once stability has been achieved, patients must continue to meet the response threshold criteria for an additional 8 weeks (ie, maintenance of stability) to qualify for randomization. During the maintenance of stability period, one excursion outside the response threshold criteria will be allowed. The excursion may occur at any time during the 8-week period with the exception of Visit 13/End of OL, but must be followed by a return to response threshold at the next visit. In the event the excursion occurs in a patient's 8th week of stability, but prior to Visit 13/End of OL, the patient should be assessed at the following scheduled visit to confirm whether randomization criteria have been met.

Patients who do not meet the response threshold criteria by Week 8 (Visit 8) or stability criteria by Week 10 (Visit 9) will be discontinued. Additionally, patients who at any time require either hospitalization (excluding protocol-allowed hospitalization during

Screening/OL periods for the purpose of washout of prior psychiatric medications) or initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator will be discontinued.

During the 8-week maintenance of stability period, patients who meet any of the following will be discontinued and will subsequently enter the SFU period:

- PANSS total score increases by ≥ 30% relative to Visit 2/Baseline, or
- Score > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control, or
- Have an increase in CGI-S score by 2 or more points relative to Visit 2/Baseline

3.3 Double-blind Treatment Period

Open-label patients who are able to maintain the response threshold criteria for 8 weeks with no more than 1 excursion of response threshold criteria will be randomized 1:1:1 to receive cariprazine at the same dose (4.5 mg/d), a reduced dose (3.0 mg/d), or placebo for up to 26 weeks. Patients will continue to receive study treatment until a relapse event occurs or until completion of the 26 weeks of randomized treatment.

Relapse is defined as the occurrence of any 1 of the following:

- Increase in PANSS total score by ≥ 30% for patients who had a PANSS total score of ≥ 50 at Randomization/Visit 13 or a ≥ 10-point increase in PANSS total score for patients who had a PANSS total score < 50 at Randomization/Visit 13
- Increase in CGI-S score by 2 or more points relative to Randomization/Visit 13
- Score of > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control
- Deliberate self-injury or aggressive/violent behavior

- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator

- Psychiatric hospitalization due to worsening of the patient's underlying condition

- Exacerbation of psychiatric illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

3.4 Safety Follow-up Period

Patients who complete the study, or who prematurely discontinue from either the OL or DB treatment periods will be followed for 4 more weeks and will have 2 evaluations for safety assessments at Visits 27 and 28 during the SFU period. During the SFU period, patients will continue as outpatients and will receive treatment as usual at the discretion of the investigator or designee. Patients will not receive IP during the SFU period.

4 Study Population and Entry Criteria

4.1 Number of Patients

Approximately 345 patients are planned to be randomized (115 per treatment arm). It is anticipated that approximately 1569 patients will be screened and 1035 patients will enter the OL treatment period. In the event that screening or randomization failure rates are higher than projected, enrollment will continue until approximately 115 patients per treatment arm are randomized.

4.2 Study Population Characteristics

The study population will include patients with schizophrenia whose diagnosis is based upon *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria, approached through a structured clinical interview (Structured Clinical Interview for DSM-5 [SCID-5] First 2015).

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent has been obtained.
2. Patients are male or female, 18 to 64 years of age, inclusive.
3. Patient meets DSM-5 criteria for schizophrenia as determined by SCID-5.
4. Diagnosis of schizophrenia for a minimum of 1 year before Visit 1.
5. Current psychotic episode < 4 weeks duration at Visit 1.
6. PANSS total score ≥ 70 and ≤ 120 at Visit 1 and Visit 2.
7. Rating of at least 4 (moderate) on at least 2 of the following 4 PANSS positive symptoms; P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution at Visit 1 and Visit 2.
8. Normal physical examination results, vital signs, clinical laboratory test results, and electrocardiogram (ECG) results or abnormal results that are judged not clinically significant by the investigator.
9. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, written authorization for use and release of health and research study information [US sites] and written data protection consent [EU sites]).
10. Ability to follow study instructions, complete study assessment tools with minimal assistance and no alteration to the assessment tools, and likely to complete all required visits.
11. Continue to meet all Visit 1 (Screening) inclusion criteria at Visit 2 (Baseline); to be assessed at Visit 2.
12. Each patient must have an identified external contact person or an identified responsible person (eg, family member, friend, social worker, case worker, or nurse) who is considered reliable by the investigator and who will provide support to the patient and act as an external contact in the event the site is having difficulty reaching the patient during the trial and to ensure observation of patient's well-being.

13. Male and female patients must agree to use a medically acceptable and highly effective method of birth control during the course of the entire study and for 12 weeks after the last dose of investigational product, as defined in Section 4.8.1.

14. Negative qualitative serum β-human chorionic gonadotropin (β-hCG) pregnancy test (women of childbearing potential only).

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

Psychiatric Criteria

1. Currently meeting DSM-5 criteria for any of the following:

    - Schizoaffective disorder, schizophreniform disorder, and other psychotic disorders
    - Bipolar I and II disorder
    - Autism spectrum disorder, intellectual development disorder, delirium, major/minor neurocognitive disorder

2. History of meeting DSM-5 criteria for substance-related disorders (ie, use disorders except caffeine- and tobacco-related) within the prior 3 months before Visit 1.

3. Positive result at Visit 1 from the urine drug screen (UDS). Patients with a positive UDS at Visit 1 for opiates, cannabinoids, amphetamines, barbiturates, or benzodiazepines may be enrolled if all of the following are satisfied:

    a) The drug was used for a legitimate medical purpose;

    b) The drug can be discontinued prior to participation in the study (except for benzodiazepines which may be continued if the patient has been taking a stable dose [ie, lorazepam up to 2 mg/d or its benzodiazepine equivalent] for at least 1 month prior to Visit 1 or if used as rescue during washout); and

    c) A repeat UDS must be performed prior to Visit 2 and must be negative, except benzodiazepine use as described 3(b).

4. History of intolerance or hypersensitivity to cariprazine or allowed rescue medications.

5. The patient is at imminent risk of injuring self or others or causing significant damage to property, as judged by the investigator.

6. The patient represents a suicide risk, as determined by meeting any of the following criteria:

    a) Patient made a suicide attempt within the past one year before Visit 1

    b) Significant risk, as judged by the investigator, based on the psychiatric interview or information collected in the C-SSRS at Visit 1 (Screening) or Visit 2 (Baseline)

Treatment-Related Criteria:

7. Patient received treatment with depot antipsychotic within 2 cycles prior to Visit 1.

8. Patient received treatment with clozapine doses > 50 mg/d in the past 2 years.

9. Patients requiring concomitant treatment with a moderate or strong cytochrome P450 (CYP) 3A4 inhibitors or CYP3A4 inducers. If applicable, these drugs must be discontinued 7 days prior to Visit 2/Baseline.

10. Patient requires concomitant treatment with any prohibited medication, supplement, or herbal product including any psychotropic drug or any drug with psychotropic activity or with a potentially psychotropic component (for exceptions allowed for concomitant treatments, refer to Section 4.8).

11. At Visit 2, patient requires pharmacologic treatment for the control of EPS.

12. Prior participation in any clinical trials involving experimental or investigational drugs within 6 months before Visit 1 or planned during the study.

Other Medical Criteria:

13. Female patients who are pregnant, planning to become pregnant during the course of the study, or are currently lactating.

14. Any concurrent medical condition including psychiatric symptoms possibly secondary to any other general medical condition (eg, Vitamin B-12/folate deficiency, Cushing syndrome, etc) that, in the judgment of the investigator, might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the patient's well-being.

15. Any cardiovascular disease (eg, hypertension) or endocrinological disease (eg, thyroid disease/disorders) that is clinically unstable, or decompensated, based on the investigator's judgment.

16. Gastric bypass or any condition that would be expected to affect drug absorption (lap band procedures and gastric sleeve are acceptable if there is no problem with absorption).

17. History of seizure disorder (with the exception of febrile seizure), stroke, significant head injury, tumor of the central nervous system, or any other condition that predisposes toward a risk of seizure.

18. Patients who meet any of the following ophthalmological criteria:

    a. A clinically significant finding of lens opacification(s) at the screening ophthalmological examination that meets any of the following:

        1. Opacification ≥ AREDS standard photo #2

            OR

        2. Best-corrected visual acuity worse than LogMar 0.1 [20/25 Snellen equivalent]

            OR

        3. Cataract surgery is planned or expected at anytime during the trial, based upon the ophthalmological examination.

    b. 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

    c. History or current findings of ocular disease (eg, open- or narrow-angle glaucoma, retinopathies, corneal diseases)

    d. History of amiodarone or systemic corticosteroid use for ≥ 3 consecutive months in the past year

e. Intraocular pressure of > 21 mm Hg in either eye

f. Unable to dilate pupil to at least 5 mm in either eye

19. Allergies to dilating drops, optic medications, or topical ocular anesthetics that are to be used in the ophthalmological examination.

20. Known human immunodeficiency virus infection.

21. Positive hepatitis C antibody on screening.

22. Positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M on screening.

23. Screening liver enzyme test (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) results > 2 × the upper limit of normal (ULN) or total bilirubin > 1 × ULN.

24. Absolute neutrophil count < 1000 per mm^3 at screening.

25. Hemoglobin A1c (HbA1c) > 7% at screening.

26. Blood alcohol concentration ≥ 0.02 g/dL at Visit 1 as measured by breathalyzer.

27. History of tardive dyskinesia (except for mild cases attributed to use of conventional agents), serotonin syndrome, or neuroleptic malignant syndrome.

Other Criteria:

28. Employee, or immediate relative of an employee, of the sponsor, any of its affiliates or partners, or the study center.

29. Inability to speak, read, or understand the local language sufficiently to understand the nature of the study, to provide signed written informed consent, or to allow the completion of all study assessments.

30. Unable or unlikely to comply with the study protocol or unsuitable for any other reason, as judged by the investigator.

4.5 Response Threshold, Stability, and Maintenance of Stability Criteria During the OL Treatment Period

Response threshold is defined as meeting all of the following criteria on or after Week 4 (Visit 6):

- PANSS total score ≤ 60, and
- ≥ 20% decrease in PANSS total score from Visit 2/Baseline, and
- Score of ≤ 4 on each of the following 7 PANSS items:
    - P1: delusions
    - P2: conceptual disorganization
    - P3: hallucinatory behavior
    - P6: suspiciousness/persecution
    - P7: hostility
    - G8: uncooperativeness
    - G14: poor impulse control; and
- CGI-S ≤ 4
- No significant tolerability issues as judged by the investigator

Note: Patients who do not meet the response threshold criteria by Week 8 (Visit 8) will be discontinued and undergo early termination (ET) procedures and subsequently complete the SFU period.

Stability is the reconfirmation of response threshold criteria at either the visit following first attainment of response threshold or, in the event of an excursion, at the second visit following first attainment. One clinical excursion outside of the response threshold range is allowed between the first attainment of response threshold criteria and the subsequent confirmation of it (ie, stability). Following the excursion, patients not meeting response threshold criteria must be discontinued and undergo ET procedures and subsequently complete the SFU period.

Note: Patients who do not meet stability criteria by Week 10 (Visit 9) will be discontinued and undergo ET procedures and subsequently complete the SFU period.

Maintenance of stability criteria: Once stability has been attained, patients must continue to meet response threshold criteria for 8 additional weeks. One excursion of response threshold is allowed during the 8-week period, provided that it does not occur at Visit 13/End of OL. If an excursion occurs, the response threshold criteria must be met at the subsequent visit. Patients not meeting response threshold criteria at the visit following an excursion must be discontinued and undergo ET procedures and subsequently complete the SFU period.

Note: If any of the following occurs after stability has been established (ie, during the 8-week maintenance of stability period), the patient is to be discontinued:

- PANSS total score increases by ≥ 30% relative to Visit 2/Baseline; or
- Score is > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/ persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control; or
- CGI-S score increases by 2 or more points relative to Baseline/Visit 2; or
- Hospitalization is required (excluding protocol-allowed hospitalization during Screening/OL periods for the purpose of washout of prior psychiatric medications); or
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator

4.6 Randomization Criteria

Randomization requirements are:

- Ability to safely tolerate cariprazine 4.5 mg/d
- Maintenance of response threshold criteria for 8 weeks following attainment of stability:
  - PANSS total score ≤ 60; and
  - ≥ 20% decrease in PANSS total score from Visit 2/Baseline; and

- Score of ≤ 4 on each of the following 7 PANSS items:
  - P1: delusions
  - P2: conceptual disorganization
  - P3: hallucinatory behavior
  - P6: suspiciousness/persecution
  - P7: hostility
  - G8: uncooperativeness
  - G14: poor impulse control; and
- CGI-S ≤ 4

4.7 Relapse Criteria During the Double-blind Treatment Period

After randomization, relapse is defined as the occurrence of any 1 of the following:

- Increase in PANSS total score by ≥ 30% for patients who had a PANSS total score of ≥ 50 at Randomization/Visit 13 or a ≥ 10-point increase in PANSS total score for patients who had a PANSS total score < 50 at Randomization/Visit 13
- Increase in CGI-S score by 2 or more points relative to Randomization/Visit 13
- Score of > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control
- Deliberate self-injury or aggressive/violent behavior
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator
- Psychiatric hospitalization due to worsening of the patient's underlying condition
- Exacerbation of psychiatric illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

4.8 Permissible and Prohibited Medications/Treatments

4.8.1 Permissible Medications/Treatments

Treatment considered necessary for the patient's welfare may be given at the discretion of the investigator. Prohibited and allowed rescue medications are detailed in Sections 4.8.2 and 4.8.3. If the permissibility of a specific medication/treatment is in question, please contact the medical monitor.

Definition of Females of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods:
For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (eg, hysterectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause.

For women of childbearing potential who may participate in the study, and are not exclusively homosexual, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant, ring) with barrier method (eg, condom, diaphragm), or condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or sexual abstinence.

For males who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: post-bilateral vasectomy, barrier contraception, or sexual abstinence.

The investigator and each patient will determine the appropriate method of contraception for the patient during their participation in the study. The investigator must discuss with the participant the need to continue contraceptive use for 12 weeks after the last dose of study drug.

If a female becomes pregnant during the study, the investigator will notify the sponsor immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient’s physician that the patient was being treated with cariprazine, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

4.8.2 Prohibited Medications/Treatments

Medications that are moderate or strong CYP3A4 inhibitors or inducers are not allowed. Patients taking moderate (eg, erythromycin, fluconazole) or strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, clarithromycin) or inducers (eg, rifampin, carbamazepine), will need to have medications discontinued 7 days prior to the start of OL IP dosing with cariprazine. Patients who cannot or should not be taken off of the CYP 3A4 inhibitor or inducer should not be enrolled. If a patient requires sustained concomitant treatment with either a moderate or strong CYP3A4 inhibitor or with a CYP3A4 inducer at any time during the study, he/she must be discontinued.

Any psychotropic drug or any drug/treatment with psychotropic activity or with a potentially psychotropic component (including medications, supplements and herbal medications) is prohibited, other than what is listed under rescue medications.

Psychotropic medications include the following:

- Antipsychotics/neuroleptics
- Antidepressants (including monoamine oxidase-B inhibitors)
- Stimulants
- Anticonvulsants/mood stabilizers
- Sedative/hypnotics/anxiolytics
- Dopamine-releasing drugs or dopamine agonists
- Psychotropic drugs not otherwise specified (including herbal products)
- Phenazepam

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

Patients will be asked to abstain from drinking alcohol during the study.

Patients who have been taking stable doses of benzodiazepines (lorazepam up to 2 mg/d or equivalent) for at least 1 month before screening can continue use.

4.8.3 Rescue Medications

Medically appropriate episodic use (up to 3 consecutive days) of narcotic analgesics for acute medical indications (eg, tooth extraction) is allowed during the study.

4.8.3.1 Insomnia

The following will be allowed but should not be prescribed prophylactically:

- Zolpidem (maximum of 10 mg/d)
- Zolpidem extended release (maximum of 12.5 mg/d)
- Zaleplon (maximum of 20 mg/d)
- Eszopiclone (maximum of 3 mg/d)
- Zopiclone (maximum of 7.5 mg/d)
- Chloral hydrate (maximum of 1000 mg/d) may be used acutely with approval from the medical monitor
- Suvorexant (maximum of 20 mg/d)

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

4.8.3.2 Extrapyramidal Symptoms or Akathisia

The following will be allowed but should not be prescribed prophylactically:

For EPS or akathisia that emerge or worsen during the study, the rescue medications listed below will be allowed. However, each of the 3 EPS scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson-Angus Scale [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 (eg, 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.

4.8.3.3 Agitation, Restlessness, and Hostility

Episodic use of lorazepam up to 2 mg/d (or equivalent benzodiazepine) and for up to 3 consecutive days at a time is allowed for agitation, restlessness, and hostility.

The medication use and events of 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.

5 Study Treatments

5.1 Study Treatments and Formulations

Capsules containing 1.5 mg of cariprazine (for up-titration only), 3.0 mg of cariprazine, and 4.5 mg of cariprazine.

5.2 Control Treatment

Matching placebo capsules.

5.3 Methods for Masking/Blinding

There will be no blinding during the OL treatment period of the study.

During the DB treatment 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.

5.4 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of study treatment, each patient who provides informed consent will be assigned a patient number that will serve as the patient identification number (PID) on all study documents for the duration of the study.

At the time of randomization, eligible patients will be randomly assigned to 1 of 3 treatment arms in a 1:1:1 ratio to receive cariprazine 4.5 or 3.0 mg/d, or placebo.

An automated interactive web response system (IWRS) will be used to manage IP dispensing during the OL treatment period of the study. IWRS will also be used for randomization and DB treatment assignment. Allergan Statistical Programming (randomization programmer) will prepare the randomization codes.

IP will be labeled with medication kit numbers. The IWRS will provide the site with the specific medication kit number(s) for each patient in the OL and DB treatment periods. Sites will receive the IWRS confirmation notifications for each transaction. All notifications will be maintained with the study source documents.

5.5 Treatment Regimen and Dosing

Table 3: Treatment Regimen and Dosing

Drug/Dose	Investigational Product Frequency	Route of Administration
Open-Label Treatment Period: Week 1 (IP dispensed at Visit 2/Baseline)		
Cariprazine 1.5 mg	Once daily	Oral (capsule)
Open-Label Treatment Period: Week 2 (IP dispensed at Visit 3)		
Cariprazine 3.0 mg	Once daily	Oral (capsule)
Open-Label Treatment Period: Weeks 3 through 18 (IP dispensed at Visits 4 through 12)[a]		
Cariprazine 4.5 mg	Once daily	Oral (capsule)
Double-Blind Treatment Period: Weeks 19 through 44 (IP dispensed at Visits 13 through 25)		
Placebo	Once daily	Oral (capsule)
Cariprazine 3.0 mg	Once daily	Oral (capsule)
Cariprazine 4.5 mg	Once daily	Oral (capsule)

All investigational products 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.

eCRF = electronic case report form; IP = investigational product; OL = open-label.

[a] Patients who meet randomization criteria (Section 4.6) on or after Week 14 are eligible for early randomization and will skip any remaining visits in the OL treatment period

5.6 Treatment Compliance

Investigational product compliance will be closely monitored by counting the number of capsules dispensed and returned, and through patient interview. Before dispensing new IP, study center personnel will make every effort to collect all unused IP and empty blister cards. Patients who take less IP or more IP than the prescribed regimen, must be counseled on the importance of taking study medication as instructed. If a patient demonstrates poor compliance during the study (< 80% or > 120% overall), the investigator should evaluate whether the patient should be discontinued from the study.

Any patient who misses ≥ 4 consecutive doses of IP must be discontinued from the study.

The study centers will keep an accurate drug disposition record that specifies the amount of IP dispensed to each patient and the date of dispensing.

5.7 Storage of Study Medications/Treatments

All IP will be packaged in blister cards and provided by Allergan Sales, LLC. Investigational product must be stored in an appropriate secure area (eg, a locked cabinet in a locked room) at room temperature (25°C or 77°F, with a permitted range of 15°C to 30°C or 59°F to 86°F) and must be protected from heat, moisture, and light.

6 Response Measures and Summary of Data Collection Methods

6.1 Diagnostic Assessments

The Structured Clinical Interview for DSM-5 is a semi-structured interview guide for making the major DSM-5 diagnoses (formerly diagnosed on axis I). This clinician-rated diagnostic assessment will be administered by the investigator, subinvestigator, or rater who has extensive professional training and experience in the diagnosis of mental illness. The SCID-5 will be considered a source document for this study.

6.2 Efficacy Assessments

The primary efficacy parameter is the time to first relapse during the DB treatment period. Time to first relapse is defined as the number of days from randomization to the first relapse.

6.2.1 Primary Efficacy Assessments

Assessment and ratings of efficacy scales will be performed by a trained rater. Every effort should be made to have patients assessed by the same rater at each scheduled timepoint.

6.2.1.1 Structured Clinical Interview for the Positive and Negative Syndrome Scale

The SCI-PANSS (SCI-PANSS Scoring Sheet in Attachment 12.2) is a 30-item rating scale specifically developed to assess both the positive and negative symptom syndromes of patients with schizophrenia (Kay 1987). The PANSS total score is rated based on a structured clinical interview with the patient and supporting clinical information obtained from family, hospital staff, or other reliable informants. This assessment provides scores in 9 clinical domains, including a positive syndrome, a negative syndrome, depression, a composite index, and general psychopathology. Each item is scored on a 7-point (1 to 7) scale.

6.2.1.2 Clinical Global Impressions–Severity

The CGI-S (Guy 1976) is a clinician-rated scale that measures the overall severity of a patient's illness in comparison with the severity of other patients the physician has observed (Attachment 12.3). The patient is rated on a scale from 1 to 7 with 1 indicating a "normal state" and 7 indicating "among the most extremely ill patients."

The CGI-S will be administered by a trained rater with extensive professional training and experience in assessing mental illness.

6.2.2 Additional Efficacy Assessments

Assessment and ratings of efficacy scales will be performed by a trained rater. Every effort should be made to have patients assessed by the same rater at each scheduled timepoint.

6.2.2.1 Clinical Global Impressions–Improvement

The Clinical Global Impressions–Improvement (CGI-I) scale (Guy 1976) is a clinician-rated scale that in this study will be used to rate total improvement or worsening of mental illness relative to Visit 2, regardless of whether the investigator considers it to be a result of drug treatment or not (Attachment 12.4). The patient will be rated on a scale from 1 to 7, with 1 indicating that the patient is very much improved and 7 indicating that the patient is very much worse.

The CGI-I will be administered by a trained rater with extensive professional training and experience in assessing mental illness.

6.2.2.2 Personal and Social Performance Scale

The Personal and Social Performance scale (PSP) is a 100-point, single-item, clinician-rated scale, which is subdivided into 10 equal intervals (Morosini 2000) (Attachment 12.9). The ratings are based mainly on the assessment of functioning in the following 4 domains: (a) socially useful activities, including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors. Ratings from 71 to 100 show mild difficulties; from 31 to 70 reflect manifest disabilities of various degrees, while ratings from 1 to 30 reflect functioning so poor that intensive support or supervision is needed.

The PSP will be administered by a trained rater with extensive professional training and experience in assessing mental illness.

6.2.2.3 Brief Assessment of Cognition in Schizophrenia

The Brief Assessment of Cognition in Schizophrenia (BACS) assesses the aspects of cognition noted to be most impaired and most strongly correlated with outcome in patients with schizophrenia (Keefe 2003). The BACS requires less than 35 minutes to complete in patients with schizophrenia. The BACS measures verbal memory, working memory, motor speed, verbal fluency, attention and speed of information processing, and executive functions.

6.3 Pharmacokinetics Measures

Not applicable.

6.4 Pharmacogenetic Sampling

Pharmacogenetic sampling is to be conducted only at study centers where the institutional review board (IRB)/independent ethics committee (IEC) has approved the pharmacogenetic portion of the study. Participation in the pharmacogenetic portion of the study is optional and will require a separate informed consent form (ICF). The pharmacogenetic ICF must be signed before the pharmacogenetic blood sample is taken. Pharmacogenetic consent may be obtained at any time between Visit 1/Screening and Week 8 (Visit 8). Pharmacogenetic sampling can be conducted at any timepoint between Visit 2/Baseline and Week 8 (Visit 8). Following consent, a blood sample will be collected to determine individual genotype status

and for pharmacogenetic bio banking. The genetic material from the blood sample will be used to study factors which may influence how patients respond to a drug or may explain the pathophysiology of the disease. Blood samples will be stored to provide a resource for potential future trials conducted by Allergan.

All pharmacogenetic samples collected will be sent to the designated central laboratory and later shipped to a biorepository for storage. Please refer to the laboratory manual for the pharmacogenetic blood sampling procedures, sample anonymization, shipping instructions, and contact information. Anonymized pharmacogenetic samples may be stored at the biorepository for potential analysis under separate protocols for up to 15 years. Samples may be stored for a longer time if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, such samples will be stored until these questions have been adequately addressed.

A patient who initially consents can withdraw that consent at any time and have his or her pharmacogenetic sample destroyed, including any by-products of the sample.

6.5 Safety Measures

Patients must be evaluated by a physician or an appropriately trained healthcare professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits shown in Table 1 and Table 2 (Schedules of Visits and Procedures).

6.5.1 Adverse Events

Adverse events (AEs) will be collected throughout the study. For all AEs, the investigator must provide an assessment of the severity, causal relationship to the IP, start and stop date, and seriousness of the event (eg, serious adverse event [SAE]), document all actions taken with regard to IP, and detail any other treatment measures taken for the AE. For events noted as SAEs, Allergan must be notified immediately to meet their reporting obligations to appropriate regulatory authorities (see Section 9.3).

6.5.2 Ocular Adverse Events of Special Interest

The sponsor is required to perform expedited reporting to worldwide regulatory authorities of ocular AESIs that meet specific criteria. Therefore, the sponsor must be notified immediately regarding any ocular AESIs that occur after informed consent is obtained.

The following serious and non-serious ocular AESIs require immediate notification:

- 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
- Color vision decrease, abnormality or change

Within 24 hours of learning of any serious or non-serious AESIs, the study site personnel must report the event on the SAE/AESI form for clinical trials.

*NOTE: When determining whether to report an event as a cataract, please take into consideration the AREDS scoring of that lens opacity. Only those changes that have reached the threshold of *equal to or greater than AREDS standard photo #2* should be reported as a cataract.

In addition to completing the appropriate form, the medical monitor may also be notified by telephone.

All ocular AESIs are to be followed by the study staff until resolution or until the ocular AESI is deemed stable. The sponsor may contact the study site to solicit additional information or follow-up on the event.

6.5.3 Clinical Laboratory Determinations

Clinical laboratory tests will be performed according to the schedules in Table 1 and Table 2. Patients will be asked to fast for at least 10 hours prior to any visits requiring clinical laboratory testing. Table 4 presents the schedule of clinical laboratory tests to be performed during this study.

Table 4: Schedule of Clinical Laboratory Tests

Category	Visit Number(s)	Parameters
Hepatitis Screening	1	Hepatitis C virus antibody, hepatitis B surface antigen, and hepatitis B core antibody total. Reflex hepatitis B core antibody immunoglobulin M will be performed for all hepatitis B core antibody total positive or reactive results

Category	Visit Number(s)	Parameters
Hematology	1, 8, 13, 18, 22, 26/ET	Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
Hemoglobin A1c	1, 8, 13, 18, 22, 26/ET	--
Chemistry	1, 8, 13, 18, 22, 26/ET	Sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, Free T3, free T4, TSH, lactate dehydrogenase, creatine phosphokinase, γ-glutamyl transpeptidase, uric acid, phosphate, lipid panel (total cholesterol, triglycerides, low density lipoproteins, high density lipoproteins), prolactin, insulin, and magnesium
Urine myoglobin	1, 8, 13, 18, 22, 26/ET	Only in patients with creatine phosphokinase levels > 1000 U/L or as clinically indicated for any rise in creatine phosphokinase levels or as necessitated by symptoms.
Urinalysis	1, 8, 13, 18, 22, 26/ET	Specific gravity, pH, protein, glucose, ketones, blood, nitrite, bilirubin, and microscopy (red blood cell count [high-power field], white blood cell count [high-power field], casts [low-power field], and crystals)
Serum β-hCG (women of childbearing potential only)	1, 8, 13, 18, 22, 26/ET, 28	--
Urine drug screen	1, 13	Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine
Blood alcohol concentration as measured by breathalyzer	1, 13	--
Repeat urine drug screen, blood alcohol concentration as measured by breathalyzer, and serum pregnancy test	At random upon request from the investigator	--

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; ET = early termination; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

6.5.4 Vital Signs

Vital sign assessments will include radial pulse rate, systolic and diastolic BP, body weight, waist circumference, and temperature. BP, pulse rate, temperature, and body weight will be measured at all visits. Whenever possible, the patient's weight should be measured at the same time of day; patients should wear their usual indoor clothing but take off their jacket and shoes.

Height (without shoes) will be measured at Visit 1 only.

Waist circumference will be measured at Visits 1, 9, 13/Randomization, 19, 26/ET.

BP and radial pulse rate will be measured in the supine position followed by the standing position. The standing measurements must be measured after a sufficient amount of time has been given to allow the BP to equilibrate in the standing state. Radial pulse rate should be measured after BP measurements. BP and radial pulse rate may be measured manually or by machine.

All BP and radial pulse rate measurements will be recorded in the source documents and eCRF. Patients should be instructed not to wear clothing with tight sleeves when they come for clinic visits. Additionally, patients should be kept as calm and undisturbed as possible while BP and pulse rate measurements are taken (eg, there should be no talking while the BP is being measured). The same arm and BP cuff should be used for all BP measurements.

6.5.5 Electrocardiograms

A 12-lead ECG will be performed at Screening (Visit 1), Visit 13/Randomization, and Visit 26/ET using a standard paper speed of 25 mm/sec. ECGs will be electronically transmitted for analysis according to the instructions provided by the ECG central reader. Measurements (in msec) will be recorded for the following parameters in lead II or lead III (other leads may be used only if it is not possible to obtain good-quality tracings from lead II or lead III): PR interval, QRS interval, RR interval (preceding the QT), and uncorrected QT interval. Copies of the ECG waveforms will also be sent to the central reader, where the ECG parameters will be measured and evaluated. The ECG tracing and cardiology report will be retained as a source document.

6.5.6 Physical Examination

A complete physical examination will be done at Screening (Visit 1) and Visit 26/ET, by a professionally trained physician or health professional licensed to perform physical examinations.

6.5.7 Ophthalmological Examination

All study centers will perform ophthalmological examinations including biomicroscopic examinations, lens assessments, best-corrected visual acuity, and color vision testing on all patients at Visits 1, 13, 26/ET (and Visit 28 for any patient with a postbaseline finding of cataracts). A complete description of the procedure is provided in Attachment 12.10.

Biomicroscopic examinations will be performed using a slit-lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva, corneas, iris, anterior chamber, vitreous, retina, macula, and optic nerve.

Biomicroscopic findings will be evaluated for the presence and severity of nuclear, cortical, and posterior subcapsular lens opacities.

6.5.8 Other Safety Assessments

Assessment and ratings of safety scales will be performed by a trained and experienced rater. Every effort should be made to have patients assessed by the same rater at each scheduled timepoint.

6.5.8.1 Extrapyramidal Symptom Scales

The following 3 scales will be used to systematically assess EPS side effects at Visits 2, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26/ET.

Abnormal Involuntary Movement Scale

The AIMS (Guy 1976) assesses abnormal involuntary movements, such as tardive dyskinesia, associated with antipsychotic drugs; it measures facial, oral, extremities, and trunk movements, as well as the patient's awareness of abnormal movements (Attachment 12.6). The first 10 items are rated on a none (0) to severe (4) scale. There are an additional 2 items on dental status that are answered yes or no.

Barnes Akathisia Rating Scale

The BARS (Barnes 1989) is a 4-item rating scale used to assess drug-induced akathisia (Attachment 12.5). The scale comprises items for rating the observable restless movements that characterize the condition, the subjective awareness of restlessness, and any distress associated with the akathisia (each on a 4-point scale from normal [0] to severe [3]). In addition, there is a global severity for akathisia rated on a 6-point scale (absent [0] to severe akathisia [5]).

Simpson-Angus Scale

The SAS (Simpson 1970) is a 10-item rating scale for assessment of antipsychotic-induced parkinsonism in both clinical practice and research settings (Attachment 12.7). Each item ranges from 0 (normal) to 4 (extreme symptoms). The scale consists of 1 item measuring gait (hypokinesia), 6 items measuring rigidity, and 3 items measuring glabella tap, tremor, and salivation, respectively.

6.5.8.2 Columbia-Suicide Severity Rating Scale

The C-SSRS (Attachment 12.8) is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (non-specific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. The C-SSRS will be completed at all study visits, except Visit 27 and Visit 28. At Visit 1 (Screening), the C-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior. At all other visits the C-SSRS will be completed for ideation and behavior since the previous visit.

The C-SSRS will be completed by a trained rater with extensive professional training.

6.6 Summary of Methods of Data Collection

An IWRS will be used to dispense IP, randomize patients, and manage IP inventory. All other data for this study will be collected using eCRFs via an electronic data capture system, except for ECG and laboratory data.

A qualified central ECG reader will be used for the analysis of all ECGs, and a central laboratory for blood and urine samples. ECG and laboratory data will be transferred to Allergan or its designee on a periodic basis throughout the study.

7 Statistical Procedures

7.1 Analysis Populations

Seven populations will be considered in the statistical analysis of this study.

7.1.1 Screened Population

The screened population will consist of all patients who signed informed consent and received a PID number.

7.1.2 Open-label Safety Population

The OL safety population will consist of all patients in the screened population who took at least 1 dose of OL cariprazine during the OL treatment period of the study.

7.1.3 Open-label Intent-to-Treat Population

The OL intent-to-treat (ITT) population will consist of all patients in the OL safety population who had at least 1 postbaseline assessment of the PANSS or CGI-S scores during the OL treatment period of the study.

7.1.4 Open-label Safety-Follow-up Population

The open-label safety-follow-up (OL SFU) population will consist of patients in the OL safety population who were not randomized.

7.1.5 Randomized Population

The randomized population will consist of all patients in the OL safety population who were randomized to a treatment group in the study.

7.1.6 Double-blind Safety Population

The DB safety population will consist of all patients in the randomized population who took at least 1 dose of DB IP.

7.1.7 Double-blind Intent-to-Treat Population

The double-blind intent-to treat (DB ITT) population will consist of all patients in the DB safety population who had at least 1 post-randomization assessment of the PANSS or CGI-S scores during the DB treatment period of the study.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

7.2.1 Primary Efficacy Variable

The primary efficacy parameter is the time to first relapse during the DB treatment period, defined as the number of days from the randomization date to the first relapse date.

Relapse is defined as the occurrence of any 1 of the following:

- Increase in PANSS total score by ≥ 30% for patients who had a PANSS total score of ≥ 50 at Randomization/Visit 13 or a ≥ 10-point increase in PANSS total score for patients who had a PANSS total score < 50 at Randomization/Visit 13
- Increase in CGI-S score by 2 or more points relative to Randomization/Visit 13
- Score of > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control
- Deliberate self-injury or aggressive/violent behavior
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator

- Psychiatric hospitalization due to worsening of the patient's underlying condition
- Exacerbation of psychiatric illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

7.2.2 Secondary Efficacy Variable

Not applicable.

7.2.3 Other Efficacy Variables

The additional efficacy parameters will include the following at scheduled postbaseline visits:

- Change from Baseline in the PANSS total score
- Change from Baseline in PANSS positive subscale score
- Change from Baseline in PANSS negative subscale score
- Change from Baseline in PANSS factor score for positive symptoms
- Change from Baseline in PANSS factor score for negative symptoms
- Percentage response (PANSS improvement ≥ 30%)
- Change from Baseline in the CGI-S score
- CGI-I score
- Change from Baseline in the BACS composite score (Z score) and BACS individual subtests
- Change from Baseline in the BACS composite T score
- Change from Baseline in PSP score and sub-domains

For the continuous endpoints, the change from Baseline refers to the change from OL Baseline during the OL treatment period, and the change from DB Baseline during the DB treatment period, unless stated otherwise.

7.3 Hypothesis and Methods of Analysis

All efficacy analyses for the OL will be performed using the OL ITT population, unless stated otherwise. Baselines for efficacy parameters in the OL treatment period will be defined as the last non-missing efficacy assessment before the first dose of OL IP. All efficacy analyses for the DB treatment period will be performed using the DB ITT population, unless stated otherwise. Baselines for the additional efficacy parameters in the DB treatment period will be defined as the last non-missing efficacy assessment before the first dose of DB IP. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance and all CIs will be 2-sided 95% CIs, unless stated otherwise.

7.3.1 Primary Efficacy Analyses

The primary efficacy parameter is the time to first relapse during the DB treatment period, defined as the number of days from the randomization date to the relapse date.

To test the primary null hypotheses that the distribution of the time to first relapse for each of the cariprazine 4.5 mg/d and 3.0 mg/d treatment groups are not different from that for the placebo treatment group, the log-rank test is used to compare the time to relapse between each cariprazine group and placebo group for the DB ITT population. Estimates of the hazard ratio and 95% CIs will be based on the Cox proportional hazards model with treatment group as explanatory variable. The Kaplan-Meier estimates for the cumulative distribution of the relapse rate for each treatment group will be provided.

The fixed-sequence testing procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. The comparison of cariprazine 4.5 mg/d versus placebo for the primary endpoint will be tested first at a 0.05 significance level using the log rank test, only when the testing is significant, the comparison of cariprazine 3.0 mg/d versus placebo will be tested.

Two sensitivity analyses will be performed to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption. The first sensitivity analysis is delta-adjusted imputation method (Zhao 2014). The delta-adjusted sensitivity analysis specifies that the hazard of having an event for subjects who discontinued before the timepoint is multiplicatively increased relative to the hazard for subjects who continued beyond the timepoint for the cariprazine treatment group. The second sensitivity analysis is based on the reference-based imputation method (Lu 2015). The reference-based sensitivity analyses use a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analyses toward the informative censoring,

which assumes that the hazard of relapse for cariprazine-treated patients who discontinued is the same as the hazard for relapse for placebo-treated patients. A multiple imputation approach will be used to implement the sensitivity analyses.

7.3.2 Secondary Efficacy Analyses

None.

7.3.3 Other Efficacy Analyses

To accommodate the flexible duration of the OL treatment period, the derived visits in the DB treatment period will be named as *Week i* post-randomization for a specific *Week i* after the first dose of the DB study medications. The total exposure to IPs for patients in *Week i* post-randomization will vary because of the flexible OL treatment period. The detailed week mapping windows will be provided in the statistical analysis plan (SAP).

Descriptive statistics will be provided by visit for additional quantitative parameters for the OL ITT population and the DB ITT population using both last-observation-carried forward (LOCF) and observed cases approaches. LOCF approach will be used to impute missing postbaseline values. Imputation of missing values will be done for the OL phase and the DB phase separately.

For the DB treatment period, the continuous variables (change from DB Baseline) will be analyzed by using a mixed-effects model for repeated measures with treatment group, country, visit, and treatment group-by-visit interaction as fixed effects and the Baseline value and Baseline-by-visit interaction as the covariates. An unstructured covariance matrix will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be performed based on post-DB Baseline scores using only the observed cases without imputation of missing values. Least squares means and their standard errors based on the model for repeated measures analysis will be plotted by treatment group and visit.

Additional categorical efficacy parameters will be analyzed in the following way:

Rates for categorical parameters (response) will be reported by treatment group and by visit for both the OL treatment period and the DB treatment period (with LOCF imputation). For the DB treatment period, logistic regression model (with LOCF imputation) will be used to model the probability of a response or the probability of a response as a function of a treatment group and the corresponding Baseline score as explanatory variables.

7.3.4 Safety Analyses

The safety analyses will be performed for the OL safety, OL SFU, and DB safety populations. The summarization will be overall for the OL treatment period in the OL safety population and for the OL SFU period in the OL SFU population. The summarization will be by treatment group for the DB treatment period and DB SFU period in the DB safety population. The summarization for the OL treatment period will use the OL safety population as the denominator. The summarization for the DB treatment period will use the DB safety population as the denominator. The summarization for the OL SFU period and DB SFU period will use the OL SFU population and the DB safety population as the denominator, respectively.

Safety parameters will include AEs, clinical laboratory parameters, vital signs, ECG parameters, ophthalmological parameters, C-SSRS, and EPS scales (AIMS, BARS, and SAS).

For each safety parameter, the last assessment made before the first dose of OL IP will be used as the Baseline for all analyses of that safety parameter, unless stated otherwise.

The derived visits in the DB treatment period will use the same strategy as described for the additional efficacy endpoints. The detailed week mapping windows will be provided in the SAP.

7.3.4.1 Adverse Events

AEs will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities* (MedDRA), Version 21.0 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the first dose of OL IP.

The number and percentage of patients reporting TEAEs during the OL treatment period will be tabulated by system organ class and preferred term, by system organ class, preferred term, and severity, and by system organ class, preferred term, and relationship to IP.

The number and percentage of patients reporting TEAEs during the DB treatment will be tabulated for each treatment group by system organ class and preferred term, by system organ class, preferred term, and severity, and by system organ class, preferred term, and relationship to IP.

The number and percentage of patients reporting TEAEs during the SFU period will be tabulated by system organ class, preferred term, and DB treatment group for the DB safety population and by system organ class and preferred term for the OL safety follow-up population.

For the OL period, DB period, or SFU period, if more than 1 AE was coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to IP.

The total number and percentage of TEAEs during the DB treatment period will also be summarized by severity and relationship to IP for each treatment group.

The number and percentage of patients with common (≥ 2% of patients in any treatment group) TEAEs during the DB treatment period will be summarized by preferred term and treatment group.

An AE that occurs more than 30 days after the last dose of DB IP will not be summarized.

An SAE that occurred between the date of the first dose of IP and 30 days after the date of the last dose of IP, inclusive, will be considered an on-therapy SAE. The number and percentage of patients who had on-therapy SAEs during the OL treatment period and the OL SFU period will be summarized by preferred term. The number and percentage of patients who had on-therapy SAEs during the DB treatment period and the DB SFU period will be summarized by preferred term and DB treatment group.

The incidence of AEs leading to premature discontinuation of IP during the OL treatment period will be summarized by preferred term. The incidence of AEs leading to premature discontinuation of IP during the DB treatment period will be summarized by preferred term and treatment group.

For the Screened Population, listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who died. All patients with SAEs, including SAEs reported during the screening period and the SFU period, and all patients discontinuing because of AEs, including AEs occurring during the screening period, will be included in these listings.

The number and percentage of patients with any EPS TEAEs during the OL period and DB period will be summarized separately. The number and percentage of patients with EPS

SAEs, and the number and percentage of patients with EPS AEs leading to premature discontinuation of IP will also be summarized.

The number and percentage of patients reporting TEAEs of ocular AESIs will be summarized overall for the OL treatment period in the OL safety population and the OL SFU period in the OL SFU population, and by treatment for the DB treatment period and the DB SFU period in the DB safety population. The listing of all reported ocular AESIs will be provided.

7.3.4.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from Baseline values at each assessment timepoint will be presented for each clinical laboratory parameter in SI units, and for selected clinical laboratory parameters in conventional units.

The number and percentage of patients with potentially clinically significant (PCS) clinical laboratory values will be presented. The criteria for PCS laboratory values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with available non-PCS Baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS Baseline values and at least 1 postbaseline PCS value. A supportive listing of patients with postbaseline PCS value will be provided, including the PID number, study center number, and Baseline and postbaseline values. A listing of all AEs for patients with PCS laboratory values will also be provided.

The number and percentage of patients with treatment-emergent significant changes in lipids parameters (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) and glucose will be tabulated by treatment group for the OL treatment period and the DB treatment period. The criteria for treatment-emergent significant changes in lipids and glucose will be detailed in the SAP. Percentages will be calculated relative to the number of patients with Baseline values meeting the specified Baseline criteria and with at least one postbaseline assessment during the specific period. The change in lipids and glucose from Baseline to the highest (lowest for HDL cholesterol) postbaseline measurement during the specific period will be summarized. Supportive listings of patients with treatment-emergent changes in lipids and glucose values will be provided.

7.3.4.3 Vital Signs

Descriptive statistics for vital signs and changes from Baseline values at each visit and at end of study will be presented overall for the OL treatment period and OL SFU period, and by treatment group for the DB treatment period and DB SFU period.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from Baseline value criteria. The criteria for PCS vital sign values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with Baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available Baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with postbaseline PCS values will be provided, including the PID number, Baseline and postbaseline values. A listing of all AEs occurring in patients who have PCS vital sign values will also be provided.

The number and percentage of patients with orthostatic hypotension will be provided by treatment group. Orthostatic hypotension is defined as a reduction of ≥ 20 mm Hg in systolic BP or a reduction of ≥ 10 mm Hg in diastolic BP when the patient changes from the supine position to the standing position. A supportive listing will be provided including the PID number, study center number, and Baseline and postbaseline systolic and diastolic BP values (supine and standing).

The definition of different hypertension status will be detailed in the SAP. Tabulations showing the number and percentage of patients with hypertension status changes from Baseline will be provided for:

- Shift of hypertension status from Baseline to end of the OL treatment period
- Shift of hypertension status from Baseline to highest category during the OL treatment period
- Shift of hypertension status from Baseline to end of the DB treatment period
- Shift of hypertension status from Baseline to highest category during the DB treatment period

Supportive listings of patients with shift in hypertension status from normotensive/prehypertension at Baseline to Stage I /Stage II will be provided.

7.3.4.4 Electrocardiogram

Descriptive statistics for ECG parameters (ie, heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB, and QTcF) and changes from Baseline values at each assessment timepoint in this study will be presented.

The number and percentage of patients with postbaseline PCS ECG values will be tabulated by treatment group for the DB treatment period. The criteria for PCS ECG values will be detailed in the SAP. The percentages will be calculated relative to the number of patients with available non-PCS Baseline values and at least 1 postbaseline assessment for the DB treatment period. The numerator will be the total number of patients with available non-PCS Baseline values and at least 1 postbaseline PCS value for the DB treatment period. A supportive tabular display of patients with postbaseline PCS values will be provided, including the PID number, Baseline, all postbaseline (including non-PCS) values, and change from Baseline. In addition, a tabular display showing all AEs that occurred in patients who had postbaseline PCS ECG values will be provided.

A shift table from Baseline to the end of study in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display showing patients with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

The number and percentage of patients with a change from Baseline QTc > 30 msec but not exceeding 60 msec and of patients with an increase > 60 msec will be tabulated by treatment group. A supportive listing that includes PID number, study center number, all QTc values (including change from Baseline values), and all AEs will be provided for all patients with postbaseline QTc changes > 30 msec.

7.3.4.5 Other Safety Parameters

Other safety parameters include EPS scales (AIMS, BARS, and SAS scores), C-SSRS, and ophthalmological parameters.

7.3.4.5.1 Extrapyramidal Symptom Scales

A patient will be considered to have treatment-emergent parkinsonism if the patient's SAS score was ≤ 3 at Baseline and > 3 at any postbaseline assessment. A patient will be considered to have treatment-emergent akathisia if the patient's BARS score was ≤ 2 at Baseline and > 2 at any postbaseline assessment. The number and percentage of patients with treatment-emergent parkinsonism or akathisia will be tabulated. Listings of patients with treatment-emergent parkinsonism or akathisia will be provided, including the PID number, Baseline and postbaseline values. Listings of all AEs for patients with treatment-emergent parkinsonism or akathisia will also be provided.

Descriptive statistics for EPS scale parameters (AIMS, BARS, and SAS) and changes from Baseline values at each assessment timepoint in this study will be presented.

7.3.4.5.2 Columbia-Suicide Severity Rating Scale

For the C-SSRS, the number and percentage of patients with suicidal ideation or suicidal behavior, as recorded on the C-SSRS scale, will be presented. The distribution of response for most severe suicidal ideation and suicidal behavior during the lifetime history, the OL and the DB treatment periods will be presented. Supportive listings will be provided, including the PID number, treatment group, visit number, lifetime history, and postbaseline values for each patient. Intensity of ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings.

7.3.4.5.3 Ophthalmological Parameters

Ophthalmological parameters include best-corrected visual acuity (BCVA); intraocular pressure (IOP); lens opacity; color discrimination; and slit-lamp biomicroscopy examination results.

Descriptive statistics for each numeric ophthalmological parameter (eg, visual acuity, IOP) and changes from Baseline at each assessment timepoint will be presented.

The number and percentage of patients with a change from Baseline in visual acuity ≥ +0.3 in each eye and in either eye will be summarized overall for the OL treatment period, and by treatment group for the DB treatment period.

The number and percentage of patients with postbaseline IOP > 21 mm Hg will be presented. A supportive listing will be provided, including PID number, Baseline and postbaseline IOP values.

The number of patients with phakic, pseudophakic, and aphakic lens status will be summarized for both the OL and DB treatment periods. For patients with phakic eyes, the number and percentage of patients with cataract will be assessed by presence and severity of nuclear, cortical, and posterior subcapsular cataract lens opacities using a 3−point scale (0: absent, 1: < standard photo #2, and 2: ≥ standard photo #2). Patients with nuclear, cortical, or posterior subcapsular cataract lens opacities will be summarized for each eye (left and right) and for either eye using the higher scale of the 2 eyes by treatment group for each period (OL, DB, and SFU periods). A patient will be counted once in the highest lens opacity

severity in the specific period. A supportive listing will be provided, including PID number, Baseline and postbaseline assessment values.

In addition, a shift table from normal Baseline to abnormal postbaseline in color discrimination, slit-lamp biomicroscopy examination results will be provided.

7.4 Subgroup Analyses

The analysis for the primary efficacy parameter will be performed within each category of the following:

- Age group (< 55 years, ≥ 55 years)
- Sex (male, female)
- Race (white, all other races)
- Region (US, Non-US)

7.5 Sample Size Calculation

The sample size and power calculations are based on the analysis of time to relapse in the DB treatment period to compare each cariprazine dose group versus placebo based on a log-rank test. The trial will be a fixed follow-up design. Patients are followed from randomization until dropout, relapse or a fixed duration of 26 weeks.

Based on the first 26 weeks' data from RGH-MD-06, the relapse hazard ratio is assumed to be 0.50, and cumulative relapse rate at Week 26 for the placebo group is 46% (Study RGH-MD-06, 2015). In addition, the cumulative dropout rate due to reasons other than relapse at 26 weeks is assumed to be 20.0%.

Using these assumptions, a total of approximately 103 in the DB phase need to be observed in order to have 85% power to detect a statistically significant difference between each cariprazine and placebo group, using 2-tailed, log-rank tests at an overall 5% level of significance. The trial should randomize approximately 345 patients, 115 patients each arm, to provide the required number of relapse events. EAST 6.0 was used to for sample size and power calculation.

A fixed-sequence procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. First, the cariprazine 4.5 mg/d group will be compared with

the placebo group in the primary endpoint; if the testing is significant at the 0.05 level, then cariprazine 3.0 mg/d arm will be compared with the placebo group.

Assume the screening failure rate is 34%, and approximately 33.3% of patients enrolled into the OL treatment period will be randomized into the DB treatment period. Then, approximately 1035 patients will be expected to be enrolled into the OL treatment period, and approximately 1569 patients are expected to be screened.

7.6 Interim Analyses

No formal interim analysis is planned.

8 Study Visit Schedule and Procedures

Table 1 and Table 2 present the study visits and procedures for OL and DB periods in the study.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Subject Privacy

The study will be discussed with the patient and/or the patient's legally authorized representative, and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization (United States only), data protection consent (Europe only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each patient that provides informed consent will be assigned a patient number that will be used on patient documentation throughout the study.

Where applicable, a central vendor will be used to verify patients' current and past research study status in order to mitigate safety concerns associated with duplicate enrollment and protocol deviations associated with multiple trial enrollment. Following proper informed consent and after issuing a patient number, each patient will be checked in the Verified

Clinical Trials database, indicated in the Schedule of Visits and Procedures (Table 1). Partial patient identifiers will be utilized but will not be accessible to the sponsor. Patients who are identified as verification failures by VCT should not continue in trial without documented approval from the sponsor.

8.2 Washout Intervals/Run-in

Patients will undergo a Screening/washout period of up to 7 days. The length and timing of the washout of prior psychiatric medications during the 7 days allotted for the Screening period is at the discretion of the investigator. Prior medications should be gradually withdrawn such that the washout is completed by Visit 2/Baseline. Please note that during the screening/washout period, psychotropic medications, other than those listed as rescue (Section 4.8.3), may not be newly initiated or reinstated. In order to ensure the safe transition of patients into the study, based upon the clinical judgment of the investigator, patients may be hospitalized during initiation of the study. This hospitalization can be for up to 14 days during the screening and OL periods (with the end of hospitalization no later than Visit 3 [Day 8] of the OL treatment period). This 14-day allowance for hospitalization may include all or part of the Screening period. Hospitalization beyond the initial 14 days allowed will require consultation with the medical monitor. Following the protocol-allowed 14 days of hospitalization (and any sponsor-allowed extension), patients should be treated as outpatients.

No run-in period will be used in this study.

8.3 Procedures for Final Study Entry

Patients meeting all eligibility criteria to continue into the OL treatment period at Visit 2 (Baseline) must meet the stability criteria specified in Section 4.5 and randomization criteria specified in Section 4.6 to be eligible for randomization (Visit 13). Rescreening of screen failures is permitted in certain situations after consultation with the Allergan medical monitor.

Also, all females of childbearing potential must have negative qualitative results on the serum pregnancy test at the Screening Visit (Visit 1).

See Section 5.4 for the method for assignment to treatment groups/randomization.

8.4 Visits and Associated Procedures

All assessments will be conducted at the appropriate visits as outlined in Table 1 and Table 2 and the timing of the visits should occur as close as possible to the specified day.

Visit 2/Baseline is expected to occur within 7 days of Visit 1; however, if required it may be conducted up to 3 days after the scheduled visit.

If necessary, Visits 3 to 28 may be conducted up to 3 days before or after the scheduled visits. The visit windows for each scheduled visit are relative to Visit 2 for Visits 3 through 13, relative to Visit 13 for Visits 14 through 26/ET, and relative to Visit 26/ET for Visits 27 and 28.

The schedule of study procedures and assessments is displayed by visit in Table 1 and Table 2. The descriptions of the procedures to be performed at each visit are provided below.

8.4.1 Screening/Visit 1 (Days –7 to –1)

The following procedures will be performed at Screening (Visit 1):

- Obtain informed consent and patient privacy; consent for pharmacogenetic sampling may also be obtained
- Verified Clinical Trials database check to be performed where applicable
- Access IWRS to register the patient and assign a PID number
- Assess inclusion/exclusion criteria
- Collect and assess medical and psychiatric history
- Administer and assess SCID-5
- Collect blood sample for hepatitis screening
- Collect samples for UDS; assess blood alcohol concentration via breathalyzer
- Collect blood samples for clinical laboratory determinations
- Collect blood samples for serum pregnancy test (women of childbearing potential only)
- Collect blood sample for hemoglobin A1c
- Review prior and concomitant medications

- Administer SCI-PANSS, CGI-S, and C-SSRS
- Collect vital signs measurements, including weight, waist circumference, and height
- Perform physical examination
- Perform ECG
- Review and assess AEs and SAEs
- Perform ophthalmological examination (Note: The screening ophthalmological examination must be completed prior to Visit 2/Baseline and the start of OL IP.)

8.4.2 Baseline/Visit 2

The following procedures will be performed at Baseline /Visit 2:

- Review and assess AEs and SAEs
- Review concomitant medications
- Assess inclusion/exclusion criteria
- Administer SCI-PANSS, BACS, CGI-S, PSP, and C-SSRS
- Evaluate EPS symptoms (AIMS/BARS/SAS)
- Collect vital signs measurements (including weight)
- Obtain consent for and/or collect blood for pharmacogenetic sampling (consent for pharmacogenetic sampling may be obtained any time between Visit 1 and Visit 8, inclusive. For patients providing consent, the sample for pharmacogenetic testing must be obtained between Visit 2 and Visit 8, inclusive)
- Access IWRS to dispense IP

8.4.3 Open-label Treatment Period (Visits 3 to 12)

The following procedures will be performed during the OL treatment period at every visit except where noted:

- Review concomitant medications

- Collect vital signs measurements (including weight)
- Collect waist circumference measurement (only Visit 9)
- Administer SCI-PANSS, CGI-S, CGI-I, and C-SSRS
- Assess PSP (only Visit 8)
- Evaluate patients for attainment of response threshold criteria (Section 4.5). Continue to assess between Visits 6 to 8 until criteria have been met. Patients not meeting response threshold criteria by Visit 8 should be discontinued and undergo procedures as for Visit 26/ET and subsequently complete the SFU period
- At Visits 7 through 9, evaluate patients for attainment of response threshold criteria (Section 4.5) if response threshold criteria were met at the preceding visit.
    - Patients who have not met stability of response threshold criteria by Week 10 (Visit 9) should be discontinued and undergo procedures as for Visit 26/ET and subsequently complete the SFU period
    - Patients who have met stability of response threshold criteria (Section 4.5) must maintain stability threshold for 8 consecutive weeks in order to be randomized, with allowance for 1 excursion
    - For patients who have met stability of response threshold criteria, evaluate randomization criteria (Section 4.6) 8 weeks after stability of response threshold criteria are met (may be as early as Visit 11). Patients who meet randomization criteria (Section 4.6) prior to Visit 13 are to undergo procedures specified for Visit 13/End of OL treatment period (Section 8.4.4; any remaining visits in the OL treatment period will be skipped).
    - Patients who have attained stability of response threshold criteria and who meet any of the following criteria will be discontinued and should undergo Visit 26/ET procedures and subsequently complete the SFU period:
        - PANSS total score increases by ≥ 30% relative to Visit 2/Baseline, or
        - Score > 4 on 1 or more of 7 PANSS items P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; or G14: poor impulse control, or

  - Patients who have an increase in CGI-S score by 2 or more points relative to Visit 2/Baseline

- Evaluate EPS symptoms (AIMS/BARS/SAS) (Visits 3, 7, 9, and 11)
- Collect blood samples for serum pregnancy test (women of childbearing potential only) (Visit 8)
- Collect blood samples for clinical laboratory determinations and for hemoglobin A1c (Visit 8)
- Collect IP blister card(s) and perform IP compliance and accountability
- Obtain consent for and collect blood for pharmacogenetic sampling (consent for pharmacogenetic sampling may be obtained any time between Visit 1 and Visit 8, inclusive. For patients providing consent, the sample for pharmacogenetic testing must be obtained between Visit 2 and Visit 8, inclusive
- Review and assess AEs and SAEs
- Access IWRS to dispense IP

8.4.4 End of Open-label Period/Randomization Visit (Visit 13)

The following procedures will be performed at Visit 13:

- Review concomitant medications
- Collect vital signs measurements, including weight
- Measure waist circumference
- Administer SCI-PANSS and CGI-S to determine whether randomization criteria (Section 4.6) have been met
  - Eligible patients: Access IWRS to randomize patient and dispense DB IP
  - Patients who do not meet randomization criteria are to undergo procedures as for Visit 26/ET and scheduled to return for the SFU Visits (Visit 27 and Visit 28)
- Assess C-SSRS, BACS, CGI-I, and PSP

- Evaluate EPS symptoms (AIMS/BARS/SAS)
- Perform ECG
- Perform ophthalmological examination. NOTE: For patients eligible for randomization, every attempt should be made to complete the Visit 13 ophthalmological examination on the same day as all other Visit 13 procedures. If the examination cannot be accommodated, it must occur within 7 days after randomization.
- Collect samples for UDS; assess blood alcohol concentration via breathalyzer
- Collect blood samples for clinical laboratory determinations
- Collect blood samples for serum pregnancy test (women of childbearing potential only)
- Collect blood sample for hemoglobin A1c
- Review and assess AEs and SAEs
- Collect IP blister cards and perform IP compliance and accountability
- Access IWRS to dispense IP

8.4.5 Double-blind Treatment Period (Visits 14 to 25)

The following procedures will be performed during the DB treatment period at every visit except as noted:

- Review concomitant medications
- Collect vital signs measurements (including weight)
- Collect waist circumference measurement (Visit 19)
- Administer SCI-PANSS and CGI-S and assess patient for relapse (per Section 4.7)
- Assess CGI-I and C-SSRS
- Assess PSP (Visits 16 and 20)

- Assess BACS (Visit 16)
- Evaluate EPS symptoms (AIMS/BARS/SAS) (Visits 15, 17, 19, 21, and 23)
- Assess patient for relapse (Section 4.7)
- Collect blood samples for clinical laboratory determinations (Visits 18 and 22)
- Collect samples for serum pregnancy test (women of childbearing potential only) (Visits 18 and 22)
- Review and assess AEs and SAEs
- Collect IP blister cards and perform IP compliance and accountability
- Access IWRS to dispense IP

8.4.6 Final or Early Termination Visit (Visit 26)

The following procedures will be performed at the final visit at the end of the DB treatment period (Visit 26) or at ET:

- Review concomitant medications
- Collect vital signs measurements, including weight and waist circumference
- Administer SCI-PANSS, BACS, CGI-S, CGI-I, PSP, and C-SSRS
- Evaluate EPS (AIMS/BARS/SAS)
- Assess patient for relapse (Section 4.7)
- Perform physical examination
- Perform ECG
- Perform ophthalmological examination.
  NOTE: every attempt should be made to complete the Visit 26/ET ophthalmological examination on the same day as all other Visit 26/ET procedures.
- Collect blood samples for clinical laboratory determinations

- Collect sample for hemoglobin A1c
- Collect sample for serum pregnancy test (women of childbearing potential only)
- Review and assess AEs and SAEs
- Collect IP blister card(s) and perform IP compliance and accountability

8.4.7 Safety Follow-up Visits (Visits 27 and 28)

Patients who complete the study, and those who prematurely discontinue from either the OL or DB treatment periods, will complete a 4-week SFU period (2 visits: one at the end of every 2 weeks). During the SFU period, patients will be stabilized on appropriate medications, and additional evaluations (laboratory studies, ECG, UDS, etc) may be performed as deemed necessary by the investigator. This period may also be used for follow-up and management of all abnormal findings and AEs observed during OL or DB treatment periods. No IP will be administered during the SFU period.

The following procedures will be carried out at the SFU Weeks 46 and 48 (Visits 27 and 28):

- Collect blood sample for serum pregnancy test (women of child-bearing potential only [Visit 28 only])
- Review concomitant medications
- Collect vital signs measurements (including weight)
- Perform a follow-up ophthalmological examination only for patients with a postbaseline finding of cataracts (Visit 28 only)
  Note: Every attempt should be made to complete the Visit 28 ophthalmological examination on the same day as all other Visit 28 procedures. If the examination cannot be accommodated, it must occur within 7 days of Visit 28.
- Review and assess AEs and SAEs

8.5 Instructions for Patients

Patients are to be instructed to take their study medication daily around the same clock time; study medication should not be taken with grapefruit juice. Patients are to be reminded to return used/partially used blister cards at every study visit. The investigator (or designee) is to ensure that concomitant medications are reviewed against the prohibited and allowed

rescue medications detailed in Section 4.8; patients are to be advised accordingly. If the permissibility of a specific medication/treatment is in question, the investigator should consult the medical monitor.

Patients are to be asked to abstain from drinking alcohol during the study.

Patients are to be asked to fast for at least 10 hours before blood and urine samples are collected at Screening (Visit 1), Visits 8, 13 (End of OL/Randomization), 18, 22, and 26/ET.

8.6 Unscheduled Visits

Additional examinations and laboratory assessments may be performed as necessary to ensure the safety and well-being of the patients during the study period. Unscheduled visit eCRF pages will be completed for each unscheduled visit. For all parameters not measured, indicate “not done.”

8.7 Compliance with Protocol

All assessments will be conducted at the appropriate visits as outlined in Table 1 and Table 2 and the timing of the visits should occur as close as possible to the specified day.
Visit 2/Baseline is expected to occur within 7 days of Visit 1. If required, Visit 2/Baseline assessments may be conducted up to 3 days after the scheduled visit. If necessary, Visits 3 to 28 may be conducted up to 3 days before or after the scheduled visits. The visit windows for each scheduled visit are relative to Visit 2 for Visits 3 through 13, relative to Visit 13 for Visits 14 through 26/ET, and relative to 26/ET for Visits 27 and 28. Every attempt should be made to complete the postbaseline ophthalmological examinations (Visits 13 and Visits 26/ET, and Visit 28 if required) on the same date as all other study procedures for that visit. At each visit, the patient will be asked if the patient changed the dose/regimen of any existing concomitant medications or initiated the use of any new concomitant medications since the last visit to ensure compliance with the protocol.

8.8 Early Discontinuation of Subjects

Patients may discontinue from the study at any time for any reason. Discontinuation is permanent; once a patient is discontinued, he/she shall not be allowed to enroll again.

Patients can be prematurely discontinued for one of the following reasons:

- AE

- Noncompliance with protocol
- Noncompliance with IP dosing regimen
- Withdrawal of consent (a clear reason must be documented when possible)
- Lost to follow-up (every effort must be made to contact the patient; a certified/traceable letter must be sent)
- Study terminated by sponsor
- Site terminated by sponsor
- Pregnancy
- Other reasons

Notification of early patient discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate eCRF page. Patients who take IP during the study (OL treatment period or the DB treatment period) and who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment. A final assessment will be defined as completion of the evaluations scheduled for Visit 26/ET. If the patient discontinues after IP is taken, the patient is also expected to return for the SFU Visits (Visit 27 and Visit 28) 2 weeks and 4 weeks after completion of the ET visit.

At a minimum, collect the following information when a patient discontinues:

1. The reason the patient discontinued;

2. The date of the last dose of IP from the trial;

3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;

4. (S)AEs;

5. Compliance with the IP administration as specified in this protocol;

6. Final Assessments: Unless there is withdrawal of consent, every effort should be made to ensure that all procedures and evaluations scheduled for Visit 26/ET and subsequently Visit 27 and Visit 28 (SFU Visits) are performed (Table 2, Schedule of Visits and Procedures).

7. Retrieve IP from the patient.

For all patients who discontinue as a result of being lost to follow-up, a determination must be noted in the eCRF as to whether the loss is related to an acute exacerbation of schizophrenia.

8.9 Withdrawal Criteria

It is the right and the duty of the investigator or subinvestigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual patient. In addition, the investigator or subinvestigator is to stop treatment of any patient with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results.

A patient must be discontinued for any of the following reasons:

1. The patient is unable to tolerate the 4.5 mg/d dose.

2. The patient fails to attain *response threshold* by Week 8 (Visit 8) or stability of response threshold criteria by Week 10 (Visit 9) (see Section 4.5);

3. After stability has been attained, except for the single allowed excursion above the response threshold prior to Visit 13/End of OL, there is a lack of ongoing stability as evidenced by PANSS total score increases by ≥ 30% relative to Visit 2/Baseline; or PANSS item score is > 4 on one or more of PANSS items P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control; or CGI-S score increases by 2 or more points relative to Baseline/Visit 2;

4. The patient required or initiated hospitalization for his/her psychiatric symptoms (excluding the discretionary hospitalization stay, which is to end no later than Visit 3 [Day 8] of the OL treatment period, or extension of the initial hospitalization described in this protocol);

5. The patient took or required prohibited medication, including initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days) to treat worsening symptoms of schizophrenia or any other psychiatric disorder as judged by the clinical impression of the investigator;

6. At the end of the OL treatment period, the patient does not meet all criteria to enter the DB treatment period (Section 4.6);

7. Positive UDS after enrollment, confirmed by retest at next scheduled visit; for exceptions see Exclusion Criterion 3 and Section 4.8.3;

8. The patient meets the criteria for relapse during the DB treatment period;

9. The patient experiences 1 of the following elevated liver enzyme conditions, which is confirmed by repeat testing within 48 to 72 hours of awareness:

   - ALT or AST > 3× ULN and total bilirubin > 2 × ULN,
   - ALT or AST > 8 × ULN,
   - ALT or AST > 5 × ULN for more than 2 weeks,
   - ALT or AST > 3 × ULN with the appearance of jaundice, worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.

10. The patient has an absolute neutrophil count of < 1000 per mm^3 and, after repeat testing within 24 hours of awareness, the values are not normalized or are not increasing;

11. A female patient becomes pregnant during treatment.

8.10 Study Termination

The study may be stopped at a study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification. A study may also be stopped by a regulatory authority.

9 Adverse Events

AEs occurring during the study will be recorded on an adverse event eCRF. If AEs occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that 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 related to the medicinal (investigational) product. In addition, during the Screening period, AEs will be assessed regardless of the administration of a pharmaceutical product.

Note: AEs must be collected once informed consent has been obtained, regardless of whether or not the subject has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as AEs unless the disease progression is greater than anticipated in the natural course of the disease.

AEs will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for AEs by asking each subject a general, non-directed question such as “How have you been feeling since the last visit?” Directed questioning and examination will then be done as appropriate. All reported AEs will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

A SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting an SAE.)

Allergan considers all cancer AEs to be SAEs. Elective abortions and abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic

pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a subject requires hospitalization is not reportable as an SAE.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the subject's entry into the study. If it has not been documented at the time of the subject's entry into the study, then it should be documented as an SAE and reported to Allergan.

9.1.3 Severity

A clinical determination will be made of the intensity of an AE. The severity assessment for a clinical AE must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an AE may be an 'all or nothing' finding which cannot be graded.

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an AE and the IP or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any AE must be recorded on the appropriate eCRF.

All AEs that are IP-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities. Any AE that is marked 'ongoing' at the exit visit must be followed up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) and for at least 30 days after the last dose of study drug must be immediately reported but no later than 24 hours after learning of an SAE. SAEs must be reported to Allergan (or agent of Allergan eg, Contract Research Organization) as listed on the Allergan study contacts list and recorded on the SAE/AESI form. All patients with an SAE must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of an SAE, the investigator must:

1. Notify Allergan immediately using the SAE/AESI form (contact details can be found on page 1 of the SAE/AESI form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and study contacts list.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the AE(s) on the SAE/AESI form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the AE(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the IP.

4. Promptly inform the governing IRB/IEC of the SAE as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Reporting of Pregnancies Occurring During the Study

Study site personnel must report every pregnancy from the time the patient signs the ICF until 12 weeks following the last dose of IP. Within 24 hours of learning of the pregnancy, the study site personnel must report the event to the sponsor's Global Patient Safety department on the clinical trial pregnancy form and fax/email it to the following SAE/pregnancy fax number/email address, even if no AE has occurred:

Fax number: +1-714-796-9504 (back-up fax number: +1-714-246-5295)

Email: IR-Clinical-SAE@allergan.com

Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a follow-up clinical trial pregnancy form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE/AESI form for clinical trials must be filed with the appropriate serious criterion (eg, hospitalization) indicated in addition to the pregnancy form.

9.5 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

Study site personnel must report every patient who meets these 3 criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the patient signs the ICF for the trial until 30 days after the final protocol-defined study visit or the last known dose of IP (if the final visit does not occur).

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 faxed/emailed to the sponsor on the SAE/AESI form as soon as possible (within 24 hours of learning of the potential Hy's Law) to the following SAE/pregnancy fax number/email address, even if no AE has occurred:

Fax number: +1-714-796-9504 (back-up fax number: +1-714-246-5295)

Email: IR-Clinical-SAE@allergan.com

The eCRF pages for potential Hy's Law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring must be initiated in conjunction with the study physician and in accordance

with the FDA "Guidance for Industry: Drug-Induced Liver Injury-Pre-Marketing Clinical Evaluation" Jul 2009.

9.6 Procedures for Unmasking of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (medical monitor) should be notified prior to unmasking study medication. The investigator should inform the sponsor (medical monitor) of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel logging into the IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

10 Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Council on Harmonization (ICH) Guideline on GCP.

10.1 Protection of Human Patients

10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative.

10.1.2 Compliance with IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance with Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

Any amendment to this protocol will be provided to the investigator in writing by the sponsor. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the investigator, has been received by the sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to the sponsor.

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject’s name will not be disclosed in these documents. The subject's name may be disclosed to the sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization (US sites only), data protection consent (European sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information (“HIPAA”), European Union Data Protection Directive 95/46/EC [“EU Directive”]).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and ECGs. The investigator's copy of the case report forms serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- Patient's name.
- Patient's contact information.
- The date that the patient entered the study, patient number, and patient randomization [or medication kit] number.
- The study title and/or the protocol number of the study and the name of Allergan.
- A statement that informed consent was obtained (including the date). A statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date).
- Dates of all patient visits.
- All concurrent medications (list all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.).
- Occurrence and status of any AEs.
- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation.
- Key study variables.

Source documentation practices must follow ALCOA-C principles (ie, records must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete).

10.4.2 Case Report Form Completion

All patient data relating to the study will be recorded on eCRFs to be provided by the sponsor through the electronic data capture system. The investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRF casebook submitted to the sponsor. The investigator must maintain and retain accurate documentation that supports the information entered into the electronic data capture system for source document verification and possible regulatory inspection.

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study-related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all IPs, and copies of case report forms should be maintained on file.

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

Investigational product will be supplied in blister cards and will be labeled with the protocol number, storage information, warning language, and instructions to take the capsules as directed. The card will also include the medication number. Immediately before dispensing the blister card, the investigator or designee will write the study center number, patient's initials (if applicable), patient number, visit number, and dispensing date on the blister card.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed or administered to the patients, the number of units returned to the investigator by the patient (if applicable), and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for all IP. Investigational product must be dispensed or administered only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All IP and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.6 Monitoring by the Sponsor

A representative of the sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Blood and urine samples for evaluation of hematology, chemistries, and urinalysis will be analyzed at a central clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification).

Patients consenting to participate in pharmacogenetic sampling will have a single blood sample collected to determine individual genotype status and for pharmacogenetic bio banking. The genetic material from the blood sample will be used to study factors which may influence how patients respond to a drug or may explain the pathophysiology of the disease. Blood samples will be stored to provide a resource for potential future trials conducted by Allergan.

All pharmacogenetic samples collected will be sent to the designated central laboratory and later shipped to a biorepository for storage.

10.8 Publications

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory Coordinating investigator will be designated prior to the writing of the Clinical Study Report.

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12 Attachments

12.1 Elements of Informed Consent

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's legally authorized representative. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; the sponsor; the IRB; or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the investigator as the contact. The guidance of the IRB/EC may be required)

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the investigator without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research

- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation

- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient

- The approximate number of patients involved in the study

- A statement of consent (eg, "I agree to participate . . .")

- A place for the patient's signature and date of signing

- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

A copy of the signed consent form must be given to the patient.

12.2 Structured Clinical Interview for the Positive and Negative Syndrome Scale (PANSS)

SCI-PANSS Scoring Sheet

☐	P1. Delusions
☐	P2. Conceptual disorganization
☐	P3. Hallucinatory behavior
☐	P4. Excitement
☐	P5. Grandiosity
☐	P6. Suspiciousness/persecution
☐	P7. Hostility
☐	N1. Blunted affect
☐	N2. Emotional withdrawal
☐	N3. Poor rapport
☐	N4. Passive/apathetic social withdrawal
☐	N5. Difficulty in abstract thinking
☐	N6. Lack of spontaneity and flow of conversation
☐	N7. Stereotyped thinking
☐	G1. Somatic concerns
☐	G2. Anxiety
☐	G3. Guilt feelings
☐	G4. Tension
☐	G5. Mannerisms and posturing
☐	G6. Depression
☐	G7. Motor retardation
☐	G8. Uncooperativeness
☐	G9. Unusual thought content
☐	G10. Disorientation
☐	G11. Poor attention
☐	G12. Lack of judgment and insight
☐	G13. Disturbance of volition
☐	G14. Poor impulse control
☐	G15. Preoccupation
☐	G16. Active social avoidance

PANSS QuikScore™ Form

Use this scale for all items:
1 = Absent
2 = Minimal
3 = Mild
4 = Moderate
5 = Moderate/Severe
6 = Severe
7 = Extreme

MHS

In the U.S.A., P.O. Box 950, North Tonawanda, NY 14120-0950, (800) 456-3003.
In Canada, 3770 Victoria Park Avenue, Toronto, ON M2H 3M6, (800) 268-6011.
Internationally, +1-416-492-2627.
Fax, +1-416-492-3343 or (888) 540-4484.

Rater Signature: _____ Date (DD/MMM/YYYY): _____

12.3 Clinical Global Impressions–Severity (CGI-S)

SEVERITY OF ILLNESS

Considering your total clinical experience with this population, how mentally ill is the patient at this time?

Check one:

1 = Normal, not at all ill

2 = Borderline ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

12.4 Clinical Global Impressions–Improvement (CGI-I)

GLOBAL IMPROVEMENT

Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his/her condition at Visit 2 (Baseline), how much has the patient changed?

Check one:

- ☐ 1 = Very much improved
- ☐ 2 = Much improved
- ☐ 3 = Minimally improved
- ☐ 4 = No change
- ☐ 5 = Minimally worse
- ☐ 6 = Much worse
- ☐ 7 = Very much worse

12.5 Barnes Akathisia Rating Scale

Rating scale for drug-induced akathisia (BARS)

Patient name:

Patient research no.:

Hospital No.:

Ward:

Rater:

Instructions

Patient should be observed while they are seated, and then standing while engaged in neutral conversation (for a minimum of 2 minutes in each position). Symptoms observed in other situations, for example while engaged in activity on the ward, may also be rated. Subsequently, the subjective phenomena should be elicited by direct questioning.

Objective

0 Normal, occasional fidgety movements of the limbs

1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, and/or rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed

2 Observed phenomena, as described in (1) above, which are present for at least half the observation period

3 Patient is constantly engaged in characteristic restless movements, and/or has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

0 Absence of inner restlessness

1 Non-specific sense of inner restlessness

2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, and/or complains of inner restlessness aggravated specifically by being required to stand still

3 Awareness of intense compulsion to move most of the time and/or reports strong desire to walk or pace most of the time

Distress related to restlessness

0 No distress

1 Mild

2 Moderate

3 Severe

Global clinical assessment of akathisia

0 Absent. No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia

1 Questionable. Non-specific inner tension and fidgety movements

2 Mild akathisia. Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress

3 Moderate akathisia. Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing

4 Marked akathisia. Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least 5 minutes. The condition is obviously distressing

5 Severe akathisia. The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

Reproduced from: A rating scale for drug-induced akathisia. T.R.E. Barnes, British Journal of Psychiatry (1989), 154, 672-676.

12.6 Abnormal Involuntary Movement Scale (AIMS)

EXAMINATION PROCEDURE

Either before or after completing the Examination Procedure, observe the patient unobtrusively, at rest (eg, in waiting room). The chair to be used in this examination should be hard, firm without arms.

1. Ask patient whether there is anything in his/her mouth (ie, gum, candy, etc.) and if there is, to remove it.

2. Ask patient about the current condition of his/her teeth. Ask patient if he/she wears dentures. Do teeth or dentures bother patient now?

3. Ask patient whether he/she notices any movements in mouth, face, hands or feet. If yes, ask to describe and to what extent they currently bother patient or interfere with their activities.

4. Have patient sit in chair with hands on knees, leg slightly apart, and feet flat on floor. (Look at entire body for movements while in this position.)

5. Ask patient to sit with hands hanging unsupported. If male, between legs, if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)

6. Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.

7. Ask patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.

8. Ask patient to tap thumb, with each finger, as rapidly as possible for 10 to 15 seconds; separately with right hand. (Observe facial and leg movements.)*

9. Flex and extend patient's left and right arms (one at a time).

10. Ask patient to stand up. (Observe profile. Observe all body areas again, hips included.)

11. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs and mouth.) *

12. Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice. *

* Activated movements

AIMS -SCORE SHEET

FACIAL AND ORAL MOVEMENTS

1. Muscles of Facial Expressions
   e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing

   0 None
   1 Minimal, may be extreme normal
   2 Mild
   3 Moderate
   4 Severe

2. Lips and Perioral Area
   e.g., puckering, pouting, smacking

   0 None
   1 Minimal, may be extreme normal
   2 Mild
   3 Moderate
   4 Severe

3. Jaw
   e.g., biting, clenching, chewing, mouth opening, lateral movement

   0 None
   1 Minimal, may be extreme normal
   2 Mild
   3 Moderate
   4 Severe

4. Tongue
   Rate only increase in movements both in and out of mouth, NOT inability to sustain movement

   0 None
   1 Minimal, may be extreme normal
   2 Mild
   3 Moderate
   4 Severe

EXTREMITY MOVEMENTS

5. Upper (arms, wrists, hands, fingers)
   Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) or athetoid movements (i.e., slow, irregular, complex, serpentine). DO NOT include tremor (i.e. repetitive, regular, rhythmic movements)

   0 None
   1 Minimal, may be extreme normal
   2 Mild
   3 Moderate
   4 Severe

6. Lower (legs, knees, ankles, toes)
e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot

0 None
1 Minimal, may be extreme normal
2 Mild
3 Moderate
4 Severe

TRUNK MOVEMENTS

7. Neck, shoulders, hips
e.g., rocking, twisting, squirming, pelvic gyrations

0 None
1 Minimal, may be extreme normal
2 Mild
3 Moderate
4 Severe

GLOBAL JUDGMENTS

8. Severity of abnormal movements

0 None/Normal
1 Minimal
2 Mild
3 Moderate
4 Severe

9. Incapacitation due to abnormal movements

0 None/Normal
1 Minimal
2 Mild
3 Moderate
4 Severe

10. Patient's awareness of abnormal movements

0 No awareness
1 Aware, no distress
2 Aware, mild distress
3 Aware, moderate distress
4 Aware, severe distress

DENTAL STATUS

11. Current problems with teeth and/or dentures

0 No
1 Yes

12. Does patient usually wear dentures?

0 No
1 Yes

12.7 Simpson-Angus Scale (SAS)

1. GAIT
The patient is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for an overall score for this item. This is rated as follows:

0 Normal
1 Diminution in swing while the patient is walking
2 Marked diminution in swing with obvious rigidity in the arm
3 Stiff gait with arms held rigidly before the abdomen
4 Stooped shuffling gait with propulsion and retropulsion

2. ARM DROPPING
The patient and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject, a stout slap is heard as the arms hit the sides. In the patient with extreme Parkinson's syndrome, the arms fall very slowly:

0 Normal, free fall with loud slap and rebound
1 Fall slowed slightly with less audible contact and little rebound
2 Fall slowed, no rebound
3 Marked slowing, no slap at all
4 Arms fall as though against resistance; as though through glue

3. SHOULDER SHAKING
The patient's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the patient's elbow. The patient's upper arm is pushed to and fro and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:

0 Normal
1 Slight stiffness and resistance
2 Moderate stiffness and resistance
3 Marked rigidity with difficulty in passive movement
4 Extreme stiffness and rigidity with almost a frozen shoulder

4. ELBOW RIGIDITY
The elbow joints are separately bent at right angles and passively extended and flexed, with the patient's biceps observed and simultaneously palpated. The resistance to this procedure is rated. (The presence of cogwheel rigidity is noted separately.)

0 Normal
1 Slight stiffness and resistance
2 Moderate stiffness and resistance
3 Marked rigidity with difficulty in passive movement
4 Extreme stiffness and rigidity with almost a frozen joint

5. FIXATION OF POSITION OR WRIST RIGIDITY
The wrist is held in one hand and the fingers held by the examiner's other hand, with the wrist moved to extension, flexion and ulner and radial deviation:

0 Normal
1 Slight stiffness and resistance
2 Moderate stiffness and resistance
3 Marked rigidity with difficulty in passive movement
4 Extreme stiffness and rigidity with almost a frozen joint

6. LEG PENDULOUSNESS
The patient sits on a table with his legs hanging down and swinging free. The ankle is grasped by the examiner and raised until the knee is partially extended. It is then allowed to fall. The resistance to falling and the lack of swinging form the basis for the score on this item:

0 The legs swing freely
1 Slight diminution in the swing of the legs
2 Moderate resistance to swing
3 Marked resistance to damping of swing
4 Complete absence of swing

7. HEAD DROPPING
The patient lies on a well-padded examining table and his head is raised by the examiner's hand. The hand is then withdrawn and the head allowed to drop. In the normal patient the head will fall upon the table. The movement is delayed in extrapyramidal system disorder and in extreme parkinsonism it is absent. The neck muscles are rigid and the head does not reach the examining table. Scoring is as follows:

0 The head falls completely with a good thump as it hits the table
1 Slight slowing in fall, mainly noted by lack of slap as head meets the table
2 Moderate slowing in the fall quite noticeable to the eye
3 Head falls stiffly and slowly
4 Head does not reach examining table

8. GLABELLA TAP
Patient is told to open eyes wide and not to blink. The glabella region is tapped at a steady, rapid speed. The number of times patient blinks in succession is noted:

0 0-5 blinks
1 6-10 blinks
2 11-15 blinks
3 16-20 blinks
4 21 and more blinks

9. TREMOR
Patient is observed walking into examining room and is then reexamined for this item:
0 Normal
1 Mild finger tremor, obvious to sight and touch
2 Tremor of hand or arm occurring spasmodically
3 Persistent tremor of one or more limbs
4 Whole body tremor

10. SALIVATION

Patient is observed while talking and then asked to open his mouth and elevate his tongue. The following ratings are given:

0 Normal
1 Excess salivation to the extent that pooling takes place if the mouth is open and the tongue raised
2 When excess salivation is present and might occasionally result in difficulty in speaking
3 Speaking with difficulty because of excess salivation
4 Frank drooling

12.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia-Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (eg, *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (eg, thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (ie, 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ____ _____ ***Most Severe Ideation:*** ***Type # (1-5) Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (eg, family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply	____

Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (eg, gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____

Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (eg, buying pills, purchasing a gun) or preparing for one's death by suicide (eg, giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:			**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?			**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (eg, surface scratches). 1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (eg, comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE

Since Last Visit Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

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SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (eg, *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (eg, thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (ie, 1-5 from above, with 1 being the least severe and 5 being the most severe). ____ _____ ***Most Severe Ideation:*** ***Type # (1-5) Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (eg, family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on (2) Mostly to get attention, revenge or a reaction from others living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on and to end/stop the pain living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (eg, gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, fee better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (eg, buying pills, purchasing a gun) or preparing for one's death by suicide (eg, giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:

Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (eg, surface scratches). 1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (eg, comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

12.9 Personal and Social Performance (PSP) Scale

The rating is based on 4 main areas: (a) socially useful activities, including work and study; (b) personal and social relationships; (c) self-care; and (d) disturbing and aggressive behaviors. Data will be captured in the following format using the PSP descriptions provided below:

	Absent	Mild	Manifest	Marked	Severe	Very Severe
a. Socially useful activities, including work and study	☐	☐	☐	☐	☐	☐
b. Personal and social relationships	☐	☐	☐	☐	☐	☐
c. Self-care	☐	☐	☐	☐	☐	☐
d. Disturbing and aggressive behaviors	☐	☐	☐	☐	☐	☐

For areas a-c, the degrees of severity are:	
Absent	
Mild	Not manifest difficulties, known only to someone who is very familiar with the person
Manifest, but not marked	Difficulties clearly noticeable by everyone, but not interfering substantially with the person's ability to perform his/her role in that area, given the person's socio-cultural context, age, sex and educational levels
Marked	Difficulties heavily interfering with role performance in that area; however, the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able to reach the previous level of functioning
Severe	Difficulties that make the person unable to any role performance in that area, if not professionally helped, or lead the person to a destructive role; however, there are no survival risks.
Very severe	Impairments and difficulties of such intensity to endanger person's survival.
For area d, the degrees of severity are:	
Absent	
Mild	Mild rudeness, unsociability or whingeing
Manifest, but not marked	Speaking too loudly or speaking to others in a too-familiar manner, or eating in a socially unacceptable manner
Marked	Insulting other in public, breaking or wrecking objects, acting frequently in a socially inappropriate but not dangerous way (eg, stripping in public or urinating in public).
Severe	Frequent verbal threats or frequent physical assaults, without intention or possibility of severe injuries.
Very severe	Frequent aggressive acts, aimed at or likely to cause severe injuries.

Occasional is defined as occurring 3 or more times in the reference period or occurring even less than 3 times but in circumstances and/or with such a previous history to convince the rater that there is a risk of recurrence in the near future. If the aggressive behavior has been present occasionally, the rating may be decreased by one degree, eg, from severe to marked.

* Main areas: a=socially useful activities, including work and study; b=personal and social relationships; c=self-care; d=disturbing and aggressive behaviors.

Guidelines for PSP Total Score

- Ratings from 71-100 reflect only mild difficulties.
- Ratings from 31-70 reflect manifest disabilities of various degrees.
- Ratings from 1-30 reflect functioning so poor that intensive support or supervision is needed.

The levels of functioning in other areas should be taken into account to adjust the rating inside the decimal level (for instance, from 31 to 40). Suicidal risk is not included in the scale.

10-point Intervals	***PSP Descriptions***
100 – 91	Excellent function in all 4 main areas*. He/she is held in high consideration for his/her qualities, copes adequately with life problems, is involved in a wide range of interests and activities
90 – 81	Good functioning in all 4 main areas, presence of only common problems or difficulties
80 - 71	Mild difficulties in 1 or more areas of a-c
70 – 61	Manifest, but not marked difficulties in 1 or more areas of a-c *or* mild difficulties in d
60 - 51	Marked difficulties in 1 of areas a-c, *or* manifest difficulties in d
50 – 41	Marked difficulties in 2 or more, *or* severe difficulties in 1 of areas a-c, with or without manifest difficulties in d
40 - 31	Severe difficulties in 1 and marked difficulties in at least 1 of areas a-c, or marked difficulties in d
30 - 21	Severe difficulties in 2 of areas a-c, *or* severe difficulties in d, with or without impairment in areas a-c
20 - 11	Severe difficulties in all areas a-d *or* very severe in d with or without impairment in general areas a-c. If the person reacts to external prompts the suggested score are 20-16, if not, the suggested scores are 15-11
10 - 1	Lack of autonomy in basic functioning with extreme behaviours but without survival risk (ratings 6-10) or with survival risk, eg, death risk due to malnutrition, dehydration, infections, inability to recognize situations of manifest dander (ratings 5-1)

12.10 Ophthalmological Examination

The ophthalmological examinations will consist of measurement of:

1. Best-corrected visual acuity (BCVA)

2. Color vision testing

3. Slit-lamp assessment of the lids, conjunctivae, corneas, iris and anterior chamber

4. Lens status and opacification: modified Age-Related Eye Disease Study (AREDS) severity scale

5. Slit-lamp assessment of the vitreous, retina, macula, and optic nerve

Best-corrected visual acuity (BCVA): BCVA will be documented at all scheduled ophthalmological visits. For the purpose of this study, every effort should be made that the same chart in the same examination room with the same lighting conditions that provide standardized chart illumination should be used for testing all study subjects at each visit where refraction and vision testing are required. Each eye will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) wall charts at a standard distance. The same distance should be used for all subsequent visits where vision testing is required. Floor markers should be used to ensure that the correct distance is measured at each examination. As far as possible the same examiner should do the testing for all visits where vision testing is required.

The appropriate lens correction will be used for each test to ensure that the test will be done with the actual best correction. The smallest line on which the majority of letters are read by each eye will be recorded (5 letters on each line, thus a maximum of 2 errors per line will be acceptable). The test will continue until a complete line is missed, ie, less than 3 characters in a line are identified.

Changes from the pre-treatment values (Screening, Visit 1) will be determined for each eye and classified as deterioration, improvement, or no change in visual acuity at each post-dose assessment. Clinically significant improvement or deterioration will be defined as a change of at least 2 standard lines (0.2 logMAR) on the ETDRS chart (Birch et al, 2002). The appropriate lens correction will be assessed before each test by a trained vision examiner using the ETDRS chart (R chart) to ensure that the test will be done with the actual best correction. As to the ETDRS charts, each eye will be tested using a different chart. The right eye will always be tested with Chart 1, and the left eye with Chart 2.

Scoring for ETDRS Chart: ETDRS is scored by the total number of letters correct. For example, reading the top line at 4 meters is a score of 35, each letter adds one to the score. In logMAR, each letter is 0.02, so a line adds 0.1 logMAR. Using this system, a correct reading of line 11 yields a score of 85 that is equivalent to 20/20 in the Snellen notation.

Color Vision Testing: Color vision testing will be performed to include both Blue-Yellow confusion and Red-Green confusion tests. For newly screened patients, testing to be completed using Hardy Rand Rittler (HRR) pseudoisochromatic color plates.

Slit-lamp assessment of the lids, conjunctivae, corneas iris and anterior chamber**:** Slit-lamp assessment of the lids, conjunctivae, corneas iris and anterior chamber will be conducted to evaluate the presence of disease and to assess anterior chamber depth and chamber angles to ascertain if chambers are too shallow to allow safe pupillary dilatation. Patients whose anterior chamber angles are too shallow for safe dilatation will be excluded from the study. Those whose angles are sufficiently deep to allow safe pupillary dilatation may have their pupils maximally dilated with appropriate mydriatics.

Intraocular pressure should be determined after completion of the biomicroscopic examination, before dilating the pupil. If necessary, IOP measurement may be repeated to obtain a reliable pressure. The most accurate measurement (as determined by the ophthalmologist) should be entered into the eCRF.

Lens Status and Opacification:

At screening and protocol-specified intervals, lens status will be assessed as phakic, pseudophakic, or aphakic.

For phakic eyes, the presence and severity of nuclear, cortical, and posterior subcapsular cataract lens opacities will be evaluated according to the modified Age-Related Eye Disease Study (AREDS) Clinical Lens Grading Protocol. Biomicroscopic findings will be compared with standard photographs from the AREDS Clinical Lens Standards grading guide. Allergan will supply the site with a copy of the guide.

Pupils should be dilated to at least 5 mm. The slit-lamp should be used at 10x magnification.

Grading will be performed as described below.

Cortical Opacities

- Use retroillumination.

- Include both anterior and posterior cortical opacities that are visible with retroillumination.
- Combine all opacities and compare total area with Cortical Standard Photograph #2 (about 25% of the visible lens).
- Standard photographs. Only Cortical Standard Photograph #2 is used in grading. Standard #2 with lines at the borders of the opacities is provided for reference.
- Grading scale
    - Opacity is absent.
    - Opacity is present, but less than Cortical Standard Photograph #2.
    - Opacity is present and is as severe as or is worse than Cortical Standard Photograph #2.

Nuclear Opacities

- Adjust the slit beam to a width of 0.3 mm and a height of 8.0 mm when using a Topcon SL-6E slit-lamp. When other slit lamps are used, set the slit beam width at 0.3 mm and height of 9.0 mm. If the Haag-Streit BX 900 Slit-lamp is used, please note that the width control knob does not indicate units in millimeters. A slit beam width of 0.3 mm may be set by turning the knob counter-clockwise to the second tick on the slit width control knob. Each tick opens the slit beam ~0.15 mm.
- Orient the slit beam at 45º to the viewing axis.
- Compare the slit-lamp appearance with Nuclear Standard Photograph #2. The primary considerations are: the **opalescence** (reflectance) **of the nucleus** and the **blurring of the normal landmarks**, ie, the dark interval at the center of the nucleus (the “sulcus”) and the short, bright bands adjacent to it anteriorly and posteriorly (the “lentils,” so named for their somewhat bean-like shape).
- Standard photographs. Only Nuclear Standard Photograph #2 is used in grading. Standard Photographs #1 and #3 are provided as examples of lenses that have less and more nuclear sclerosis, respectively, than Standard Photograph #2.
- Grading scale

- Opacity is absent.
- Opacity is present, but less than Nuclear Standard Photograph #2.
- Opacity is present and is as severe as or is worse than Nuclear Standard Photograph #2.

Posterior Subcapsular (PSC) Opacities

- Use retroillumination and include PSC opacities visible with it.
- Standard photographs. Only PSC Standard Photograph #2 is used for grading. PSC Standard Photograph #2 with lines at the borders of the opacity is provided for reference.
- Grading scale
  - Opacity is absent.
  - Opacity is present, but less than PSC Standard Photograph #2.
  - Opacity is present and is as severe as or is worse than PSC Standard Photograph #2.

Every attempt should be made to have the same ophthalmologist perform both Baseline and follow-up examinations.

Slit-lamp assessment of the vitreous, retina, macula, and optic nerve: When the lens examination is completed, the ophthalmologist will perform an examination of the vitreous, retina, macula, and optic nerve. Findings from these examinations will be recorded as normal or abnormal; abnormal findings will be specified with descriptive text.

12.11 Package Insert

The appropriate package insert will be supplied to investigators in countries where the product is marketed.

12.12 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
β-hCG	β-human chorionic gonadotropin
BCVA	best-corrected visual acuity
BP	blood pressure
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
C-SSRS	Columbia–Suicide Severity Rating Scale
CYP	cytochrome P450
DB	double-blind
DB ITT	double-blind intent-to-treat
DSM-5	Diagnostic & Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	electronic case report form
EPS	extrapyramidal symptoms
ET	Early Termination
EU	European Union
GBD	Global Burden of Disease
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HRR	Hardy Rand Rittler
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IOP	intraocular pressure
IP	investigational product
IRB	Institutional Review Board

ITT	Intent-to-treat
IWRS	interactive web response system
LOCF	last-observation-carried forward
NEAE	newly emergent adverse event
OL	open-label
OL SFU	open-label safety follow-up
PANSS	Positive and Negative Syndrome Scale
PCS	potentially clinically significant
PID	patient identification number
PSP	Personal and Social Performance Scale
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SCID-5	Structured Clinical Interview for DSM-5
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SFU	safety follow-up
TEAE	treatment-emergent adverse event
UDS	urine drug screen
US	United States
ULN	upper limit of normal
WHO	World Health Organization

12.13 Protocol Amendment 1 Summary

Title: 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 Patients With Schizophrenia

Protocol RGH-MD-24 Amendment 1

Date of amendment: 21 December 2017

The protocol was revised to clarify relapse and discontinuation criteria, clarify plans for summarization of ophthalmological data, clarify plans for summarization of safety data collected during the SFU period, and to remove an erroneous statement in Section 12.10 (Ophthalmological Examination). Following is a summary of content-oriented changes that were made to the protocol. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Title page	Updated sponsor address to: 5 Giralda Farms Madison, NJ 07940 USA	Update to current address
Protocol Summary; Section 3.2 Open-label Treatment Period; Section 4.6 Randomization Criteria; Section 8.9 Withdrawal Criteria	The discontinuation criteria associated with the requirement for either hospitalization or the initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or benzodiazepine were clarified to read as follows (new text in bold font): Additionally, patients who require **either** hospitalization (excluding protocol-allowed hospitalization during Screening/OL periods for the purpose of washout of prior psychiatric medications) or initiation of **treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days)** to treat **worsening** symptoms of schizophrenia **or** any **other psychiatric disorder as judged by** the **clinical impression of the investigator** will be discontinued.	Clarification
Protocol Summary; Section 3.3 Double-blind Treatment Period; Section 4.7 Relapse Criteria During the Double-blind Treatment Period; Section 7.2.1 Primary Efficacy Variable	The first of the 7 defined relapse criteria was revised to read (new text in bold font): • Increase in PANSS total score by ≥ 30% **for patients who had a PANSS total score of ≥ 50 at Randomization/Visit 13 or a ≥ 10-point increase in PANSS total score for patients who had a PANSS total score < 50** at Randomization/Visit 13	Clarification

Section	Revision	Rationale
Protocol Summary; Section 3.3 Double-blind Treatment Period; Section 4.7 Relapse Criteria During the Double-blind Treatment Period; Section 7.2.1 Primary Efficacy Variable	The fifth of the 7 defined relapse criteria was revised to read (new text in bold font): • Initiation **of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam or equivalent or for more than 3 consecutive days)** to treat worsening symptoms of schizophrenia **or any** other **psychiatric disorder as judged by the clinical impression of the investigator**	Clarification
Section 6.4 Pharmacogenetic Sampling	The following sentence was added: Pharmacogenetic consent may be obtained at any time between Visit 1/Screening and Week 8 (Visit 8).	Clarification
Section 6.5.7 6.5.7Ophthalmological Examination	The following sentence was added: Patients with a finding of cataracts at any time during the study must be discontinued.	Clarification and consistency with patient safety considerations.
Section 6.5.8.2 Columbia-Suicide Severity Rating Scale	The following sentence was revised to read as follows (new text in bold font): The C-SSRS will be completed at all study visits, except Visit 27 **and Visit 28**.	Clarification
Section 7.1.4 Open-label Safety-Follow-up Population	A new analysis population was added, defined as follows: The open-label safety-follow-up (OL SFU) population will consist of patients in the OL safety population who were not randomized.	Clarification
Section 7.3.4 Safety Analyses	The planned summarization of the safety data collected during the SFU period was clarified to read (new text in bold font): The safety analyses will be performed for the OL safety, **OL SFU**, and DB safety populations. The summarization will be overall for the OL **treatment period in the OL safety population** and **for the OL SFU period in the OL SFU population**. **The summarization will be** by treatment group for the DB **treatment** period and **DB** SFU period **in the DB safety population**. The summarization for the OL treatment period will use the OL safety population as the denominator. The summarization for the DB treatment period will use the DB safety population as the denominator. The summarization for the **OL SFU period and DB** SFU period will use the **OL SFU population and the** DB safety population as the denominator**, respectively**.	Clarification
Section 7.3.4.3 Vital Signs	The definition of different hypertension status will be detailed in the SAP.	Clarification

Section	Revision	Rationale
Section 7.3.4.1 Adverse Events	New text added for summarization of ocular events of special interest, as follows: The number and percentage of patients reporting TEAEs of ocular events of special interest will be summarized overall for the OL treatment period in the open-label safety population and the OL SFU period in the OL SFU population, and by treatment for the DB treatment period and the DB SFU period in the double-blind safety population. The listing of all reported ocular events of special interest will be provided.	For clarification and consistency with other cariprazine studies.
Section 7.3.4.5.3 Ophthalmological Parameters	Description of summarization of BCVA outliers revised as follows (new text in bold font): The number and percentage of patients with **a change from Baseline** in **visual acuity ≥ +0.3 in each eye and in either eye** will be summarized overall for the OL treatment period, and by treatment group for the DB treatment period. The threshold for tabulation of postbaseline IOP values was revised from 25 mm Hg to 21 mm Hg; revised sentence reads (new text in bold font): The number and percentage of patients with postbaseline IOP > **21** mm Hg will be presented.	For clarification and consistency with other cariprazine studies.
Section 8.4.5 Double-blind Treatment Period (Visits 14 to 25); Section 8.4.6 Final or Early Termination Visit (Visit 26)	The following bullet point was added: • Assess patient for relapse (per Section 4.7)	Clarification
Section 12.10 Ophthalmological Examination	Deleted the following statement: ~~At Screening, the presence of pseudophakic or aphakic eyes will lead to a screen failure~~.	To harmonize the ophthalmologic examination instructions with eligibility criteria.

12.14 Protocol Amendment 2 Summary

Title: 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 Patients With Schizophrenia

Protocol RGH-MD-24 Amendment 2

Date of Amendment 2: 16 April 2018

Amendment Summary

This summary includes changes made to Protocol RGH-MD-24 Amendment 1 (21 December 2017).

Minor editorial and document formatting revisions have not been summarized. The following is a summary of the major changes that were made to each section of the protocol, and a brief rationale for these changes.

Section	Revision	Rationale
Global	• *Updated PANSS to SCI-PANSS where applicable* • *Changed "Threshold Symptoms" to "response criteria" where applicable*	For clarity
Protocol Summary Section 3.2 Open-label Treatment Period	• *Revision: included provision for a drug holiday in the event of tolerability issues on the 4.5 mg/d dose during the OLP*	Added to adjust for tolerability issues arising from dose escalation
Table 1 schedule of visits and procedures Section 4.2 Study Population Characteristics Section 4.3 Inclusion Criteria #3 Section 6.1 Diagnostic Assessments Section 8.4.1 Screening/Visit 1 (Days -7 to -1)	• *Replaced the scale used to make the diagnostic assessment from MINI to SCID-5* • *Removed EPS assessment from Visit 1*	Operational change
Section 3 Study Design	*Text regarding OL period was clarified globally*	For clarity
Section 4.4 Exclusion Criteria	*Exclusion around urine drug screen has been clarified*	For clarity

Section	Revision	Rationale
Protocol Summary Section 4.1 Number of Patients Section 7.5 Sample Size Calculation	*Sample size was changed*	Assumptions for sample size calculation were updated to reflect modified relapse data based on feedback from FDA during the review of the schizophrenia maintenance sNDA.
Section 4.5 Response Threshold, Stability, and Maintenance of Stability Criteria During the OL Treatment Period	*Text was clarified to defined stability and maintenance*	For clarity
Section 6.5.7 Ophthalmological Examination Appendix 12.10	*Added: anterior chamber and iris to slit-lamp examination*	These are standard components of a slit-lamp examination.
Section 9.4 Reporting of Pregnancies Occurring During the Study	*Changed period for reporting of pregnancies during the study from 30 days after last dose to 3 months following last dose.*	The reporting period for pregnancies is being extended in order to harmonize pregnancy reporting globally.
Section 12.2 Structured Clinical Interview for the Positive and Negative Syndrome Scale (PANSS) SCI-PANSS Scoring Sheet	*Replaced* SCI-PANSS Scoring Sheet	Updated for clarity
Section 12.9 PSP Scale	*Updated with full copy of scale*	For clarity
Appendix 12.10	*Deleted "At the end of the retinal evaluation the IOP will be measured again to ensure that there has not been a large rise in IOP postmydriasis. "*	Requirement is being removed as this is not typically done during an ophthalmic exam
In Schedule of Visits and Procedures and globally throughout protocol:	*Deleted any statement requiring patients with a postbaseline finding of cataracts to be discontinued (eg, "Patients with a finding of cataracts at any time during the study must be discontinued.) (This deletion does not impact exclusion criteria)*	This requirement is being removed to align with US Package Insert. If a cataract does occur, the patient will have a reassessment by an ophthalmologist at end of SFU (ie, following drug discontinuation)

12.15 Protocol Amendment #3 Summary

Title: 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 Patients With Schizophrenia

Study RGH-MD-24 Amendment 3

Date of Amendment 3: 28 November 2018

Amendment Summary

This summary includes changes made to Protocol RGH-MD-24 Amendment 2 (16 April 2018).

Minor editorial and document formatting revisions have not been summarized. The following is a summary of the major changes that were made to each section of the protocol, and a brief rationale for these changes.

Section	Major Revision	Rationale
Global	Corrected Serious Adverse Event Reporting Fax Number	To correct an error
Global	Changed Forest Laboratories to Allergan Sales	For clarity
Title Page	Added text to clarify the location of the Emergency Telephone Numbers	For clarity
Protocol Summary, Screening/Washout period	Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated	For clarity
Protocol Summary, Screening/Washout period	Added text to clarify that Day 8 is Visit 3	For clarity
Protocol Summary, Table 1	Added visit windows of + 3 days for Visit 2/Baseline and ± 3 days for Visit 3 through 13	For clarity
Protocol Summary, Table 1	Added "concentration by Breathalyzer" to Urine Drug Screen/Blood Alcohol	To expedite turnaround time for blood alcohol concentration results
Protocol Summary, Table 2	Added visit windows of + 3 days for Visit 2/Baseline and ± 3 days for Visit 14 through 28	For clarity
Protocol Summary, Table 2	Added serum pregnancy test at Visit 28	For clarity and for consistency with approved labeling
Protocol Summary, Table 2	Added text to clarify the timing of visits	For clarity
Section 3.1 Screening/Washout Period	Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated	For clarity and internal consistency
Section 3.1 Screening/Washout Period	Added text to clarity that Day 8 is Visit 3	For clarity and internal consistency
Section 4.3 Inclusion Criteria, criterion 13	Added text to clarify the need to use birth control for 12 weeks after the last dose of investigational product	For clarity and for consistency with approved labeling
Section 4.3 Inclusion Criteria, criterion 14	Added text to clarify that the serum pregnancy test is qualitative	For clarity
Section 4.4 Exclusion Criteria, criterion 2	Added text to clarify use disorders	For clarity and consistency across cariprazine programs
Section 4.4 Exclusion Criteria, criterion 3b	Added text to clarify that a positive UDS is not exclusionary if the drug was used as rescue medication during washout	For clarity
Section 4.4 Exclusion Criteria, criterion 9	Added text to exclude moderate CYP3A4 inhibitors	For clarity and for consistency with approved labeling
Section 4.4 Exclusion Criteria, criterion 15	Change example of endocrinological disease	For clarity
Section 4.4 Exclusion Criteria, criteria 18a and 18f	Added text to clarify cataracts as "lens opacifications" and changed 6 mm to 5 mm	For clarity and to align protocol with AREDS requirements

Section	Major Revision	Rationale
Section 4.4 Exclusion Criteria, criteria 24, 25, and 26	Added: 24. Absolute neutrophil count < 1000 per mm^3 at screening 25. Hemeglobin A1c (HbA1c) > 7% at screening 26. Blood alcohol concentration > 0.02 g/dL at Visit 1 as measured by breathalyzer	Criterion 24 has been added to align with withdrawal criteria. Criterion 25 has been added to clarify definition of stable endocrinological disease, and criterion 26 has been added to clarify expectation around alcohol use

Section	Major Revision	Rationale
Section 4.8.1 Permissible Medications/Treatments	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	For clarity and for consistency with approved labeling
Section 4.8.2 Prohibited Medications/Treatments	Added text to clarify that moderate CYP3A4 inhibitors are also prohibited, psychotropic drugs not listed under rescue medications are prohibited, and phenazepam is prohibited	For clarity and internal consistency
Section 4.8.3.1 Insomnia	Added Suvorexant (maximum of 20 mg/d) to the list of allowed medications for insomnia	The list of allowable medications has been augmented to included additional rescue medication options
Section 4.8.3.2 Extrapyramidal Symptoms or Akathisia	Added Biperiden to permissible rescue medications for EPS or akathisia and removed dosing guidance	For clarity and to align with other protocols across the program
Section 5.5 Treatment Regimen and Dosing, Table 3 footnote	Added: All investigational products 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.	To clarify that dosing times can be switched but must allow for 24 hours between doses
Section 5.6 Treatment Compliance	Added text to state that any patient who misses ≥ 4 consecutive doses of IP must be discontinued from the study	To clarify the definition of non-compliance
Section 6.2.1.2 Clinical Global Impressions-Severity	Changed text to state that the rating scale must be performed by a trained rater	For clarity
Section 6.2.2.1 Clinical Global Impressions-Improvement	Changed text to state that the rating scale must be performed by a trained rater	For clarity
Section 6.2.2.2 Personal and Social Performance Scale	Changed text to state that the rating scale must be performed by a trained rater	For clarity
Section 6.5.2 Ocular Events of Special Interest	Changed text to clarify that serious ocular events must be reported and how serious or non-serious events are to be reported	For clarity
Section 6.5.3 Clinical Laboratory Determinations, Table 4	Added text to include a serum pregnancy test at Visit 8 and 28	For internal consistency with changes to Tables 1 and 2

Section	Major Revision	Rationale
Section 6.5.3 Clinical Laboratory Determinations, Table 4	Added "concentration as measured by breathalyzer" to Blood alcohol	To expedite turnaround time for blood alcohol concentration results
Section 6.5.8.2 Columbia-Suicide Severity Rating Scale	Added text to state that the rating scale must be performed by a trained rater	For clarity
Section 7.3.4.1 Adverse Events	Replaced all text to define how AEs and TEAEs will be coded and summarized	To reflect current sponsor standards
Section 8.2 Washout Intervals/Run-in	Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated	For clarity and internal consistency
Section 8.2 Washout Intervals/Run-in	Added text to clarify that Day 8 is Visit 3	For clarity and internal consistency
Section 8.3 Procedures for Final Study Entry	Added text to allow rescreening under certain situations after consultation with the Allergan medical monitor	To allow additional flexibility in allowing potentially eligible patients to be reconsidered for the study
Section 8.3 Procedures for Final Study Entry	Added text to clarify that the serum pregnancy test is qualitative	For clarity
Section 8.4 Visits and Associated Procedures	Added text to clarify the timing of visits	For clarity
Section 8.4.1 Screening/Visit 1 (Days -7 to -1)	Changed text to clarify how blood alcohol concentration is assessed	For clarity
Section 8.4.3 Open-label Treatment Period (Visits 3 to 12)	Added serum pregnancy at Visit 8	For clarity and to align with contraception guidance
Section 8.4.4 End of OL Period/Randomization Visit (Visit 13)	Changed text to clarify how blood alcohol concentration is assessed	For clarity
Section 8.4.7 Safety Follow-up Visits (Visits 27 and 28)	Edited text to make serum pregnancy test mandatory at Visit 28	For clarity and to align with contraception guidance
8.7 Compliance with Protocol	Added text to clarify the timing of visits	For clarity
Section 8.9 Withdrawal Criteria, number 4	Added text to clarify that Day 8 is Visit 3	For clarity and internal consistency
Section 8.9 Withdrawal Criteria, number 7	Added text to number 7 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	For clarity
Section 8.9 Withdrawal Criteria, number 10	Added text to number 10 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	For clarity

Section	Major Revision	Rationale
Section 9.4 Reporting of Pregnancies Occurring During the Study	Changed 3 months to 12 weeks	To align with contraception language
Section 10.4.1 Source Documents	Added text to clarify that source documents must follow ALCOA-C	For clarity
Section 12.9 Personal and Social Performance Scale, Guidelines for PSP Total Score	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	To correct the scoring guidelines
Section 12.10 Ophthalmological Examination	Deleted text listing wall chart standard distances	For flexibility and clarity

12.16 Protocol Amendment #4 Summary

Title: 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 Patients With Schizophrenia

Study RGH-MD-24 Amendment 4

Date of Amendment 4: 17 December 2019

Amendment Summary

This summary includes changes made to Protocol RGH-MD-24 Amendment 3 (28 November 2018).

Minor editorial and document formatting revisions have not been summarized. The following is a summary of the major changes that were made to each section of the protocol, and a brief rationale for these changes.

Section	Major Revision	Rationale
Global	Phrase ocular events of special interest changed to ocular AESIs.	For clarity.
Global	There is no longer a distinct SAE reporting form and AESI reporting form. It is a combined SAE/AESI form.	To reflect an administrative change in forms.
4.4 Exclusion Criteria	Exclusion Criterion #18a revised.	In light of ophthalmology consultation and FDA feedback, criterion revised to allow for inclusion of patients with non-clinically significant opacifications in order to facilitate recruitment.
6.5.2 Ocular Adverse Events of Special Interest	Addition of a text note with associated asterisk to clarify reporting requirements specifically around cataracts.	Text amended to provide direction regarding cataract reporting when using the AREDS grading system, consistent with regulatory feedback.
9.1.2 Serious Adverse Event	Text revised to clarify which pregnancy outcomes or genetic abnormalities are considered SAEs.	For clarity.
12.10 Ophthalmological Examination	Protocol was updated to specify that color vision testing is to be completed using HRR color plates for newly screened patients.	To standardize data collection.