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A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CARIPRAZINE AS AN ADJUNCT TO ANTIDEPRESSANTS IN THE TREATMENT OF PATIENTS WITH MAJOR DEPRESSIVE DISORDER WHO HAVE HAD AN INADEQUATE RESPONSE TO ANTIDEPRESSANTS ALONE

Protocol Number:	3111-302-001	
Amendment Number:	3	
Phase:	3	
Name of Investigational Product:	Cariprazine	
Sponsor:	Allergan Sales, LLC 5 Giralda Farms, Madison, NJ 07940	Allergan Ltd. Marlow International, The Parkway, Marlow Buckinghamshire SL7 1YL United Kingdom
Regulatory Agency Identifying No.	IND number 104,466 (US), EudraCT number 2018-003164-31	
Emergency Telephone Numbers:	Refer to the Study Contacts List in the Investigator Site File or Trial Master File	
Serious Adverse Event Reporting Fax Numbers: Email:	+1-714-796-9504 (Back Up Fax No.: +1-714-246-5295) IR-Clinical-SAE@allergan.com	
Allergan Medical Safety Physician Contact Information:	Refer to the Study Contacts List in the Investigator Site File or Trial Master File	
Sponsor Signatory:	[redacted] MD Vice President, Neuroscience Development	

Refer to the final page of this protocol for approval signature and date of approval.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	July 2020
Amendment 2 (not implemented)	March 2020 (not implemented)
Amendment 1	December 2018
Original Protocol	July 2018

The following information can be found on FDA Form 1572 (US) and/or in the study contacts list in the Investigator site file 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.

Protocol Amendment #3 Summary

Title: A Double-Blind, Placebo-Controlled Study of Cariprazine as an Adjunct to Antidepressants in the Treatment of Patients With Major Depressive Disorder who Have had an Inadequate Response to Antidepressants Alone

Amendment Summary

Protocol 3111-302-001 Amendment #2 was approved by the Sponsor in March 2020, but not implemented due to a change in strategy; pertinent changes from amendment #2 that will be implemented are summarized in the table below. This summary includes the complete list of changes made from Protocol 3111-302-001 Amendment #1 (19 Dec 2018) to Amendment #3.

Following is a summary of changes that were made to each section of the protocol, and a brief rationale for these changes.

Minor editorial and document formatting revisions, including updates to abbreviations have not been summarized.

Section	Revision	Rationale
Protocol Summary, Study Design: *Structure*	Revised text to clarify expectation around inadequate response to 1-3 ADTs in the current episode.	For clarity
Protocol Summary, Study Design: *Duration, Visit Schedule*	Added text to extend the screening period an additional 7 days if needed with Sponsor approval.	To facilitate enrollment
Protocol Summary, Study Population Characteristics: *Number of Patients*	Increased potential screening pool from approximately 1125 to approximately 1700.	To account for a higher than expected screen failure rate
Protocol Summary, Study Population Characteristics: *Key Inclusion Criteria*	Revised text to clarify expectation around inadequate response to 1-3 ADTs in the current episode.	For clarity
General Statistical Methods and Types of Analyses: *Sample Size Calculation*	Increased potential screening pool from approximately 1125 to approximately 1700.	To account for a higher than expected screen failure rate
Figure 1 Study Schema	Figure 1 was revised to add text to extend the screening period up to an additional 7 days if necessary as approved by the Sponsor.	To facilitate enrollment

Section	Revision	Rationale
Schedule of Visits and Procedures, Table 1	Footnote d, blood alcohol removed Footnote e, clarified that blood alcohol concentration is assessed by Breathalyzer; statement that blood alcohol concentration was to be assessed at Visit 1 only was deleted. Footnote e, was also added to serum pregnancy test. Footnote k "May be up to an additional 7 days (up to 21 days) if necessary with Sponsor approval" was added to indicate extended screening period.	For consistency Footnote streamlined for clarity For consistency To facilitate enrollment
Section 3 Study Design: Study Duration, Screening/Washout Period	Added text to extend the screening period up to an additional 7 days if needed with Sponsor approval.	To facilitate enrollment
Section 4.1 Number of Patients	Increased potential screening pool from approximately 1125 to approximately 1700.	To account for an increased screen failure rate
Section 4.2 Study Population Characteristics and Section 4.3 Inclusion Criteria: Inclusion criterion number 5.	Extended the maximum duration of current major depressive episode at screening from "not exceeding 18 months" to "less than 24 months".	Window for depressive episode has been widened to facilitate recruitment while still excluding potential cases of dysthymia.
Section 4.3 Inclusion Criteria: Inclusion criterion number 8.	Text was changed/added: 8. In the current depressive episode, patients must have an inadequate response (< 50% improvement) to 1 to 3 antidepressants of adequate dose and adequate duration, as measured by the modified ATRQ. Adequate dose is defined as a dose above the minimum labeled dose (per package insert). Adequate duration is defined as continuous ADT treatment for at least 6 weeks, with a minimum of 3 of 6 weeks above the minimal dose.	Text amended for clarity.
Section 4.4 Exclusion Criteria: Exclusion Criterion 12	Added text to also exclude "treatment with esketamine".	Exclusion expanded to account for recent approval of esketamine
Section 4.4 Exclusion Criteria: Exclusion Criterion 15	Lowered restriction of participation in another study from within 6 months to within 3 months of Visit 1.	To enhance enrollment
Section 4.4 Exclusion Criteria: Exclusion Criterion 25	Added text to except patients with negative reflex HCV RNA titer test from being excluded.	Criterion is being amended to facilitate recruitment of otherwise eligible patients, without increasing safety risk.
Section 4.4 Exclusion Criteria: Exclusion Criterion 30	Changed exclusion criterion on Hemoglobin A1c to > 8% (instead of > 7%).	Criterion is being amended to facilitate recruitment of otherwise eligible patients, without increasing safety risk.

Section	Revision	Rationale
Section 4.5.1.1 Definition of Females of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods	Additional permitted hormonal contraceptive (ring) added.	To reflect current available contraceptive products
Section 4.5.2 Prohibited Medications and Treatments	Text revised to clarify that the concomitant study ADT is excluded from this restriction. Text revised to clarify the expectation around alcohol consumption during the study.	For clarity For clarity
Section 6.1.2 SAFER Criteria Inventory	Added text to clarify that phone interviews should not occur on-site.	For patient comfort and data quality
Section 6.6.2 Ocular Events of Special Interest	Added text to clarify that the ocular events to report to the Sponsor are ocular adverse events of special interest.	For clarity
Section 6.6.3: Table 3	Added text to reflect the amended Exclusion Criterion 25: Reflex HCV RNA titer test will be performed for all Hepatitis C virus antibody positive or reactive results. Added Absolute Neutrophil Count (ANC) to the table.	To facilitate recruitment of otherwise eligible patients, without increasing safety risk. For consistency
Section 7.4 Other Analyses	Added text to clarify that any additional analyses related to COVID-19 that might be needed, would be detailed in the SAP.	To account for potential analyses that may be needed in light of COVID-19.
Section 8.2 Washout Interval	Added text to extend the screening period up to an additional 7 days if needed with Sponsor approval.	To facilitate enrollment
Section 8.3 Procedures for Final Study Entry	Added text to permit rescreening of screen failures in certain situations after consultation with the Allergan Medical Monitor.	To facilitate enrollment
Section 8.4 Visits and Associated Procedures	Added text to address modifications to study visits during COVID-19.	For consistency with COVID-19 protocol addendum – dated 29-APR-2020
Section 8.5 Instructions for the Patients	Text revised to clarify the expectation around alcohol consumption during the study.	For clarity
Section 8.9 Withdrawal Criteria	Deleted withdrawal criterion #2 regarding using prohibited medications.	To facilitate patient retention when appropriate
Section 9.4 Reporting of Pregnancies Occurring During the Study	Added text to clarify that serum pregnancy tests can be done at any time if a pregnancy is suspected by the investigator. Also added statement that if a serum pregnancy test comes back as borderline, it should be repeated and consultation with the Allergan Medical Monitor is required.	For clarity and patient safety

Section	Revision	Rationale
Section 12.2 Protocol Modifications for COVID-19	Global Protocol Amendment #1 COVID-19 addendum (dated 29-APR-2020) was wholly incorporated as Section 12.2 with the following modifications:	For completeness
Purpose of Protocol Addendum	-Heading deleted and introductory text revised to reflect its incorporation into the global protocol	To improve readability
Section 12.2.1. Planned Changes in Research	-Introductory text revised and criterion regarding withdrawal due to 4 or more missed doses of IP or ADT revised to state patients should be withdrawn if more than 7 doses of IP or ADT are missed due to COVID-related reasons	Text revised to provide specific guidance around missed consecutive doses
Section 12.2.4.1 In-Home Study Visits and Section 12.2.4.2 Clinical Laboratory Assessments	-References to Amendment #1 were updated to Amendment #3.	To reflect latest protocol version

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, Independent Ethics Committee, 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: 3

Study Objective: To evaluate the efficacy, safety, and tolerability of cariprazine 1.5 mg/day and 3 mg/day compared with placebo as an adjunctive treatment to ongoing antidepressant therapy (ADT) in patients with major depressive disorder (MDD) who have had an inadequate response to antidepressants alone.

Clinical Hypotheses: In the treatment of patients with MDD who have had an inadequate response to ADT alone, cariprazine as an adjunctive treatment to ADT is safe and more effective than placebo + ADT.

Study Design

Structure: This is a global, multicenter, randomized, double-blind (DB), placebo-controlled, parallel-group, fixed-dose study comparing cariprazine 1.5 mg/day and cariprazine 3 mg/day with placebo as an adjunctive treatment to ongoing ADT in outpatients with a diagnosis of MDD (via the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition [DSM-5]) who have an inadequate response, as measured by the modified Antidepressant Treatment Response Questionnaire (ATRQ), to 1 to 3 antidepressants administered during the current episode at an adequate dose and adequate duration. Adequate dose is defined as a dose above the minimum labeled dose (per package insert). Adequate duration is defined as continuous ADT treatment for at least 6 weeks, with a minimum of 3 of 6 weeks above the minimal dose. The study schema is presented in Figure 1.

Duration: The study will consist of up to 14 days of screening (with up to an additional 7 days if needed with Sponsor approval) and washout of prohibited medications followed by 6 weeks of DB treatment followed by a 4-week safety follow-up. At the end of the screening period, patients meeting the entry criteria for this study will be randomized (1:1:1) to 1 of 3 DB treatment groups:

- cariprazine 1.5 mg/day + ADT
- cariprazine 3 mg/day + ADT
- placebo + ADT

Study Treatment Groups: cariprazine 1.5 mg/day + ADT and cariprazine 3 mg/day + ADT

Controls: matching placebo + ADT

Dosage/Dose Regimen: Investigational product (cariprazine or placebo) in the form of capsules packaged in blister packs will be provided by the Sponsor. No investigational product will be administered during the screening/washout period; patients will continue the same antidepressant and dose they were on at Screening. Patients who are taking more than one antidepressant at Screening, regardless of the indication, will need to discontinue all other antidepressants prior to Baseline (Visit 2). During the DB treatment period (6 weeks), patients will take 1 capsule orally per day in addition to their ongoing ADT. Patients in the 1.5 mg/day + ADT arm will take 1.5 mg + ADT starting at Visit 2 (Week 0). Patients in the 3 mg/day + ADT arm will take 1.5 mg + ADT starting at Visit 2 (Week 0) for 2 weeks and then titrate to 3 mg/day + ADT starting at Visit 4 (Week 2). Patients will be supplied with identically appearing capsules of either cariprazine 1.5 mg, cariprazine 3 mg, or placebo. After completion of the DB treatment period, patients will continue as outpatients during the safety follow-up period and will receive treatment as usual at the discretion of the investigator or designee; no investigational product will be administered.

Randomization/Stratification: After the screening period, eligible patients will be randomized in a 1:1:1 ratio to cariprazine 1.5 mg/day + ADT, cariprazine 3 mg/day + ADT, or placebo + ADT.

Visit Schedule: There are 7 visits including screening/washout (up to 14 days, with up to an additional 7 days if needed with Sponsor approval), the DB treatment period (6 weeks), and the safety follow-up visit (4 weeks) as shown in Table 1.

Study Population Characteristics

Number of Patients: The study will screen approximately 1700 patients to randomize 750 patients in a 1:1:1 ratio to cariprazine 1.5 mg/day + ADT, cariprazine 3 mg/day + ADT, and placebo + ADT groups. In the event that screen failure rates are higher than projected, enrollment will continue until approximately 250 patients per treatment arm are randomized.

Condition/Disease: Major depressive disorder

Key Inclusion Criteria: Male or female 18 to 65 years of age; meeting DSM-5 criteria for MDD; having a total score ≥ 22 on the Hamilton Depression Rating Scale–17 items (HAMD-17) and having an inadequate response, as measured by the modified ATRQ, to 1-3 antidepressants administered during the current episode at an adequate dose and adequate duration. Adequate dose is defined as a dose above the minimum labeled dose (per package insert). Adequate duration is defined as continuous ADT treatment for at least 6 weeks, with a minimum of 3 of 6 weeks above the minimal dose.

Key Exclusion Criteria: Any current psychiatric diagnosis other than MDD (including those with current intellectual development disability) with the exception of specific phobias. History of meeting DSM-5 for any substance-related disorders (ie, use disorders except caffeine- and tobacco-related) and addictive disorders within the 6 months before Visit 1.

Response Measures

Primary Efficacy Parameter: Montgomery-Åsberg Depression Rating Scale (MADRS).

Pharmacokinetics: Samples will be collected for determination of the plasma concentrations of cariprazine and its metabolites. A total of 3 blood samples will be collected during the study, as shown in Table 1.

Pharmacogenetic Sampling: One blood sample will be collected from randomized patients at any time point between Visit 2/Baseline (Week 0) and Visit 6/ET (Week 6) for pharmacogenetic biobanking. Participation is optional.

Safety: Adverse event recording, clinical laboratory parameters (hematology, chemistry, urinalysis, prolactin), vital sign parameters (including blood pressure, pulse rate), body mass index, weight, waist circumference, physical examinations, electrocardiograms, Columbia–Suicide Severity Rating Scale, Young Mania Rating Scale, and measures of extrapyramidal symptoms: Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and Simpson-Angus Scale.

General Statistical Methods and Types of Analyses: Efficacy analyses will be based on the modified intent-to-treat population, consisting of all randomized patients with ≥ 1 postbaseline assessment of the MADRS total score.

The primary efficacy parameter will be the change from baseline to Week 6 in the MADRS total score. The primary analysis will be performed using a mixed-effects model for repeated measures with treatment group, country, ADT failure category (one ADT failure, more than one ADT failure), visit, and treatment group-by-visit interaction as fixed effects, and the baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-patient scores. The Hochberg procedure will be used to control the overall type I error rate at a 0.05 level (2-sided) for multiple comparisons of 2 active doses with placebo for the primary endpoint.

Safety analyses will be based on the safety population consisting of all randomized patients who received at least 1 dose of DB investigational product. All safety parameters will be summarized descriptively.

Sample Size Calculation: The study will screen approximately 1700 patients to randomize 750 patients in a 1:1:1 ratio to cariprazine 1.5 mg/day + ADT, cariprazine 3 mg/day + ADT, and placebo + ADT groups. A sample size of 250 patients per arm will provide approximately 90% statistical power to show at least 1 of the 2 cariprazine doses is statistically significantly more efficacious than placebo in the primary endpoint, assuming an effect size of 0.286 and a dropout rate of 15% at Week 6. The sample size and power were calculated adjusting for multiple comparisons using the Hochberg procedure.

Figure 1 Study Schema

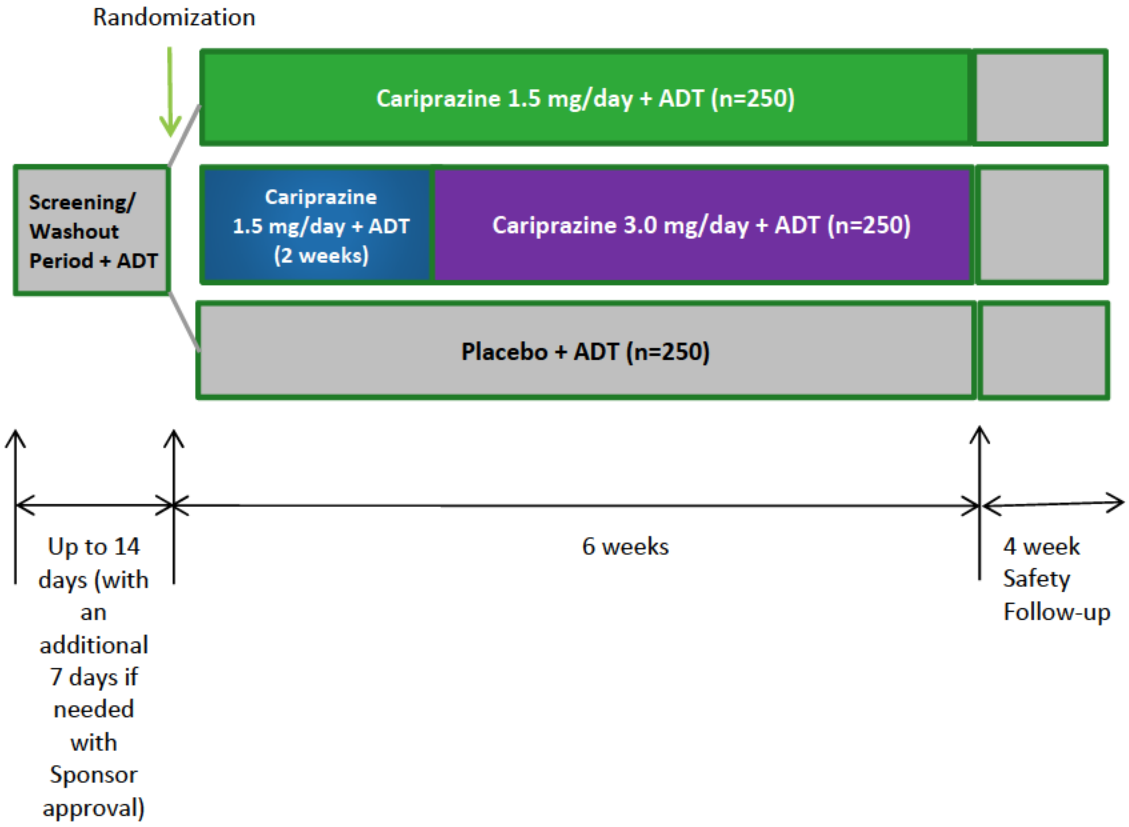

Table 1 Schedule of Visits and Procedures

Study Period	**Screening**	**Baseline**	**Double-blind Treatment**				**Safety Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**	**7**
Study Week	**Up to -2 [k]**	**0**	**1**	**2**	**4**	**6[a,b]**	**10**
Study Day	**Up to -14[k]**	**1**	**8**	**15**	**29**	**43**	**71**
Visit Windows		**(within 14 days of start of screening procedures)[k]**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**
Informed Consent	X						
Verified Clinical Trials Check[c]	X						
Medical and Psychiatric Histories	X						
Prior Medication History	X						
Inclusion/Exclusion Criteria	X	X					
Randomization		X					
Clinical Laboratory Tests[d,e]	X					X	
Serum Pregnancy Test[d,e]	X					X	X
Hepatitis Serology	X						
Hemoglobin A1c	X						
Urine Drug Screen[e]	X						
Blood Alcohol Concentration (by Breathalyzer)[e]	X						
Vital Signs[f]	X	X	X	X	X	X	X
Electrocardiogram	X					X	
Physical Examination	X					X	
SCID-5	X						
SAFER Remote Telephone Interview[g]	X						
Evaluate SAFER Score Qualification[g]		X					
Modified ATRQ	X						
HAMD-17	X	X				X	
YMRS	X	X				X	
MADRS	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	
CGI-I			X	X	X	X	

Study Period	**Screening**	**Baseline**	**Double-blind Treatment**				**Safety Follow-up**
Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**	**7**
Study Week	**Up to -2 [k]**	**0**	**1**	**2**	**4**	**6[a,b]**	**10**
Study Day	**Up to -14[k]**	**1**	**8**	**15**	**29**	**43**	**71**
Visit Windows		**(within 14 days of start of screening procedures)[k]**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**
HAM-A		X		X		X	
SF-12		X				X	
BARS/AIMS/SAS		X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Dispense IP		X	X	X	X		
Drug Return and Compliance			X	X	X	X	
ADT Compliance		X	X	X	X	X	
Pharmacogenetic Consent[h]	X	X					
Pharmacogenetic Sample[i]		X					
Pharmacokinetic Sample[j]				X	X	X	

Note: After completion of Visit 6/ET, patients will be treated at the discretion of the investigator or designee.

ADT = antidepressant therapy; AIMS = Abnormal Involuntary Movement Scale; ATRQ = Antidepressant Treatment Response Questionnaire; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = Hamilton Depression Rating Scale–17 items; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; SAS = Simpson-Angus Scale; SF-12 = Short Form-12 v2 Health Survey; YMRS = Young Mania Rating Scale.

[a] Performed for all patients, including those prematurely discontinued after randomization (Visit 2).

[b] Clinical findings upon termination must be followed until the condition returns to prestudy status or can be explained as unrelated to investigational product. If necessary, an additional follow-up visit should be scheduled.

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

[d] Clinical laboratory tests include hematology, serum chemistry, urinalysis (including urine myoglobin 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), as well as serum pregnancy test in women of childbearing potential.

[e] Urine drug screen, blood alcohol concentration (by Breathalyzer), and serum pregnancy test can be repeated at random at request of investigator.

[f] Height will be measured only at Visit 1 (Screening). Waist circumference will be measured at Visits 2 and 6/ET.

[g] SAFER/remote telephone interview will be scheduled and implemented before Visit 2 (Baseline) for patients who meet the screening criteria at Visit 1. The patient's SAFER evaluation score should be reviewed before Visit 2 to confirm eligibility.

[h] Pharmacogenetic consent may be obtained at any time between Visit 1 (Screening) and Visit 6 (Week 6).

[i] Pharmacogenetic sample (1 per patient for the entire study) may be obtained from randomized patients at any time between Visit 2 (Baseline) and Visit 6 (Week 6).

[j] Can be taken at any time during visits 4, 5 and 6/ET.

[k] May be up to an additional 7 days (up to 21 days) if needed with Sponsor approval.

1 Background and Clinical Rationale

Major depressive disorder (MDD) is a highly disabling, serious condition that is associated with significant morbidity and mortality. MDD manifests as a major depressive episode (which may be singular or recurrent) in which the affected individual experiences 1) depressed mood, or 2) loss of interest or pleasure (as well as other symptoms) for most of the day, nearly every day, for at least 2 weeks. MDD affects approximately 14.8 million American adults, or about 6.7% of the US population 18 years of age and older, in a given year (Kessler et al, 2005). Worldwide, about 15% of the adult population is at lifetime risk of developing MDD (Kessler et al, 1994).

Depression may cause serious, long-lasting symptoms and often disrupts a person's ability to perform routine tasks. According to the World Health Organization, depression is one of the leading causes of disability, measured as years lived with disability, in the world today among persons age 5 years and older and is the fourth most important contributor to the global burden of disease, measured as disability-adjusted life years (Mathers and Loncar, 2006). In 2010, mental and substance use disorders accounted for nearly 184 million disability-adjusted life years worldwide; depressive disorders accounted for 40.5% of this total burden (Whiteford et al, 2013). The total economic burden of treating depression in the United States was $83.1 billion, with workplace costs, including missed days and lack of productivity due to illness, accounting for most of the total economic burden (62%). Other economic burdens in 2000 included $26.1 billion (31%) for treatment costs and $5.4 billion (7%) for suicide-related costs (Greenberg et al, 2003).

MDD is a leading cause of disability in the United States (Murray et al, 2013). Moreover, MDD is known to be a significant risk factor for suicide and ischemic heart disease, as it accounted for 16 million of the disability-adjusted life years associated with suicide and 4 million of the disability-adjusted life years associated with ischemic heart disease. Research has shown that untreated depression has both a functional (social and work role) as well as a neuroanatomical (hippocampal shrinkage) effect on the patient (Videbech and Ravnkilde, 2004). Given the disease burden and link to suicidality as well as increased mortality with other comorbid conditions, MDD is a serious and life-threatening condition that is a leading cause of disability in the world.

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors in Major Depressive Disorder

Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors currently represent the first line of treatment of depression in the United States.

Unfortunately, a large number of patients do not experience therapeutic benefit from these first-line agents (Rosenzweig-Lipson et al, 2007). Lack of sufficient response to adequate treatment remains a critical problem in the management of patients with MDD. Up to two thirds of patients treated with first-line antidepressant monotherapy do not reach full remission, and as many as a third become treatment resistant (Fava and Davidson, 1996; Trivedi et al, 2006). Not achieving remission has been shown to be predictive of poorer psychosocial functioning, higher rates of relapse, and higher rates of rehospitalization (McIntyre and O'Donovan, 2004). The results of the STAR*D study suggest that with successive failures of treatment, patients are less and less likely to respond to subsequent treatment, and those who do respond are more likely to relapse (Rush et al, 2006). Present strategies available to treat patients who do not respond to first-line antidepressant monotherapy include switching of antidepressant (either within or between classes); combination therapy in which multiple antidepressants are used simultaneously; augmentation of ongoing antidepressant monotherapy with adjunctive use of drugs such as mood stabilizers or atypical antipsychotics (Boland and Keller, 2006); and the use of nonpharmacologic treatments including psychotherapy and phototherapy, vagus nerve stimulation, transcranial magnetic stimulation, and electroconvulsive therapy.

Atypical Antipsychotics as Adjunctive Therapy in Major Depressive Disorder

The drugs currently approved for use as adjunctive therapy to antidepressants for the treatment of MDD—namely, the atypical antipsychotics—are Abilify® (aripiprazole; Abilify® Package Insert, 2017), Seroquel XR® (quetiapine fumarate; Seroquel XR® Package Insert, 2017), and Rexulti® (brexpiprazole; Rexulti® Package Insert, 2018). Abilify (aripiprazole) was approved in 2007 for adjunctive treatment in adult patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria for MDD who had had an inadequate response to prior antidepressant therapy (ADT). Aripiprazole and brexpiprazole are both dopamine partial agonists like cariprazine. Both have shown efficacy in the treatment of depression as an adjunctive treatment to ADT. Seroquel XR was approved in 2009 for adjunctive treatment in adult patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria for MDD. Quetiapine is an atypical antipsychotic with relatively high affinity for D_2 and 5-HT_{2a} receptors and an active metabolite that has inhibitory affects at the norepinephrine transporter. Olanzapine in combination with fluoxetine has been shown to be effective in the treatment of treatment-resistant depression and is currently marketed for that indication as Symbyax® (Symbyax® Package Insert).

Cariprazine is an orally active and potent partial agonist at central dopamine D_3/D_2 and serotonin 5-HT_{1A} receptors and an antagonist at serotonin 5-HT_{2A} receptors developed by Gedeon Richter PLC and Allergan Sales, LLC.

On 17 September 2015, cariprazine (Vraylar®) was approved by the US FDA for the treatment of schizophrenia (1.5 mg to 6 mg/day) and for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults (3 mg to 6 mg/day) (Vraylar® Package Insert 2017). On 13 July 2017, Allergan's development partner, Gedeon Richter, was granted marketing authorization in the European Union for cariprazine (Reagila®) (Reagila® Package Insert 2017) for the treatment of schizophrenia in adult patients (1.5 to 6 mg/day).

Cariprazine has also demonstrated efficacy in the treatment of bipolar depression in three studies (RGH-MD-53, RGH-MD-54 and RGH-MD-56). Cariprazine doses of 1.5 and 3 mg have demonstrated efficacy in the treatment of bipolar depression.

The mechanism of action of cariprazine in schizophrenia and bipolar I disorder has not been fully elucidated. However, the efficacy of cariprazine could be mediated through a combination of partial agonist activity at central dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors. Cariprazine forms 2 major metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), that have in vitro receptor binding profiles similar to the parent drug.

A unique feature of cariprazine is that it binds with significantly higher affinity to D_3 than to D_2 receptors. Cariprazine displays partial agonist as well as antagonist activity on biosynthesis- and release-modulating presynaptic D_2 receptors and has preferential dopaminergic actions in the limbic regions. However, cariprazine is more potent than aripiprazole, and the degree of its apparent partial agonist activity is greater than aripiprazole's. Cariprazine also has considerable affinity for, and is a partial agonist and antagonist at, the serotonin 5-HT_{1A} and 5-HT_{2B} receptors, respectively. Antidepressant- and/or anxiolytic-like effects of cariprazine may also be mediated through these receptors.

2 Study Objectives and Clinical Hypotheses

2.1 Study Objective

The objective of this study is to evaluate the efficacy, safety, and tolerability of cariprazine 1.5 mg/day and 3 mg/day compared with placebo as an adjunctive treatment to ADT in patients with MDD who have had an inadequate response to antidepressants alone.

2.2 Clinical Hypotheses

In the treatment of patients with MDD who have had an inadequate response to ADT alone, cariprazine as an adjunctive treatment to ADT is safe and more effective than placebo as an adjunctive treatment to ADT.

3 Study Design

This is a global, multicenter, randomized, double-blind (DB), placebo-controlled, parallel-group, fixed-dose study comparing cariprazine 1.5 mg/day and cariprazine 3 mg/day with placebo as an adjunctive treatment to ongoing ADT in outpatients with a diagnosis of MDD (via the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5]) who have had an inadequate response to ADT in the current episode as measured by the modified Antidepressant Treatment Response Questionnaire (ATRQ). The study schema is presented in Figure 1.

Dose Selection and Rationale: Cariprazine has been evaluated as an adjunctive treatment to ADT in three flexibly-dosed clinical trials (RGH-MD-71, RGH-MD-72, and RGH-MD-75) in patients who have had an inadequate response to ADT alone. In those trials, the dose of cariprazine ranged from 0.1 mg to 4.5 mg. In one trial (RGH-MD-75), cariprazine 2 mg to 4.5 mg + ADT was found to be superior to placebo + ADT, as measured by the change from baseline to Week 6 on the MADRS total score. In this patient population, cariprazine doses lower than 2 mg did not demonstrate efficacy as an adjunctive treatment to ADT. However, in 3 monotherapy fixed-dose trials conducted in patients with depressive episodes associated with bipolar I disorder (RGH-MD-53, RGH-MD-54, and RGH-MD-56) cariprazine 1.5 mg was shown to be superior to placebo as a monotherapy treatment of depression. Cariprazine 1.5 and 3 mg/day have both demonstrated superior efficacy in the monotherapy treatment of bipolar depression.

The bipolar depression studies utilized a different titration schedule than previously employed for bipolar mania. This alternate dosing regimen and lower dose contributed to

improvements in tolerability. In the phase III bipolar depression program, all patients were started on cariprazine 1.5 mg. Patients assigned to 1.5 mg remained on dose for the remainder of the study, whereas, patients assigned to cariprazine 3 mg remained on cariprazine 1.5mg for 14 days before being uptitrated to 3 mg for the remainder of the study. Accordingly, based on the above-mentioned studies in MDD and bipolar depression, the doses for investigation in Study 3111-302-001 will be 1.5 mg/day and 3 mg/day as an adjunctive treatment to ADT.

Another area to consider is dopamine D2/D3 receptor occupancy. Cariprazine 1.5 mg/day D2 occupancy is 59% while its D3 occupancy is 83%. At 3 mg/day, D2 occupancy for cariprazine is 72% and D3 is 90% (Study RGH-PK-15). While no specific occupancy data are available to guide a dosing decision for adjunctive use of an antipsychotic agent with antidepressants, we do know that 2 other dopamine partial agonists with approved indications as an adjunctive treatment to antidepressants (aripiprazole 5 to 15 mg/day and brexpiprazole 2 mg/day to 4 mg/day) have rates of D2 receptor occupancy ranging from 60% to 90% (aripiprazole 80% to 90%; brexpiprazole 60% to 67%). The low D2 occupancy of cariprazine at 1.5 mg/day and 3 mg/day may provide enough receptor blockade to affect mood without adversely affecting movement. The occupancy of D3 and $5HT_{1A}$ receptors may also play an important role in the antidepressant efficacy of cariprazine.

Study Duration: The study will consist of up to 14 days of screening (with up to an additional 7 days if needed with Sponsor approval) and washout of prohibited medications followed by 6 weeks of DB treatment followed by a 4-week safety follow-up.

Screening/Washout Period: Patients with MDD with inadequate response to ongoing ADT in the current episode will undergo a screening period where consent, eligibility assessment, and withdrawal of prohibited medications will occur for up to 14 days (with up to an additional 7 days if needed with Sponsor approval). During the screening period, the patients will continue to take the ADT at the same dose to which they are having an inadequate response. Patients who are taking more than one antidepressant at Screening, regardless of the indication, will need to discontinue all other antidepressants prior to Baseline (Visit 2).

The length and timing of the washout of prior psychiatric medications during the 14 days allotted for the screening period is at the discretion of the investigator (with up to an additional 7 days if needed with Sponsor approval). Prior medications should be gradually withdrawn such that the washout is completed by Baseline (Visit 2). Please note that during the washout period psychotropic medications other than those listed as rescue (Section 4.5.3) may not be newly initiated or reinitiated.

Randomization/DB Treatment Period: 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 1.5 mg/day + ADT or 3 mg/day + ADT, or placebo + ADT. Investigational product (IP) will be administered orally once daily for 6 weeks.

Dosage and Dosing Regimen: Investigational product (cariprazine or placebo) in the form of capsules packaged in blister packs will be provided by the Sponsor. No investigational product will be administered during the screening/washout period; patients will continue on the ADT they were on at Screening. During the DB treatment period (6 weeks), patients will take 1 capsule orally per day in addition to their ongoing ADT. Patients in the 1.5 mg/day + ADT arm will take 1.5 mg + ADT starting at Visit 2 (Week 0). Patients in the 3 mg/day + ADT arm will take 1.5 mg + ADT starting at Visit 2 (Week 0) for 2 weeks and then 3 mg/day + ADT starting at Visit 4 (Week 2). Patients will be supplied with identically appearing capsules of either cariprazine 1.5 mg, cariprazine 3 mg, or placebo. After completion of the DB treatment period, patients will continue as outpatients during the safety follow-up period and will receive treatment as usual at the discretion of the investigator or designee; no investigational product will be administered.

4 Study Population and Entry Criteria

4.1 Number of Patients

The study will screen approximately 1700 patients to randomize approximately 750 patients in a 1:1:1 ratio to cariprazine 1.5 mg, cariprazine 3 mg, and placebo groups. In the event that screen failure rates are higher than projected, enrollment will continue until approximately 250 patients per treatment arm are randomized.

When the randomization target has been met, patients who have been screened, but who are not yet randomized, will be allowed to continue in the study until they fail to meet randomization criteria, prematurely discontinue, or complete the study.

4.2 Study Population Characteristics

The study population will include patients meeting criteria for MDD with a current major depressive episode of at least 8 weeks to less than 24 months in duration and an inadequate response to ongoing ADT in the current episode.

The diagnosis will be based upon *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria (American Psychiatric Association, 2013), approached

through a structured clinical interview (Structured Clinical Interview for DSM-5 [SCID-5]), and the ADT inadequate response will be determined using the modified ATRQ.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent has been obtained
2. 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])
3. Patient is male or female 18 to 65 years of age, inclusive, at the time of consent
4. Patient must be an outpatient at the time of Visit 1 (Screening)
5. Patient meets the DSM-5 criteria for MDD based on SCID-5, with a current major depressive episode of at least 8 weeks to less than 24 months in duration at Visit 1/Screening. A diagnosis of MDD with psychotic features will be acceptable
6. Diagnosis of MDD confirmed through a formal adjudication process (see Section 6.1)
7. Patient demonstrates ability to follow study instructions and likely to complete all required visits
8. In the current depressive episode, patient must have an inadequate response (< 50% improvement) to 1 to 3 antidepressants of adequate dose and adequate duration, as measured by the modified ATRQ. Adequate dose is defined as a dose above the minimum labeled dose (per package insert). Adequate duration is defined as continuous ADT treatment for at least 6 weeks, with a minimum of 3 of 6 weeks above the minimal dose.
9. Only one antidepressant (of sufficient dose per package insert and taken for at least 6 weeks) will be allowed at randomization and patients must agree to continue taking the same ADT dosing regimen through completion of Visit 6/ET. Patients who are taking more than one antidepressant at Screening, regardless of the indication, will need to discontinue all other antidepressants prior to Baseline (Visit 2)
10. Patient must have a minimum score of 22 on the rater-administered Hamilton Depression Rating Scale–17 items (HAMD-17) at both Screening (Visit 1) and Baseline (Visit 2)

11. Patient has a score of 2 or higher on Item 1 of the HAMD-17 rating scale at Visits 1 and 2

12. Patient has normal physical examination findings, clinical laboratory test results, and electrocardiogram (ECG) results from Screening (Visit 1), or abnormal results that are judged to be clinically insignificant by the investigator

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 4.5.1.1

14. Women of childbearing potential (only) must have a negative qualitative serum β-human chorionic gonadotropin pregnancy test prior to Visit 2

4.4 Exclusion Criteria

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

1. Diagnosis of any current psychiatric diagnosis other than MDD (including those with current intellectual development disability) with the exception of specific phobias

2. History of manic or hypomanic episodes

3. Patients with a YMRS score ≥ 12

4. Patient has a history of meeting DSM-5 diagnosis for any substance-related disorders (ie, use disorders except caffeine- and tobacco-related) within the 3 months before Visit 1 (Screening)

5. Patient had a positive result at Visit 1 (Screening) from the urine drug screen (UDS) for any prohibited drugs. Exception: patients with a positive UDS at Visit 1 for opiates, cannabinoids, amphetamines, barbiturates, or benzodiazepines may be allowed in the study provided:

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

    b. The drug can be discontinued prior to further 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/day or its benzodiazepine equivalent] for at least 1 month prior to Visit 1 (Screening) 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 in 4(b) and Section 4.5.3

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 year prior to Visit 1 (Screening)

    b. Patient had a score of 4 or greater on Item 10 of the MADRS at Visit 1 (Screening) or Visit 2 (Baseline)

    c. Patient had a score of 3 or greater on Item 3 of the HAMD-17 at Visit 1 (Screening) or Visit 2 (Baseline)

    d. Patient is at significant risk, as judged by the investigator, based on the psychiatric interview or information collected in the Columbia–Suicide Severity Rating Scale (C-SSRS) at Visit 1 (Screening) or Visit 2 (Baseline)

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

8. Patient has a history of intolerance or hypersensitivity to cariprazine or other drugs of the same class or to rescue medications

Treatment-Related Criteria:

9. Per ATRQ, patient failed to respond to > 3 trials of ADTs given at an adequate dose (as defined by the ADT package insert) and duration of ≥ 6 weeks during the present episode

10. Patient was treated with monoamine oxidase inhibitors in the current episode

11. Patient has history of treatment with clozapine > 50 mg/day or any depot antipsychotic at any time prior to Visit 1 (Screening)

12. Patient has history of treatment with esketamine, electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the 6 months before Visit 1 (whichever is longer) or previous lack of response to treatment with esketamine, electroconvulsive therapy, vagus nerve stimulation, or transcranial magnetic stimulation

13. Patients who require concomitant treatment with moderate or strong cytochrome P450 3A4 (CYP3A4) inhibitors or any CYP3A4 inducers. If applicable, these treatments must be discontinued at least 10 days prior to Visit 2 (Baseline)

14. 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 Sections 4.5.2 and 4.5.3)

15. Participation in any clinical study, involving experimental or investigational drugs or devices during the study or within 3 months before Visit 1 (or at least 5 half-lives of the drug, whichever is longer)

16. Initiation or termination of psychotherapy for depression within the 3 months preceding Visit 1 (Screening), or plans to initiate, terminate, or change such therapy during the course of the study

Other Medical Criteria:

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

18. Any concurrent medical condition 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

19. Any cardiovascular disease that is clinically significant, unstable, or decompensated including history of congenital QTc prolongation or QTc prolongation (screening ECG with QTcF $\geq$ 450 msec for men and QTcF $\geq$ 470 msec for women)

20. Any disease (eg, hypertension) that is clinically unstable or decompensated, based on the investigator's judgment

21. Newly diagnosed or clinically uncontrolled hypo- or hyperthyroidism as evident on clinical laboratory test results at Visit 1 (Screening). Patients diagnosed previously with hypo- or hyperthyroidism have to be stabilized on appropriate pharmacotherapy with no change in dosage for at least 1 month before Visit 1 (Screening)

22. Psychiatric symptoms possibly secondary to any other general medical condition

23. 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 to seizure

24. Known human immunodeficiency virus infection

25. Positive hepatitis C antibody on screening, with the exception of patients for whom the reflex HCV RNA titer test is negative

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

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

28. Absolute neutrophil count (ANC) < 1000 per mm^3 at Visit 1 (Screening)

29. Blood alcohol concentration ≥ 0.02 g/dL at Visit 1 (Screening) as measured by breathalyzer

30. Hemoglobin A1c > 8% at Visit 1 (Screening)

31. History of tardive dyskinesia, serotonin syndrome, or neuroleptic malignant syndrome

32. Known history of cataracts or retinal detachment

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

Other Criteria:

34. Patient is an employee, or immediate relative of an employee, of Allergan, any of its affiliates or partners, or the study center

35. Patient demonstrates an inability to speak, read, or understand the local language sufficiently to understand the nature of the study, to provide written informed consent, or to allow the completion of all study assessments

36. Patient is unable or unlikely to comply with the study protocol or unsuitable for any other reason, including other conditions that might indicate that the patient is unsuitable for the study as judged by the investigator

Eligibility Criteria to be Assessed at Visit 2

37. Not meeting the Visit 1 (Screening) inclusion criteria or meeting any of the Visit 1 exclusion criteria

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Treatment considered necessary for the patient's welfare may be given at the discretion of the Investigator. Prohibited and allowed escape medications are detailed in Sections 4.5.2 and 4.5.3, respectively. If the permissibility of a specific medication/treatment is in question, please contact the Allergan Medical Monitor.

4.5.1.1 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For the 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: postbilateral vasectomy, barrier contraception, or sexual abstinence.

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

If a female patient 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.

4.5.2 Prohibited Medications/Treatments

Medications that are moderate or strong CYP3A4 inhibitors or are CYP3A4 inducers, with the exception of the concomitant study ADT, are not allowed. Patients taking moderate (eg, erythromycin, fluconazole) or strong CYP3A4 inhibitors (eg, itraconazole, ketoconazole, clarithromycin) or CYP3A4 inducers (eg, rifampin, carbamazepine) will need to have medications discontinued 10 days prior to the start of treatment with DB IP. Patients who cannot or should not be taken off the CYP3A4 inhibitor or inducer should not be enrolled. If a patient requires concomitant treatment with either a moderate or strong CYP3A4 inhibitor or a CYP3A4 inducer at any time during the study, he or 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 inhibitors) except the ongoing ADT
- Stimulants
- Anticonvulsants/mood stabilizers
- Sedatives/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 patient as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

Patients will be asked to limit drinking alcohol and abstain from using illicit drugs during the study.

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

4.5.3 Rescue Medications

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

For insomnia the following will be allowed but should not be prescribed prophylactically:

- Zolpidem (maximum of 10 mg/day)
- Zolpidem extended release (maximum of 12.5 mg/day)
- Zaleplon (maximum of 20 mg/day)
- Eszopiclone (maximum of 3.0 mg/day)
- Zopiclone (maximum of 7.5 mg/day)
- Chloral hydrate (maximum of 1000 mg/day) may be used acutely with approval from the Allergan Medical Monitor
- Suvorexant (maximum of 20 mg/day)

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

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

For EPS or akathisia that emerges or worsens 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
- Biperiden
- Diphenhydramine
- Trihexyphenidyl
- Propranolol. Daily dose of propranolol depends on heart rate and blood pressure (BP).

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.

For agitation, restlessness, and hostility:

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

Efficacy assessments should not be performed within 8 hours of administration of lorazepam or equivalent benzodiazepine, or within 24 hours of administration of diazepam. Abrupt discontinuation of benzodiazepines is not advised.

5 Study Treatments

5.1 Study Treatments and Formulations

Capsules containing 1.5 mg of cariprazine and 3.0 mg of cariprazine.

5.2 Control Treatment

Matching placebo capsules.

5.3 Methods for Masking/Blinding

During the DB period, all IP (cariprazine or placebo) will be provided in identical blister cards to maintain masking throughout the study. All patients will be instructed to take 1 capsule of IP once daily at approximately the same time each day, in addition to the background ADT.

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 via an automated interactive web response system (IWRS) that will serve as the patient identification number on all study documents.

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 1.5 mg/day or 3 mg/day, or placebo. Stratified randomization will be used for this study with strata defined by two factors: ADT failure category (one ADT failure, more than one ADT failure) and country.

An IWRS will be used for patient randomization and to manage all aspects of IP during the study. 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 randomized patient during the DB treatment period (cariprazine 1.5 mg/day and 3 mg/day, or placebo). 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

No IP will be administered during the screening/washout period or the safety follow-up period. Patients will continue on their background ADT during the screening/washout period. During the safety follow-up period, the investigator may initiate alternative treatment as clinically necessary.

During the DB treatment period (6 weeks), patients will take 1 capsule of IP, orally, per day in addition to their ongoing ADT as shown in Table 2.

Table 2 Treatment Regimen and Dosing

Drug/Dose	Investigational Product Frequency	Route of Administration
Double-Blind Treatment Period (Visit 2 through Visit 6)		
Placebo	Once daily	Oral (capsule)
Cariprazine 1.5 mg	Once daily	Oral (capsule)
Cariprazine 3 mg (1.5 mg/day for 2 weeks, starting at Visit 2 [Baseline]; 3 mg/day from Visit 4 [Week 2] through Visit 6 [Week 6])	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.

5.6 Treatment Compliance

5.6.1 IP Compliance

IP compliance will be closely monitored by counting the number of capsules dispensed and returned, and through patient interviews at study visits. 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, measured by capsule counts and patient interviews), the Investigator should evaluate whether the patient should be discontinued from the study.

The study centers will monitor patient compliance at every visit and maintain an accurate drug disposition record which specifies the amount of IP administered to each patient and the date of administration. The site's drug disposition record will be considered source documentation.

Any patient who misses ≥ 4 consecutive doses of IP and/or ongoing ADT must be discontinued from the study.

5.6.2 ADT Compliance

Background ADT medication compliance will also be closely monitored. Patients will continue on the same antidepressant and dose of ADT they were on at baseline. Patients should be questioned to determine if there were any missed doses or changes in dose between visits. Every effort should be made to have patients bring their background ADT to study

Visits 2, 3, 4, 5, and 6 for verification of patient-reported compliance by pill/capsule count (to the extent possible) and patient interviews at study visits. Patients who take less ADT or more ADT than the prescribed regimen, must be counselled on the importance of taking ADT as instructed. If a patient demonstrates poor compliance with their ongoing ADT during the study (< 80% or > 120% overall, measured by pill/capsule count and patient interview), the Investigator should evaluate whether the patient should be discontinued from the study. Any patient who misses ≥ 4 consecutive doses of IP and/or ongoing ADT must be discontinued from the study. Patients, who in the current episode, have had an inadequate response to at least 1 ADT given at a dose above the minimum and for at least 6 weeks, can be enrolled.

5.7 Storage of Study Medications/Treatments

IP (cariprazine and placebo) will be packaged in blister cards and provided by Allergan, and must be stored in an appropriate secure area (eg, a locked cabinet in a locked room) at room temperature (20°C to 25°C or 68°F to 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

6.1.1 The Structured Clinical Interview for DSM-5 (SCID-5)

The SCID-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 an 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.

6.1.2 SAFER Criteria Inventory

The SAFER criteria inventory (Targum et al, 2008) is a clinician-rated scale that is used to facilitate the identification of appropriate and valid patients for clinical trials. The scale will confirm that the identified patients have acute symptoms that reflect the current state of illness and that these symptoms can be assessed with the appropriate rating instruments. The scale will be administered to the patients remotely via telephone by clinicians from the Massachusetts General Hospital Clinical Trial Network and Institute (MGH CTNI) at Visit 1 (Screening). In addition, the MGH CTNI SAFER raters will also remotely administer the HAMD-17 and the modified ATRQ. After the assessments are evaluated, MGH CTNI will

notify the study center, indicating whether the patient meets eligibility criteria to continue in the study. MGH CTNI will only perform the SAFER, HAMD-17, and modified ATRQ interviews at Visit 1 and only for patients who have already met the inclusion and exclusion criteria assessed at Visit 1. To ensure the highest quality and for patient comfort, these calls should not be conducted while the patient is on-site, unless approved by the Sponsor.

Study center staff will schedule the telephone assessment (SAFER interview) with raters from MGH CTNI. Patients who do not meet the SAFER criteria will be screen failed. The information collected by MGH CTNI will be copied and transmitted to the study centers to retain as source documentation. Sites will acknowledge receipt of the SAFER scale, HAMD-17 and modified ATRQ interview results via a check-box in an eCRF.

6.1.3 The Modified Antidepressant Treatment Response Questionnaire

The ATRQ (Fava 2003) is a clinician-administered questionnaire that will be used to determine whether the patient meets inclusion criteria for prior ADT treatment and response requirements. A modified ATRQ, completed by a clinician at the study site who has been certified in administration of the ATRQ, will be used to assess prior antidepressant exposure and response within the current depressive episode. The clinician will identify the antidepressants the patient had previously taken within the current episode; indicating the dose range and duration. The clinician will then select the level of response the patient had to the antidepressant which resulted in the greatest response.

The number of ADTs in the current episode to which the patient had an inadequate response will include any ADT with < 50% reduction in depressive symptoms if given at adequate doses (as defined by the ADT package insert; with at least 1 ADT having been escalated above the minimum dose) and with a duration of at least 6 weeks during the present episode.

6.2 Efficacy Endpoints

6.2.1 Primary Efficacy

The primary efficacy parameter will be the change from baseline to Week 6 in the MADRS total score.

Assessment and ratings of the primary efficacy scale 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 Montgomery-Åsberg Depression Rating Scale

The MADRS (Montgomery and Åsberg, 1979) is a 10-item, clinician-rated scale that evaluates the patient's depressive symptomatology during the past week. Patients are rated on items assessing feelings of sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, difficulty in concentration, and lack of interest. Each item is scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity.

6.2.2 Additional Efficacy Variables

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 The Hamilton Anxiety Rating Scale

The Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959) is a clinician-rated scale which consists of 14 items, each rated on a 5-point scale ranging from 0 (not present) to 4 (very severe). The highest possible score is 56, which represents the most severe form of anxiety; the lowest possible score is 0, which represents an absence of anxiety. This instrument will be administered by an experienced rater meeting the training requirements and qualifications set by the Sponsor.

6.2.2.2 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 in other patients the physician has observed. 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 an investigator, subinvestigator or rater with extensive professional training and experience in assessing mental illness.

6.2.2.3 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 from Visit 2, regardless of whether the investigator considers it to be a result of drug treatment or not. 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 an investigator, subinvestigator or rater with extensive professional training and experience in assessing mental illness.

6.2.2.4 Hamilton Depression Rating Scale–17 Items

The HAMD-17 (Hamilton 1960; Hamilton 1967; Miller et al, 1985) is a clinician-rated, 17-item scale used to rate the patient's depressive state based on feelings of depression, guilt, suicidality, anxiety, agitation, level of insight, patterns of insomnia, loss of interest in work and other activities, weight loss, hypochondriasis, and degree of psychomotor retardation. It also can be used to identify genital and somatic symptoms. This instrument will be administered by an experienced rater meeting the training requirements and qualifications set by the Sponsor.

6.3 Health Outcome Measures

The 12-item Short Form (SF)-12v2 health survey, a shortened version of the 36-item Short Form (SF-36) survey, is a generic assessment of health-related quality of life from the patient's perspective. It measures 8 concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (physiologic distress and physiologic well-being) (Ware et al, 1996). The 8 scales are aggregated into 2 summary measures: the Physical Component Summary (PCS-12) and the Mental Component Summary (MCS-12) scores, which range from 0 to 100, with higher scores indicating better quality of life.

6.4 Pharmacokinetics Measures

Samples for determination of the plasma concentrations of cariprazine and its metabolites DCAR and DDCAR will be collected at 3 timepoints during the study, Visit 4 (Week 2), Visit 5 (Week 4) and Visit 6 (Week 6). Samples may be collected at any time during the visit. The date and time of plasma sampling will be recorded in the eCRF along with the date and approximate time of the previous 2 doses of IP. Every effort should be made to collect pharmacokinetic (PK) samples for each patient. However, if for reasons of safety or patient refusal, blood sampling is not possible, the PK sample can be omitted. In the event that a PK sample is missed, the reason must be recorded in the eCRF.

For details on blood sample collection, plasma separation, storage, and shipment, refer to instructions from the central laboratory.

6.5 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 Visit 6 (Week 6). Pharmacogenetic sampling (one sample per patient) can be conducted at any time point between Visit 2 (Baseline) and Visit 6 (Week 6). Following consent, a single blood sample will be collected to determine individual genotype status and for pharmacogenetic biobanking. 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 studies 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.

6.6 Safety Measures

Patients must be evaluated by a physician or an appropriately trained health care 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, the schedule of visits and procedures.

6.6.1 Adverse Events

Subjective 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 the IP, and detail any other treatment measures taken for the AE. Treatment for an AE is entered as a concomitant medication on the AE CRF. For events noted

as SAEs, Allergan must be notified immediately to meet their reporting obligations to appropriate regulatory authorities (see Section 9.3).

6.6.2 Ocular Events of Special Interest

The Sponsor is required to inform worldwide regulatory authorities of ocular events of special interest. Therefore, the Sponsor must be notified immediately regarding any ocular adverse events of special interest that occur after informed consent is obtained.

The following are considered ocular AEs of special interest, whether serious or nonserious, and 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 ocular event of special interest, the study site personnel must report the event, whether serious or nonserious, on the SAE/AESI form.

All ocular events of special interest are to be followed by the study staff until resolution or until the ocular event of special interest is deemed stable. The Sponsor may contact the study site to solicit additional information or follow up on the event.

6.6.3 Clinical Laboratory Determinations

Clinical laboratory tests will be performed according to the schedule in Table 3. Patients will be asked to fast for at least 10 hours prior to any visit requiring clinical laboratory testing.

Table 3 Schedule of Clinical Laboratory Tests

Category	Visit Number(s)	Parameter(s)
Hepatitis Serology	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. Reflex HCV RNA titer test will be performed for all Hepatitis C virus antibody positive or reactive results.
Screening Hemoglobin A1c	1	Hemoglobin A1c
Hematology	1 and Visit 6/ET	Absolute and differential white blood cell count, Absolute Neutrophil Count (ANC), erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
Chemistry	1 and Visit 6/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 drug screen	1	Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine
Urine myoglobin	1 and Visit 6/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 and Visit 6/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
Blood alcohol concentration	1	Blood alcohol concentration by Breathalyzer
Serum β-hCG (women of childbearing potential only)	1, Visit 6/ET, and Visit 7 Safety Follow-up Visit	—
Repeat urine drug screen, blood alcohol level, and serum pregnancy test	At random upon request from the Investigator	—

ET = early termination; AST = aspartate aminotransferase; ALT = alanine aminotransferase; β-hCG = β-human chorionic gonadotropin; HCV = Hepatitis C virus; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

6.6.4 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 remove their jackets and shoes.

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

Waist circumference will be measured at Visits 2 and 6/early termination (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 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.

6.6.5 Electrocardiograms

A 12-lead ECG will be performed at Visit 1 (Screening) and Visit 6 or 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. Sites will transmit all ECGs to the ECG central reader.

6.6.6 Other Safety Assessments

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

6.6.6.1 Extrapyramidal Symptoms Scales

The following 3 scales will be used to systematically assess extrapyramidal side effects at Visits 2, 3, 4, 5, 6, or at 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. 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. The scale comprises 3 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 item rated on a 6-point scale (absent [0] to severe akathisia [5]).

Simpson-Angus Scale

The SAS (Simpson and Angus, 1970) is a 10-item rating scale for assessment of antipsychotic-induced parkinsonism in both clinical practice and research settings. 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.

6.6.6.2 Columbia–Suicide Severity Rating Scale

The C-SSRS 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 (nonspecific 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. At Visit 1 (Screening), the C-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior, including a 12-month lookback. At all other visits the C-SSRS will be completed for ideation and behavior since the previous visit.

The C-SSRS must be completed by an investigator, subinvestigator or trained rater, all of whom must have extensive professional training.

6.6.6.3 Young Mania Rating Scale

The YMRS (Young et al, 1978) is an 11-item scale that assesses manic symptoms based on the patient's perception of his or her condition over the previous 48 hours, as well as the physician's clinical observations during the interview. The 11 items are elevated mood, increased motor activity-energy, sexual interest, sleep, irritability, rate and amount of speech, language-thought disorder, content, disruptive-aggressive behavior, appearance, and insight. The severity of the abnormality is rated on a 5-point (0 to 4) or 9-point (0 to 8) scale. Possible scores range from 0 to 60.

This scale will be administered by a trained rater with expertise in evaluating manic patients.

6.7 Summary of Methods of Data Collection

An IWRS will be used to screen patients, 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 and central laboratory vendor will be used for the analysis of all ECGs and 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

7.1.1 Patient Populations

Four populations will be considered in the statistical analysis of the study.

7.1.1.1 Screened Population

The screened population will consist of all screened patients who sign informed consent.

7.1.1.2 Randomized Population

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

7.1.1.3 Safety Population

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

7.1.1.4 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will consist of all randomized patients with ≥ 1 postbaseline assessment of the MADRS total score.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

7.2.1 Primary Efficacy Variable

The primary efficacy parameter is the change from baseline to Week 6 in the MADRS total score.

7.2.2 Additional Efficacy Variables

Additional efficacy parameters will include the following at postbaseline visits described in Table 1:

- Change from baseline in the CGI-S score
- CGI-I score
- CGI-I response (CGI-I score ≤ 2)
- MADRS response (≥ 50% reduction from baseline in MADRS total score)
- MADRS remission (MADRS total score ≤ 10)
- Change from baseline in the HAMD-17 total score
- Change from baseline in the HAM-A total score

7.3 Hypothesis and Methods of Analysis

All efficacy analyses will be based on the mITT population. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the date of the first dose of DB IP. All statistical hypothesis tests will be 2-sided 5%-level of significance tests for main effects. All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

To compare with historic studies, some analyses based on the imputed data using the last-observation-carried-forward (LOCF) approach, will be presented for all efficacy parameters. Only the postbaseline total score of a parameter will be imputed; individual item scores will not be carried forward. The baseline value will be carried forward only for the intermittent missing values immediately after baseline. If all the postbaseline values are missing, the baseline value will not be carried forward.

7.3.1 Primary Efficacy Analyses

The primary estimand is provided below through specification of the population, the variable, the handling of intercurrent events, and the population-level summary.

Population

The target population are patients with MDD who have had an inadequate response to antidepressant therapy in the current episode and who satisfy the inclusion and exclusion criteria as specified in the protocol.

The analysis population is defined to be the mITT population consisting of all randomized patients with ≥ 1 postbaseline assessment of the MADRS total score as specified in protocol Section 7.1.1.4.

Variable

The variable is the same as the primary efficacy endpoint, which is the change from baseline to Week 6 in the MADRS total score.

Accounting of Intercurrent Events

Intercurrent events and their handling rules are described as follows:

- Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. Patients are still taking assigned drugs as specified in the protocol while taking allowed rescue medications. The clinical objective is to assess the efficacy of the treatment regardless of allowed rescue medication use.

- To evaluate the efficacy at Week 6 in the mITT population, patients are assumed to adhere to the assigned treatment for the duration of the study. As a result, data after the discontinuation from the study treatment due to all reasons will not be included in the primary analysis and they will be assumed as missing at random.

Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between each cariprazine group and placebo.

To address the primary hypotheses that each dose of cariprazine is superior to placebo in the reduction of MADRS total score after 6 weeks of treatment, the change from baseline in MADRS total score will be analyzed using a mixed-effects model for repeated measures (MMRM) with treatment group, country, ADT failure category, 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 to model the covariance of within-patient scores. The Kenward-Roger approximation (Kenward and Roger, 1997) will be used to estimate denominator degrees of freedom. In the event of non-convergence of the model using unstructured covariance matrix, a structured covariance matrix will be used in combination with empirical variance estimate (ie, sandwich estimator) to address the potential mis-specified situation. The following sequence of alternative covariance structures (First-order antedependence [ANTE (1)], Toeplitz [TOEP], First-order autoregressive [AR(1)] and compound symmetry[CS]) will be considered in the MMRM until convergence.

The analysis will be performed based on all postbaseline scores using only the observed cases without imputation of missing values. The treatment difference in the primary endpoint

at Week 6 for each active treatment group versus placebo in the mITT population will be estimated and reported along with the corresponding 95% CI and the p-value.

The Hochberg procedure (Hochberg 1988) will be used to control the overall type I error rate at a 0.05 level (2-sided) for multiple comparisons of 2 active doses with placebo for the primary endpoint. Statistical significance will be determined by comparing the adjusted p-values to $\alpha = 0.050$.

The study will be considered positive if at least 1 dose arm of cariprazine is statistically superior to placebo for change from baseline in MADRS total score at Week 6 after multiplicity adjustment.

A sensitivity analysis using a pattern-mixture model based on non–future-dependent missing value restrictions (Kenward et al, 2003) will be performed to assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption. The details of this sensitivity analyses are as follows:

The pattern for the pattern-mixture model will be defined by the patient's last visit with an observed value. The observed MADRS total score at a visit is assumed to have a linear relationship with the patient's prior measurements. The missing values will be imputed under the assumption that the distribution of a missing observation differs from the observed only by a shift parameter value Δ. The dataset with missing values imputed will be analyzed using an analysis-of-covariance (ANCOVA) model with treatment group, country, and ADT failure category, as factors and baseline MADRS total score as a covariate for between–treatment-group comparison at Week 6. The imputation of missing values and the analysis will be performed multiple times, and the inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique. The values for Δ will be selected as 0 to 6, inclusively. This range is selected because the mean reduction of MADRS score from baseline within a treatment group at Week 6 is likely to be within 15 points (Bauer et al, 2009; El-Khalili et al, 2010), and a Δ value of 6 accounts for 40% of treatment efficacy.

The second sensitivity analysis will consider dropout reasons while imputing missing values after the discontinuation. Patients who discontinued due to lack of efficacy in the cariprazine arms are assumed to have no treatment effect after the discontinuation. These patients are assumed to copy the profile of placebo arm and missing values are imputed based on the distribution estimated from the placebo group under the MAR using copy-reference approach (Carpenter et al, 2013). The rest of missing values in the placebo arm and cariprazine arms

will be imputed using the observed data in their respective group under the MAR assumption.

Mean treatment difference (raw mean difference ± standard error) in change in primary endpoint between each cariprazine dose and placebo with missing values imputed using the LOCF approach will be plotted against country. In addition, summary statistics will be provided by center to examine the consistency of treatment effect across the study centers.

The impact of dropouts on the efficacy outcomes will be explored graphically by plotting the time courses of mean changes by dropout reason.

Results of analyses from MMRM and from ANCOVA models will also be reported for each visit between baseline and Week 6.

To compare with historic studies, the LOCF approach will be used with an ANCOVA model that has treatment group, country and ADT failure category as factors and the baseline value as the covariate.

7.3.2 Other Efficacy Analyses

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

Analysis of CGI-I score, change from baseline in HAMD-17 total score, change from baseline in HAM-A total score, and change from baseline in CGI-S will be performed using a similar MMRM to that used for the primary analysis. Baseline CGI-S score will be used as a covariate for the analysis of change in CGI-I score. In addition, these parameters will be analyzed using ANCOVA (with LOCF imputation) as used for the analysis of primary efficacy parameters.

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

Rates for categorical parameters (response and remission) will be reported by treatment group and by visit; a logistic regression model (with LOCF imputation) will be used to model the probability of a response or the probability of a remission as a function of a treatment group and the corresponding baseline score (CGI-S for the analysis of the CGI-I response) as explanatory variables.

7.3.3 Safety Analyses

The safety analysis will be performed using the safety population. The safety parameters will include AEs, clinical laboratory parameters, vital signs, ECG parameters, EPS scales, the C-SSRS and the YMRS. For each safety parameter, the last assessment made before the first dose of DB IP will be used as the baseline for all analyses of that safety parameter. The summarization will be by treatment group for both double-blind and safety follow-up periods.

7.3.3.1 Adverse Events

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 DB IP.

For the DB treatment, the number and percentage of patients reporting TEAEs in each treatment group 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 the IP. If more than 1 AE is 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 the IP.

The distribution of TEAEs by severity and relationship to the IP will be summarized by treatment group.

The TEAEs during the safety follow-up period will be summarized by body system, preferred term, and treatment group for the safety population.

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

The number and percentage of patients with common (≥ 2% of patients in any treatment group) TEAEs, on-therapy SAEs, and AEs leading to premature discontinuation of IP will be summarized by preferred term and treatment group and sorted by decreasing frequency for the test treatment. An SAE will be defined as an on-therapy SAE if it occurred on or after the date of the first dose of DB IP and within 30 days of the date of the last dose of DB IP.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any). All patients with SAEs, including SAEs reported during the screening period and the safety follow-up period, and patients

discontinuing because of AEs occurring before the start of DB IP will be included in these listings.

The number and percentage of patients reporting TEAEs of ocular events of special interest will be summarized. A listing of all reported ocular events of special interest will be provided.

7.3.3.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter. In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters; these will be detailed in the statistical analysis plan (SAP).

The number and percentage of patients with potentially clinically significant (PCS) postbaseline clinical laboratory values will be tabulated by treatment group. 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 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the patient identification number, study center number, and baseline and postbaseline values. A listing of all AEs occurring in patients who have PCS laboratory values will also be provided.

The number and percentage of patients with treatment-emergent significant changes in lipid parameters (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) and glucose will be tabulated by treatment group for 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 1 postbaseline assessment. The change in lipids and glucose from baseline to the highest (lowest for high-density lipoprotein cholesterol) postbaseline measurement will be summarized. Supportive listings of patients with treatment-emergent changes in lipids and glucose values will be provided.

The number and percentage of patients meeting potential Hy's Law criteria will be tabulated by DB treatment group starting from the first dose of DB IP to within 30 days after the last dose of DB IP for the safety population. A supportive listing will be provided.

7.3.3.3 Vital Signs

Descriptive statistics for vital signs and changes from baseline values at each visit and at the end of the DB treatment period will be presented by treatment group.

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 patient identification number, study center number, and 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 measured after the patient stands up after resting in the supine position. Standing measurements should be taken after a sufficient amount of time has passed to allow the BP to equilibrate in the standing state. A supportive listing will be provided including the patient identification 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 DB treatment period
- Shift of hypertension status from baseline to highest category during the DB treatment period

Supportive listings of patients who have a shift in hypertension status from normotensive/prehypertension at Baseline to stage I/stage II hypertension will be provided.

7.3.3.4 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 will be presented by treatment group.

The number and percentage of patients with PCS postbaseline ECG values will be tabulated by treatment group. 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. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the patient identification number, study center number, and baseline and postbaseline values.

In addition, a listing of all AEs occurring in patients who have PCS ECG values and a listing of patients with clinically significant postbaseline ECG abnormalities, as reported by the Investigator and/or the central ECG laboratory, will also 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 the patient identification number, study center number, all QTc values (including change from baseline values), and all AEs will be provided for all patients who have postbaseline QTc changes > 30 msec.

7.3.3.5 Other Safety Parameters

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

The number and percentage of patients with treatment-emergent mania will be presented by treatment group. Treatment-emergent mania will be defined as an YMRS total score of 16 or greater at any postbaseline visit. Descriptive statistics for YMRS total score and change from baseline values at each assessment time point will be presented by treatment group.

A patient will be considered to have treatment-emergent parkinsonism if the patient's SAS score was ≤ 3 at baseline and > 3 at any DB 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 DB assessment. The number and percentage of patients reporting treatment-emergent parkinsonism or treatment-emergent akathisia will be tabulated by treatment group. Listings

of patients with treatment-emergent parkinsonism and patients with treatment-emergent akathisia will be provided and will include the patient identification number, study center number, and baseline and postbaseline values. Listings of all AEs occurring in patients who have treatment-emergent parkinsonism or treatment-emergent 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.

The number and percentage of patients with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the patient's lifetime, during the DB treatment period, and during the safety follow-up period will also be presented by treatment group for the safety population. Supportive listings will be provided and will include the patient identification number, study center number, lifetime history, and postbaseline values. Intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings. A listing of all AEs occurring in patients who have suicidal ideation or suicidal behavior will also be provided.

7.4 Other Analyses

Patient disposition, demographics and other baseline characteristics, prior and concomitant medication, extent of exposure and treatment compliance will be summarized and described in detail in the SAP.

Any potential additional analyses of efficacy and safety data due to the impact of COVID-19, (infection or disruption) on patient treatment (discontinuation or interruptions) and follow-up (data collection via alternative modality, missing or late visits, or complete lost-to-follow-up) will be described in the SAP.

7.4.1 Pharmacokinetic Parameters

Plasma samples will be analyzed for the concentrations of cariprazine and its metabolites DCAR and DDCAR using a validated bioanalytical method. A population PK approach will be used to estimate individual-level drug-exposure parameters (eg, steady-state area-under-the-curve [AUC], steady-state maximum concentration [C_{max}], steady-state minimum concentration [C_{min}]) for each of the 3 analytes. This will be performed via the use of appropriate nonlinear mixed-effects modeling software. The relationship, if any, between effectiveness and drug-exposure parameters will be explored. These analyses will be reported separately.

7.4.2 Health Outcome Measure Analyses

The SF-12 will be administered at Visit 2 and Visit 6/ET.

Analysis of change from baseline in the PCS-12 and MCS-12 score at Week 6 will be conducted using the ANCOVA model that has treatment group and study center as factors and the baseline value as the covariate.

7.5 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a 95% CI) for each cariprazine dose versus placebo for the primary efficacy variable will be estimated within each category of the following classification variables:

- ADT failure category (one ADT failure, more than one ADT failure)
- Region (US, NonUS)

7.6 Interim Analyses

No interim analysis is planned for this study.

7.7 Sample Size Calculation

The study will randomize approximately 750 patients in a 1:1:1 ratio to cariprazine 1.5 mg/day, cariprazine 3 mg/day, and placebo groups. A sample size of 250 patients per arm will provide approximately 84% statistical power to show statistically significantly higher effect in each dose of cariprazine versus placebo based on the mITT analysis set. The study has approximately 90% statistical power to show that at least 1 of the 2 cariprazine doses is statistically significantly more efficacious than placebo in the primary endpoint. These calculations assumed an effect size of 0.286. All statistical powers presented in this section were calculated adjusting for multiple comparisons using the Hochberg procedure with the family-wise type I error rate being controlled at a 0.05 level (2-sided). The dropout rate is assumed to be 15% at Week 6. Within-person correlation for the primary endpoint is assumed to be 0.58. This value is used in the sample size calculation to calculate an inflation factor that accounts for information loss due to the missing data at Week 6 for longitudinal data collection.

Assumptions of effect size, intracorrelation and dropout rate are based on cariprazine Study RGH-MD-75.

8 Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the schedule of visits and procedures, and Section 6 for details of tests and rating scales.

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 Patient Privacy

The study will be discussed with the patient 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 reviewed in the Verified Clinical Trials (VCT) database, indicated in the schedule of visits and procedures (Table 1). Partial identifiers will be utilized. Patients who are identified as verification failures by VCT should not continue participation without documented approval from the Sponsor.

8.2 Washout Interval

Patients with MDD with inadequate response to ongoing ADT in the current episode will undergo a washout of prohibited medications for up to 14 days during the screening period, with up to an additional 7 days if needed with Sponsor approval (see Section 4.5.2). During the washout, the patients will continue to take the ADT that they are not responding to.

The length and timing of the washout of prior psychiatric medications during the 14 days allotted for the screening period is at the discretion of the investigator (with up to an additional 7 days if needed with Sponsor approval). Prior medications should be gradually withdrawn such that the washout is completed by Baseline (Visit 2). Please note that during the washout period psychotropic medications other than those listed as rescue (Section 4.5.3) may not be newly initiated or reinitiated.

8.3 Procedures for Final Study Entry

Final study eligibility, for patients meeting SAFER criteria, will be determined at Visit 2 (Baseline Visit). Patients should continue to meet the inclusion and exclusion criteria as specified in Sections 4.3 and 4.4.

A patient is considered to have entered the study at the time of randomization to treatment at Visit 2 (Baseline).

Rescreening of screen failures is permitted in certain situations after consultation with the Allergan Medical Monitor.

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

8.4 Visits and Associated Procedures

The schedule of study procedures and assessments is tabulated by visit in the schedule of visits and procedures in (Table 1). A description of individual procedures is provided in Sections 6.1, 6.2, 6.3, 6.4, 6.5, and 6.6. Evaluations should be performed by the same evaluator throughout the study whenever possible. During the study, every effort should be made to perform the study procedures as indicated in (Table 1). The descriptions of the procedures to be performed at each visit are provided below.

As a result of the ongoing COVID-19 pandemic, some in-person study visits may not be possible due to public health concerns. When these public health concerns interfere with the conduct of in-person clinic visits, site visits may be conducted via an alternative format. Refer to Section 12.2 for allowable protocol modifications during the COVID-19 pandemic.

8.4.1 Screening (Visit 1)

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

- Obtain informed consent and patient privacy authorization/consent; consent for pharmacogenetic sampling may also be obtained
- Access IWRS to register the patient and assign a patient identification number
- Perform Verified Clinical Trials check
- Assess inclusion/exclusion criteria
- Collect and assess medical and psychiatric history
- Administer and assess SCID-5
- Collect blood samples for hepatitis serology
- Collect samples for UDS
- Perform blood alcohol concentration assessment with Breathalyzer
- Collect blood samples for serum pregnancy test (women of childbearing potential only)
- Collect blood samples for clinical laboratory tests
- Collect blood sample for hemoglobin A1c
- Review prior and concomitant medications
- Assess modified ATRQ, MADRS, HAMD-17, CGI-S, C-SSRS and YMRS
- Collect vital signs measurements, including weight and height
- Perform physical examination
- Perform ECG and transmit to central reader
- Review and assess AEs and SAEs
- For patients meeting initial inclusion/exclusion criteria, schedule and ensure the SAFER interview is conducted prior to Visit 2 (Baseline Visit)

8.4.2 Baseline (Visit 2)

The following procedures will be carried out at Baseline (Visit 2):

- Evaluate results from SAFER interview to confirm patient eligibility to continue in study
- Assess all other inclusion/exclusion criteria
- Review concomitant medications and assess ADT compliance
- Assess MADRS, HAMD-17, HAM-A, YMRS, CGI-S and C-SSRS
- Evaluate EPS (AIMS/BARS/SAS)
- Administer SF-12
- Collect vital signs measurements (including weight and waist circumference)
- If not already obtained at Screening (Visit 1), obtain consent for and collect blood for the pharmacogenetic sample. Consent for pharmacogenetic sampling may be obtained any time between Visit 1 and Visit 6/ET, inclusive. A single sample can be obtained any time between Visit 2 and Visit 6/ET, inclusive
- Review and assess AEs and SAEs
- Access IWRS to randomize patient and then dispense IP

8.4.3 Double-blind Treatment Period (Visits 3 to 6/ET)

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

- Review concomitant medications and assess ADT compliance
- Collect IP blister cards, perform drug accountability and assess IP compliance
- Assess MADRS, CGI-S, CGI-I, and C-SSRS; HAM-A (Visits 4 and 6/ET only), YMRS (Visit 6/ET only) and HAMD-17 (Visit 6/ET only)
- Evaluate EPS (AIMS/BARS/SAS)
- Administer SF-12 (Visit 6/ET only)
- Collect vital signs measurements (including weight)
- Collect waist circumference measurement (Visit 6/ET only)

- Review and assess AEs and SAEs
- Collect blood sample for serum pregnancy test for women of childbearing potential (Visit 6/ET only)
- Collect blood samples for clinical laboratory determinations (Visit 6/ET only)
- Collect blood for PK evaluation (any time during Visits 4, 5 and 6/ET)
- If not already obtained previously, obtain consent for and collect blood for the pharmacogenetic sample. A single sample can be obtained at any time between Visit 2 and Visit 6/ET, inclusive
- Perform ECG (Visit 6/ET only)
- Perform physical examination (Visit 6/ET only)
- Access IWRS to dispense IP (Visit 3 through Visit 5), and register patient completing Visit 6/ET

Note: After completion of Visit 6/ET, patients will receive treatment for their MDD as deemed necessary by the Investigator or designee.

8.4.4 Safety Follow-up (Visit 7)

The following procedures will be carried out at the Safety Follow-up Visit (Visit 7/Week 10):

- Review concomitant medications
- Collect vital signs measurements (including weight)
- Collect blood sample for serum pregnancy test (women of childbearing potential only)
- Review and assess AEs and SAEs
- Assess C-SSRS

8.5 Instructions for the Patients

- Patients are to be instructed to take their study medication daily around the same clock time, with or without food; study medication should not be taken with grapefruit juice

- Patients are to continue to take their ADT as instructed throughout the study and to bring their ADT to visits for compliance review
- Patients are to be reminded to return used/partially used IP 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 Sections 4.5.2 and 4.5.3; patients are to be advised accordingly. If the permissibility of a specific medication/treatment is in question, the Investigator should consult the Allergan Medical Monitor.
- Patients are to be asked to limit alcohol consumption and abstain from using illicit drugs 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) and Visit 6/ET

8.6 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the Investigator. Additional examinations may be performed as necessary to ensure the safety and well-being of patients during the study. An eCRF will be completed for each unscheduled visit.

8.7 Compliance with Protocol

Participating patients should be able to adhere to the completion of required questionnaires and testing parameters as described in this protocol.

Data will be recorded on the appropriate eCRF supported by appropriate source documentation. At each visit, patients should be asked if any concomitant medications had been used, if they had undergone any concurrent procedures (nonstudy procedures), and if they had been in compliance with the protocol since the previous visit.

For compliance with IP and ADT see Sections 5.6.1 and 5.6.2, respectively.

8.8 Early Discontinuation of Patients

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 from the study and subsequently enter the safety follow-up period for one of the following reasons:

- AE
- Noncompliance with protocol
- Noncompliance with IP dosing regimen and/or ongoing ADT dosing regimen
- Withdrawal of consent (a clear reason must be documented when possible)
- Patient decision to not continue in the study
- 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 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 6/ET. If the patient discontinues after IP is taken, the patient is also expected to return for the Safety Follow-up Visit (Visit 7) 4 weeks after completion of the ET Visit.

At a minimum, the following information should be collected when a patient is discontinued:

1. The reason the patient discontinued
2. The date of the last dose of IP taken by the patient. All IP should also be retrieved from the patient.
3. The date of the last study 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 6/ET and subsequently Visit 7 (Safety Follow-up Visit) are performed (Table 1, and Section 8.4).

Discontinued patients will not be replaced, and re-screening will not be allowed.

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 from the study for any of the following reasons:

1. The patient misses ≥ 4 consecutive doses of IP and/or ongoing ADT
2. The patient required or initiated hospitalization for his/her psychiatric symptoms
3. The patient decompensates psychiatrically (becomes acutely suicidal, homicidal or psychotic) and in the judgment of the Investigator cannot be safely managed in the study
4. The patient has a positive UDS at any time during the study; for exceptions see Exclusion Criterion 4 and Section 4.5.3
5. The patient experiences 1 of the following elevated liver enzyme conditions, which is confirmed by repeat testing:

    - 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

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

7. 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. The Sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

9 Adverse Events

AEs occurring during the study will be recorded on an AE eCRF. If AEs occur, the first concern will be the safety of the study patients.

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient 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 patient has been administered IP.

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 patient 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 eCRF.

9.1.2 Serious Adverse Event

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, is life-threatening, 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 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 SAEs).

Allergan considers all cancer AEs as SAEs. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as an SAE.

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

Any preplanned surgery or procedure should be clearly documented in the site source documents by the Investigator or designee at the time of the patient's entry into the study. If it has not been documented at the time of the patient's screening visit (Visit 1), 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 intensity assessment for an AE must be completed using the following definitions as guidelines:

Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient.

Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

9.1.4 Relationship to Study Drug

A determination will be made of the relationship (if any) between an AE and the study drug 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 drug-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 last 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 DB IP 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) as listed on the Allergan Study Contacts List and recorded on the SAE/AESI Form. All patients with an SAE must be followed and the outcomes reported. The Investigator must supply the Sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports, 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 the 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 investigational drug

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 after the last dose of IP. Serum pregnancy tests are scheduled at screening and at Visit 6/ET and Visit 7 (EOS). If a pregnancy is suspected at any other time, an unscheduled serum pregnancy test should be performed. If any β-hCG test comes back as borderline, it should be repeated and consultation with the Allergan Medical Monitor is required. Within 24 hours of learning of the pregnancy, the study site personnel must report the event to Allergan's Global Patient Safety department on the clinical trial pregnancy form and fax/email it to the SAE fax number/email address on the cover page of this protocol, even if no AE has occurred. 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 reported 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 $\geq 3 \times$ ULN AND
- Total bilirubin $\geq 2 \times$ ULN AND
- Alkaline phosphatase $< 2 \times$ ULN

Study site personnel must report every patient who meets these 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 study until 30 days after last known dose of study treatment.

A laboratory alert for potential Hy's laws cases will be in place, and the laboratory must notify Investigators and the Sponsor (Allergan) immediately when the above criteria have been met. A potential Hy's law case must be reported to Allergan on an SAE/AESI Form as soon as possible (within 24 hours of learning of the potential Hy's law case) to the SAE/Pregnancy fax number, even if no AE has occurred. The eCRF 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 should be initiated in conjunction with the Allergan Medical Monitor and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. The patient should return to the study site and be evaluated as soon as possible, preferably within 48 hours from the time the Investigator becomes aware of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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 (Allergan Medical Safety Physician) should be notified prior to unmasking study medication. The Investigator should inform the Sponsor (Allergan Medical Safety Physician) 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 calling 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 GCP regulations and guidelines, eg, 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.

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 reapproval or review at least annually (US sites). 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 Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.3.1 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

The Investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change of telephone numbers).

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 IP may ultimately be marketed, but the patient's name

or other personal identifying information will not be disclosed in these documents. The patient'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 patient prior to enrollment into the study in accordance with the applicable privacy requirements (eg, HIPAA [United States]; European Union Data Protection Directive 95/46/EC [EU]).

- Patients will be assigned a unique identifier. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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

- A statement that informed consent was obtained (including the date). A statement that written authorization (US sites only), data protection consent (European sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- 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
- Dates of all patient visits
- All concurrent medications (list all prescription and nonprescription medications being taken at the time of screening. 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 principles, ie, records must be attributable, legible, contemporaneous, original, and accurate.

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, as required.

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 electronic copies of CRFs 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

IP will be supplied in blister cards and will be labeled with the protocol number, storage information, warning language, instructions to take the capsules as directed, and any other required information. 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 number, visit number, and dispensing date on the blister card.

10.5.2 Investigational Product Supply Inventory

The Investigator must keep an accurate accounting of the number of investigational product units received from Allergan, dispensed or administered to the patients, returned to the Investigator by the patient, and returned to Allergan during and at the completion of the study. A detailed inventory must be completed for all IP. IP must be dispensed or

administered to patients in the study only by an appropriately qualified person. The medication is to be used in accordance with the protocol.

10.5.3 Return or Disposal of Study Medications/Treatments

It is the Investigator's responsibility to ensure that patients return all unused IP, and all empty blister packs, to the site. All IP will be returned to Allergan or Allergan designee for destruction. All unused IP must be returned to Allergan during the course of the study when a patient discontinues from the study, upon drug expiration, and at the end of the study.

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

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

Blood samples obtained for analysis of cariprazine and its metabolites DCAR and DDCAR will be stored by the central clinical laboratory until ready for analysis. Analysis will be performed using a validated method and a laboratory that meets Good Laboratory Practice requirements. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.

Patients consenting to participate in pharmacogenetic sampling will have a single blood sample collected to determine individual genotype status and for pharmacogenetic biobanking. The genetic material from the blood sample will be used to study factors that may influence how patients respond to a drug or may explain the pathophysiology of the

disease. These 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.

11 References

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12 Attachments

12.1 Scales and Questionnaires

Please refer to the Study Scales and Questionnaire Binder for reference copies of questionnaires and scales.

12.2 Protocol Modifications for COVID-19

As a result of the novel coronavirus disease 2019 (COVID-19) pandemic, the following protocol modifications can be followed for active patients in Study 3111-302-001, who have completed all assessments through Visit 2 (inclusive) per Table 1, Schedule of Visits and Procedures and have been randomized via the Interactive Web Response System (IWRS). The instructions and procedures specified herein will supersede those specified in the Schedule of Visits and Procedures only in local, regional or national circumstances that limit the conduct of the Global Protocol as a direct result of the COVID-19 pandemic (including any potential re-emergence of this coronavirus). Please refer to Table 1 of the Global Protocol (or Country-Specific protocol, if applicable) for the visit assessments and procedures required at Visit 1 and Visit 2, including the full inclusion and exclusion criteria to be evaluated prior to randomization. The following procedures apply in cases where patients are either unable or unwilling to attend study visits as a result of the pandemic.

12.2.1 Planned changes in research

In response to the impact of COVID-19 to study patients and site staff, the following modifications to the study plan are allowable for sites and patients facing extenuating circumstances:

- Allowing wider visit windows when necessary
- Replacing protocol mandated in-person study visits with one or more of the following:
    - home visits
    - telemedicine virtual visits (preferred method if/when home visits are not feasible)
    - telephone/video calls (no recording will be performed)
- Allowing blood draws at alternative or commercial laboratories (where available)
- Study sites shipping investigational products (IP) to research patients (where permissible by local/statutory or country law) and where approved by Sponsor
- Extending the window for consecutive missed doses of IP specifically resulting from COVID-19-related circumstances from 4 or more days to more than 7 days, prior to requiring withdrawal of the patient from the study (see Section 12.2.6.)

12.2.2 Remote Assessment of Efficacy

Efficacy assessments must always be conducted by a rater that has been certified by Signant Health to rate that assessment for this study. Every effort should be made to have patients assessed by the same rater at each scheduled timepoint. For efficacy assessments that are conducted remotely (eg, by telephone, telemedicine virtual visit, video call) or in-home by

qualified site staff, the following assessments are required to be completed in the course of the remote visit. **Note:** The source documents and eCRF should clearly denote which assessments have been completed remotely.

- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Hamilton Anxiety Rating Scale (HAM-A)
- Clinical Global Impression-Severity scale (CGI-S)
- Clinical Global Impression-Improvement scale (CGI-I)
- Hamilton Depression Rating Scale–17 Items (HAMD-17)

12.2.3 Remote Assessment of Health Outcome measures

In the event that Visit 6/Early Termination (ET) is being conducted remotely (eg, by telephone, telemedicine virtual visit, video call), study staff should verbally administer the Short-Form 12 (SF-12) to the patient and record the patient's responses in the source. The source document should capture the name of study personnel administering the SF-12, the date and time of administration, as well as clearly document that the responses were obtained verbally due to COVID-19. For in-home visits, study staff should have patient complete the SF-12 per protocol.

12.2.4 Remote Assessment of Safety

For safety assessments that are conducted remotely (eg, by telephone, telemedicine virtual visit, video call), the following assessments are required to be completed in the course of the remote visit. **Note:** The source documents and eCRF (as applicable) should clearly denote which assessments have been completed remotely.

- Adverse Events/Serious Adverse Event Assessment
- Concomitant medication assessment
- Columbia-Suicide Severity Rating Scale (C-SSRS) - Must be conducted by a certified rater. Every effort should be made to have patients assessed by the same rater at each scheduled timepoint. In the event the rater certified for this study is unavailable, a rater certified on the C-SSRS for another Allergan trial may conduct the assessment.
- Young Mania Rating Scale (YMRS)
- Movement scales (BARS/AIMS/SAS) – Must be conducted by a certified rater. Telemedicine virtual visits (where available) or video calls (without recording) are the preferred method of remote assessment. If a scale item cannot be assessed, the item may be skipped and the source should indicate the item could not be assessed. Every effort should be made to have patients assessed by the same rater at each scheduled timepoint.

12.2.4.1 In-Home Study Visits

Where possible via in-home visits by study personnel or contracted vendor (where applicable), the following safety assessments should also be completed, in addition to the safety assessments above. **Note:** For any clinical laboratory determinations, specimen collection, handling and processing must be carried out in accordance with the central laboratory manual. Due to considerations of the processing time required, pharmacokinetic (PK) samples should not be collected during in-home visits. If processing cannot be completed within the time specified in the central laboratory manual for any other samples, collection of those samples should be omitted.

- Collection of samples for clinical laboratory assessments (in accordance with Table 3- Schedule of Clinical Laboratory Tests of the Global Protocol (Amendment #3) or Country-Specific Protocol, if applicable.)
- Serum pregnancy testing
- Electrocardiogram (ECG)
- Vital signs (with or without weight)
- Physical examination

12.2.4.2 Clinical Laboratory Assessments

All attempts should be made to complete clinical laboratory assessments, including pregnancy testing, in accordance with Table 3- Schedule of Clinical Laboratory Tests of the Global Protocol (Amendment #3) or Country-Specific Protocol, if applicable. As an alternative to patients having laboratory assessments on-site, or conducted via an in-home visit by study personnel, laboratory assessments may also be conducted at an alternate laboratory facility, if necessary (eg, general practitioner's office, commercial laboratory etc.). In this case, the data is intended to facilitate the safety oversight of the patient and will be filed in the source document only and not recorded in the eCRF. If a patient is unable or unwilling to travel to an alternate laboratory facility, the laboratory assessment at the scheduled timepoint may be omitted. For women of childbearing potential, study sites may provide urine pregnancy test kits for at-home testing. Study personnel should document the patient's verbal confirmation of pregnancy test results in the source document. Results of at-home urine pregnancy tests will not be recorded in the eCRF. Every attempt should be made to have patient complete as an Unscheduled assessment during the Safety Follow-up (SFU) period. Clinical findings upon termination must be followed until the condition returns to prestudy status or can be explained as unrelated to investigational product. If necessary, an additional follow-up visit should be scheduled.

12.2.4.3 Electrocardiogram (ECG)

If visit is being performed remotely, this assessment may be omitted at the protocol-specified timepoint. Every attempt should be made to have patient complete as an Unscheduled assessment during the Safety Follow-up (SFU) period. Clinical findings upon termination must be followed until the condition returns to prestudy status or can be explained as unrelated to investigational product. If necessary, an additional follow-up visit should be scheduled.

12.2.4.4 Physical Examination

If visit is being performed remotely, this assessment may be omitted at the protocol-specified timepoint. Every attempt should be made to have patient complete as an Unscheduled assessment during the SFU period. Clinical findings upon termination must be followed until the condition returns to prestudy status or can be explained as unrelated to investigational product. If necessary, an additional follow-up visit should be scheduled.

12.2.4.5 Vital Signs

If visit is being performed remotely, this assessment may be omitted at the protocol-specified timepoint. Vital signs should be obtained at the next scheduled in-home or in-person visit.

12.2.5 Visit 6/ET- End of Double-Blind and Early Termination Visit

Every attempt should be made to complete the Visit 6/ET efficacy, safety and health outcome assessments on the same date. In the event that a remote visit for Visit 6/ET is not possible at the scheduled timepoint, all Visit 6/ET efficacy assessments should be completed within 2 weeks of the last dose of IP. If Visit 6/ET is completed as a remote visit without the assessment of clinical laboratory parameters (including pregnancy testing, if applicable), physical examination and/or ECG, the patient should be brought back for safety assessments during the SFU period. Patients who have missed the safety assessments scheduled for Visit 6/ET and are unable to return for these assessments during the SFU period should be encouraged to return to the site for a final assessment of safety when possible. All attempts should be made to make a final assessment of safety even if it falls beyond the end of the Safety Follow-up period. If Visit 6/ET procedures are being completed more than 2 weeks after the last dose of IP, efficacy assessments should be omitted.

12.2.6 Treatment compliance

Investigational Product compliance is to be assessed at every visit during the Double-Blind Treatment period. Wherever possible, IP compliance will be closely monitored by counting the number of capsules dispensed and returned, and through patient interview. For remote visits where a pill count by site staff may not be possible, patient reported compliance is to be documented. If a remote visit is occurring through a video/telemedicine virtual call, study staff should make every effort to visually verify number of capsules remaining in the blister card. Otherwise, patient reported verification of IP capsules remaining should be documented in the source.

To minimize undue burden on the patient, IP return may be less frequent during the time that visits are being conducted remotely but should occur no less frequently than monthly.

Background ADT medication compliance is also to be assessed at every visit. Patients should be questioned to determine if there were any missed doses or changes in dose between visits. Every effort should be made to have patients bring their background ADT to in-person study visits for verification of patient-reported compliance by pill/capsule count (to the extent possible) and patient interviews. For remote visits where a pill count by site staff may not be possible, patient reported compliance is to be documented.

Patients who take less IP or ADT or more IP or ADT than the prescribed regimen must be counseled on the importance of taking study medications 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. It is recognized that patients may miss doses of investigational product or his/her ADT due to circumstances related to COVID-19 (eg, unanticipated study window extension, delay in receipt of IP shipment from site to patient). There will be an allowance of up to 7 consecutive missed doses before requiring that a patient be discontinued from the study. The PI must ensure that the reason for missed doses is adequately assessed and determined to be related to logistical challenges related to COVID-19 and not that the reason is related to a causally-related adverse event, general non-adherence with the protocol, etc. Given the aforementioned concession, patients missing 4 or more doses should not be automatically withdrawn from the study treatment and the study as a result of the pandemic.

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

Table 4 COVID-19 Modified Schedule of Visits and Procedures (Applicable to Randomized Patients who have completed Visit 2)

Study Period	Screening	Baseline	Double-blind Treatment				Safety Follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6/ET**	**7**
Study Week	**Up to -2**	**0**	**1**	**2**	**4**	**6**	**10**
Study Day*	**Up to -14**	**1**	**8**	**15**	**29**	**43**	**71**
COVID-19 Informed Consent/Reconsent (where applicable)	Refer to Global Protocol or Country-Specific Amendment for Visit 1 Procedures	Refer to Global Protocol or Country-Specific Amendment for Visit 2 Procedures	(X)	(X)	(X)	(X)	(X)
Clinical Laboratory Tests[a]						X	
Serum Pregnancy Test[a]						X	X
Vital Signs[b]			X	X	X	X	X
Electrocardiogram[c]						X	
Physical Examination[c]						X	
HAMD-17						X	
YMRS						X	
MADRS			X	X	X	X	
CGI-S			X	X	X	X	
CGI-I			X	X	X	X	
HAM-A				X		X	
SF-12[d]						X	
BARS/AIMS/SAS[e]			X	X	X	X	
C-SSRS[f]			X	X	X	X	X
Adverse Events			X	X	X	X	X
Concomitant Medications			X	X	X	X	X
Access IWRS for IP assignment			X	X	X		
Dispense IP[g]			X	X	X		
IP Compliance and Accountability[h]			X	X	X	X	
ADT Compliance[h]			X	X	X	X	
IP Return[i]			X	X	X	X	
Pharmacokinetic Sample (at any time during visit)[j]				X	X	X	
Pharmacogenetic Consent			X				
Pharmacogenetic Sample[l]			X				

*Note: If necessary, Visits 3 to 7 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 7. **In extenuating circumstances, the visit window for Visits 3 to 7 (inclusive) may be extended an additional 4 days (ie, +7 days) from the scheduled visit. All attempts should be made to conduct the visit within the pre-defined ± 3 day window as well as to avoid a potential lapse in IP during the extension of a visit window.**

ADT = antidepressant therapy; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; ET = early termination; HAM-A = Hamilton Anxiety Rating Scale; HAMD-17 = Hamilton Depression Rating Scale–17 items;
IP = investigational product; IWRS = interactive web-response system; MADRS = Montgomery-Åsberg Depression Rating Scale; PI = Principal Investigator; SAS = Simpson-Angus Scale; SF-12 = Short Form-12 v2 Health Survey; WOCBP = women of child-bearing potential; YMRS = Young Mania Rating Scale. .

[a] Clinical laboratory assessments, including serum pregnancy testing (WOCBP only) may be performed at an off-site laboratory facility if needed. If patient is unable or unwilling to travel to an alternate laboratory facility, the laboratory assessment at the scheduled timepoint may be omitted. For WOCBP, study sites may provide urine pregnancy test kits for at-home testing. Study personnel should document the patient's verbal confirmation of pregnancy test results in the source document. Patient should have clinical laboratory testing performed as an Unscheduled assessment during the Safety Follow-up period. Clinical findings upon termination must be followed until the condition returns to prestudy status or can be explained as unrelated to investigational product. If necessary, an additional follow-up visit should be scheduled.

[b] If visit is being performed remotely, this assessment may be omitted. Vital signs should be obtained at the next scheduled in-home or in-person visit.

[c] If visit is being performed remotely, this assessment may be omitted at this timepoint. Patient should have this assessment performed as an Unscheduled assessment during the Safety Follow-up period. Clinical findings upon termination must be followed until the condition returns to prestudy status or can be explained as unrelated to investigational product. If necessary, an additional follow-up visit should be scheduled.

[d] If visit is being performed remotely, study staff should verbally administer the Short-Form 12 (SF-12) to the patient and record the patient's responses in the source.

[e] Movement scales may be conducted remotely if needed. Where possible, telemedicine virtual visits or video calls (without recording) should be used to conduct this assessment remotely. If a scale item cannot be assessed, the item may be skipped and the source should indicate the item could not be assessed. Movement scales may only be conducted by raters certified on the scale.

[f] C-SSRS may be assessed remotely if needed by a certified rater. Clinicians with a valid C-SSRS certification for another Allergan study may rate C-SSRS in the event the study-certified rater is unavailable to complete the assessment.

[g] As an alternative to in-person drug dispensing, IP may be dispensed via a secure delivery method (where permissible by local, statutory, federal/country law) and after approval by Sponsor.

[h] Assessment of compliance should be performed at each visit. For remote visits where a pill count by site staff may not be possible, patient reported compliance is to be documented. Patient reported verification of IP capsules remaining should be documented.

[i] To minimize undue burden on the patient, IP return may be less frequent during the time that visits are being conducted remotely but should occur no less frequently than monthly.

[j] If visit is being performed remotely or at an alternate laboratory facility, this assessment may be omitted. In consideration of the processing time required, pharmacokinetic samples should not be collected during in-home visits.

[k] Pharmacogenetic consent may be obtained at any time between Visit 1(Screening) and Visit 6 (Week 6). Pharmacogenetic consent may not be obtained remotely.

[1] Pharmacogenetic sample (1 per patient for the entire study) may be obtained from randomized patients at any time between Visit 2 (Baseline) and Visit 6 (Week 6). To be omitted if sampling is not possible due to remote visits being completed.

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
ADT	antidepressant therapy
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATRQ	Antidepressant Treatment Response Questionnaire
BARS	Barnes Akathisia Rating Scale
BP	blood pressure
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions–Improvement
CGI-S	Clinical Global Impressions–Severity
COVID-19	Coronavirus disease 2019
C-SSRS	Columbia–Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DB	double-blind
DCAR	desmethyl cariprazine
DDCAR	didesmethyl cariprazine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EPS	extrapyramidal symptoms
ET	early termination
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HAM-A	Hamilton Anxiety Rating Scale
HAMD-17	Hamilton Depression Rating Scale–17 items
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IWRS	interactive web response system
LOCF	last observation carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MCS-12	Mental Component Summary-12
MDD	major depressive disorder
MGH CTNI	Massachusetts General Hospital Clinical Trial Network
MMRM	mixed-effects model for repeated measures

Term/Abbreviation	Definition
mITT	modified intent-to-treat
PCS	potentially clinically significant
PCS-12	Physical Component Summary-12
PK	pharmacokinetic
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RNA	Ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Scale
SCID-5	Structured Clinical Interview for DSM-5
SF-12	Short Form-12 health survey questionnaire
SFU	Safety Follow-up
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal
VCT	Verified Clinical Trial
YMRS	Young Mania Rating Scale

12.4 Protocol Amendment #1 Summary

Title: A Double-Blind, Placebo-Controlled Study of Cariprazine as an Adjunct to Antidepressants in the Treatment of Patients With Major Depressive Disorder who Have had an Inadequate Response to Antidepressants Alone

Study 3111-302-001 Amendment 1

Date of Amendment: 19 Dec 2018

Amendment Summary

This summary includes changes made to Protocol 3111-302-001 (23 Jul 2018).
Following is a summary of changes that were made to each section of the protocol, and a brief rationale for these changes.

Minor editorial and document formatting revisions have not been summarized.

Section	**Revision**	**Rationale**
Title page	Added the EudraCT number.	Number became available.
Protocol Summary, Study Design and Study Population Characteristics	Restructured the description of patients who may participate in the study.	For clarity
Protocol Summary, Study Design: *Duration, Visit Schedule*	Added text to extend the safety follow-up period from 1 to 4 weeks:	Because of the long half-life of cariprazine and its active metabolites, the Sponsor has extended the safety follow-up period from 1 week to 4 weeks.
Figure 1 Study Schema	Figure 1 was revised to show the extended 4-week safety follow-up period.	Revised to reflect the longer safety follow-up period.

Section	Revision	Rationale
Schedule of Visits and Procedures, Table 1	Changed the **Safety Follow-up** Visit 7 ~~Week 7~~ to Visit 7/Week 10, Study ~~Day 50~~ becomes Study Day 71. New row added for: Blood Alcohol Concentration by Breathalyzer performed at Screening (Visit 1). New row added for: Serum pregnancy text (now also performed at Safety Follow-up. Added text to Footnote e: Blood alcohol concentration as measured by Breathalyzer will be assessed only at Visit 1 (Screening). Expanded the time-window for collection of the pharmacogenetic consent to allow collection between Visit 1 (Screening), and Visit 6/ET.	Revised to reflect the longer safety follow-up period. Blood alcohol at Visit 1 as measured by Breathalyzer was added to expedite turnaround time for blood alcohol concentration results at Screening. Additional serum pregnancy test was added for clarity and to align with European Union contraception requirements. To make collection of the sample more likely.
Section 3 Study Design: Study Duration, Screening/Washout Period	Study Duration: Added text to extend the safety follow-up from 1 to 4 weeks Added text to the Screening/Washout Period to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated; also that the length and timing of the washout of prior psychiatric medications during the 14 days allotted for screening is at the discretion of the investigator.	Safety follow-up period increased from 1 to 4 weeks. For clarity and internal consistency.
Section 4.3 Inclusion Criterion 8	Text added to inclusion criterion 8: Patient must have an inadequate response (< 50% improvement), as measured by the modified ATRQ, to 1 to 3 antidepressants administered during the current episode at an adequate dose (as per package insert) and for at least 6 weeks duration, with at least one dose escalation during the current depressive episode. Patients with an inadequate response to at least 1 ADT in the current episode that is above the minimum dose (as per package insert) for at least 6 weeks in the current episode, can be enrolled.	Clarity.
Section 4.3 Inclusion Criterion 13	Duration of use for birth control has been extended to 12 weeks. 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 4.5.1.1	Updated for consistency with European Union contraception requirements.

Section	Revision	Rationale
Section 4.4 Exclusion Criteria 2 and 11	An additional exclusion criterion has been added: 2. History of manic or hypomanic episodes And exclusion criterion 11 has been deleted: ~~11.Patient has history of having received an anticonvulsant/mood stabilizer within a year prior to Visit 1~~	Exclusion criterion 2 was added and exclusion criterion #11 was removed to clarify that bipolar disorder is exclusionary.
Section 4.4 Exclusion Criterion 4	Exclusion for addictive disorders was removed and the duration shortened to 3 months: Patient has a history of meeting DSM-5 diagnosis for any substance-related disorders (ie, use disorders except caffeine- and tobacco-related) ~~and addictive disorders~~ within the ~~6~~ 3 months before Visit 1 (Screening).	For consistency across cariprazine programs.
Section 4.4 Exclusion Criterion 5	Two additional drugs (amphetamines and barbiturates) were added as exceptions to Exclusion Criterion 4: Exception: patients with a positive UDS at Visit 1 for opiates, cannabinoids, amphetamines, barbiturates, or benzodiazepines may be allowed in the study provided…	For clarity and consistency with other protocols in the program.
Section 4.4 Exclusion Criterion 13 and Section 4.5.2 Prohibited Medications/Treatments	Added text to clarify that moderate CYP3A4 inhibitors (eg, erythromycin or fluconazole) are also prohibited. Added text that rescue meds other than what is listed under rescue medications are prohibited.	For clarity and internal consistency.
Section 4.4 Exclusion Criteria 29 and 30	Added exclusion criteria for blood alcohol concentration and hemoglobin A1c measured at Screening (Visit 1). 29. Blood alcohol concentration ≥ 0.02 g/dL at Visit 1 (Screening) as measured by breathalyzer 30. Hemoglobin A1c >7% at Visit 1 (Screening)	Blood alcohol at Visit 1 as measured by Breathalyzer was added to expedite turnaround time for blood alcohol concentration results. Hemoglobin A1c – eligibility criteria added to clarify Sponsor's expectation of stable endocrinological disease, particularly diabetes.
Section 4.5.1.1 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 to align with European Union contraception requirements.

Section	Revision	Rationale
Section 5.5 Treatment Regiment and Dosing, Table 2, footnote	A footnote has been added after Table 2:<u>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.</u>	To clarify how dosing times can be switched (ie, must allow for 24 hours between doses).
Section 6.1.3 The Modified Antidepressant Treatment Response Questionnaire	Added text to clarify that the modified ATRQ must be completed by a clinician at the study site who has been certified in administration of the ATRQ.	For clarity and internal consistency.
Section 6.5 Pharmacogenetic Sampling	Expanded the time-window for obtaining consent for the pharmacogenetic blood sample to allow collection between <u>Visit 1 (Screening),</u> and Visit 6/ET.	For clarity and internal consistency.
Section 6.6.2 Ocular Events of Special Interest	Adjusted text to clarify that the Sponsor is required ~~to perform expedited reporting~~ <u>to inform worldwide</u> regulatory authorities of ocular events of special interest.	For clarity.
Section 6.6.3 Clinical Laboratory Determinations	Text was added to Table 3 Schedule of Clinical Laboratory Tests: Blood alcohol <u>concentration</u> ~~level~~ (parameter added): <u>Blood alcohol concentration by Breathalyzer</u> Serum β-hCG (women of childbearing potential only) (visit added): 1, Visit 6/ET, <u>and Visit 7 Safety Follow-up Visit</u>	Blood alcohol at Visit 1 as measured by Breathalyzer was added to expedite turnaround time for blood alcohol concentration results. Additional serum pregnancy test was added for safety and to align with European Union contraception requirements.
Section 6.6.6.2 Columbia–Suicide Severity Rating Scale	Included a 12-month lookback to the C-SSRS completed at Visit 1 (Screening).	Patient Safety
Section 7.3.1 Primary Efficacy Analyses	Specified primary estimand; pre-specified a sequence of alternative covariance structures in the MMRM analysis in case of a convergence problem for unstructured covariance matrix. Added one more sensitivity analysis	Specified primary estimand and alternative covariance structures according to FDA's comments; added one more sensitivity analysis.

Section	Revision	Rationale
Section 8.2 Washout Interval	Added text to clarify that psychotropic medications, not listed as rescue medications, may not be newly initiated or reinstated; also that the length and timing of the washout of prior psychiatric medications during the 14 days allotted for screening is at the discretion of the investigator.	For clarity and internal consistency.
Section 8.4.1 Screening (Visit 1)	Text added to indicate that the consent for the pharmacogenetic blood sample may also be obtained at Visit 1 (Screening). Text added to indicate how blood alcohol concentration is assessed: Perform blood alcohol concentration assessment with Breathalyzer	For clarity and internal consistency. Blood alcohol at Visit 1 as measured by Breathalyzer was added to expedite turnaround time for blood alcohol concentration results.
Section 8.4.2 Baseline (Visit 2), and Section 8.4.3 Double-blind Treatment Period (Visits 3 to 6/ET)	Added a reminder that consent for the pharmacogenetic blood sample may also be obtained at Baseline (Visit 2) if not already obtained, and that consent can be obtained any time between Visit 1 and Visit 6/ET, inclusive.	For clarity and internal consistency.
Section 8.4.3 Double-blind Treatment Period (Visits 3 to 6/ET)	Added: Collect blood sample for serum pregnancy test for women of childbearing potential (Visit 6/ET only).	For clarity and to align with contraception guidance.
Section 8.4.4 Safety Follow-up (Visit 7)	Text added to make serum pregnancy test mandatory at the safety follow-up: Collect blood sample for serum pregnancy test	For clarity and to align with contraception guidance.
Section 8.5 Instructions for Patients	Removed text: ~~On study visit days, patients will continue to administer IP and ADT at home around the same clock time(s).~~	For clarity and consistency with other protocols in the program.
Section 8.9 Withdrawal Criteria	Text changed from 48 to 24 hours of awareness: The patient has an absolute neutrophil count of < 1000 per mm^3 and, after repeat testing within ~~48~~ 24 hours of awareness, the values are not normalized or are not increasing.	For clarity.
Section 9.4 Reporting of Pregnancies Occurring During the Study	The reporting period for pregnancies was changed from 3 months to 12 weeks.	Updated for consistency with approved labeling.
Section 11 References	Additional reference inserted.	To support additional sensitivity analyses.