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A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL, MULTICENTER CLINICAL TRIAL EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF CARIPRAZINE IN A DOSE-REDUCTION PARADIGM IN THE PREVENTION OF RELAPSE IN BIPOLAR I DISORDER PATIENTS WHOSE CURRENT EPISODE IS MANIC OR DEPRESSIVE, WITH OR WITHOUT MIXED FEATURES

Protocol Number:	RGH-MD-25
Phase:	3B
Name of Investigational Product:	Cariprazine
Sponsor:	AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064-6148 USA AbbVie Ltd. 1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire SL7 1YL United Kingdom AbbVie Deutschland GmbH & Co. KG Knollstrasse, Ludwigshafen 67061, Germany
Emergency Telephone Number:	Refer to the Study Contacts List in the Investigator Site File or Trial Master File
Serious Adverse Event Reporting Fax Number:	+1-714-796-9504/ +1-714-246-5295 IR-Clinical-SAE@abbvie.com
Medical Safety Physician:	Refer to study contacts list.

AbbVie Signatory:	[redacted] Vice President Head, Development Neurosciences
Protocol Date:	12 December 2016
Protocol Amendment 1 Date:	25 August 2017
Protocol Amendment 2 Date:	28 March 2018
Protocol Amendment 3 Date:	20 November 2018
Protocol Amendment 4 Date:	17 December 2019
COVID-19 Global Protocol Addendum (incorporated in Amendment 5)	08 May 2020
Protocol Amendment 5 Date:	09 June 2022

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

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

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

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

Investigator Printed Name	Investigator Signature	Date

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Protocol Summary

Study Compound: Cariprazine

Phase: 3B

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

Clinical Hypotheses: 1) In bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive, with or without mixed features, cariprazine at 3.0 mg/d is safe and effective in preventing relapse when compared to placebo; 2) In bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive, with or without mixed features and who were initially stabilized on a target dose of 3.0 mg/d, cariprazine at 1.5 mg/d is safe and effective in preventing relapse when compared to placebo.

Study Design

Structure: This is a multicenter, multinational, double-blind (DB), placebo-controlled, randomized withdrawal study evaluating the safety and efficacy of cariprazine compared with placebo in the prevention of relapse in bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive, with or without mixed features. The study schema is presented in Figure 1.

Duration:

Screening/Washout period: Patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for bipolar I disorder whose current episode (ie, index episode) is manic or depressive, with or without mixed features will undergo a screening and washout period of up to 7 days, during which consent, eligibility assessment, and withdrawal of prior psychiatric and additional prohibited medications will occur. The length and timing of the washout of prior psychiatric medications during the 7 days allotted for the screening period is at the discretion of the investigator. Prior medications should be gradually withdrawn such that the washout is completed by Visit 2/Baseline. Please note that during the screening/washout period, psychotropic medications, other than those listed as rescue (Section 4.8.3), may not be newly initiated or reinstated. In order to ensure the safe transition of patients into the study, based upon the clinical judgment of the investigator, patients may be hospitalized during initiation of the study. This hospitalization can be for up to 14 days during the screening and open-label (OL) periods (with the end of hospitalization no later than Visit 3 [Day 8] of the OL treatment period). This 14-day allowance for hospitalization may include all or part of the screening period. Hospitalization beyond the initial 14 days allowed will require consultation with the AbbVie medical monitor. Following the protocol-allowed 14 days of hospitalization (and any sponsor-allowed extension), patients should be treated as outpatients.

Open-label Treatment Period: Patients who continue to meet eligibility criteria at Visit 2/Baseline will enter an OL treatment period for up to 16 weeks. Note that, since patients need to respond to initial treatment and subsequently meet stability criteria and maintain it for 8 weeks before being randomized, there will be some patients who will meet the criteria earlier than others.

Patients will be started on cariprazine 1.5 mg/d with a target dose of 3.0 mg/d. During the initial 8 weeks of the OL period, patients will be assessed for remission of symptoms, defined as Young Mania Rating Scale (YMRS) total score ≤ 12 and Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≤ 12 and Clinical Global Impressions-Severity (CGI-S) ≤ 3. Per protocol, the earliest any patient can achieve remission is Day 15 (Visit 4). This is to ensure all patients are on cariprazine 3.0 mg/d for at least one week. The patient is considered stabilized once remission (ie, YMRS and MADRS total scores are both ≤ 12 and CGI-S ≤ 3) has been established and maintained at the subsequent visit. The earliest any patient can achieve stability is Day 22 (Visit 5). Stabilized patients will then be treated for an additional 8 weeks of OL cariprazine 3.0 mg/d. Patients who do not achieve remission by Week 6 (Visit 7) or stability by Week 8 (Visit 8) will be discontinued from the

study. Additionally, patients who require hospitalization (excluding protocol-specified allowed hospitalization) or who require the initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms as judged by the clinical impression of the investigator at any time during the OL treatment period, will be discontinued.

Following the attainment of stability, YMRS total score ≤ 12 and MADRS total score ≤ 12 and CGI-S ≤ 3 must be maintained for an additional 8 weeks, with the exception of allowing 1 excursion (YMRS > 12 and/or MADRS > 12). If an excursion occurs, the YMRS and MADRS scores must return to the remission threshold (ie, ≤ 12) at the subsequent visit. The excursion (YMRS > 12 and/or MADRS > 12) may occur at any time during the 8-week stability period with the exception of Visit 12/End of OL, but must be followed by a return to remission threshold at the next visit. In the event the excursion occurs in the 8th week of stability but prior to Visit 12/End of OL, patients should be assessed at the following visit to confirm whether randomization criteria have been met. Previously stabilized patients whose efficacy scores increase to YMRS ≥ 17, MADRS ≥ 20, or CGI-S ≥ 4 during OL treatment will be discontinued from the study. Once stabilization has occurred and been maintained as described above, the patient will be randomized.

Randomization/Double-blind Treatment Period: OL patients who are able to maintain stability criteria for at least 8 weeks with no more than 1 excursion above the remission threshold will be randomized 1:1:1 to receive cariprazine at the same dose (3.0 mg/d), cariprazine at a reduced dose (1.5 mg/d), or placebo for up to 39 weeks. Patients will continue to receive study drug until a relapse event (manic or depressive) occurs or until completion of the 39 weeks of randomized treatment. Relapse will be defined as the occurrence of any 1 of the following:

- YMRS total score ≥ 17
- MADRS total score ≥ 20
- CGI-S ≥ 4
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms as judged by the clinical impression of the investigator
- Psychiatric hospitalization
- Exacerbation of illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

For patients who meet relapse criteria, the investigator will categorize the relapse event(s) as manic or depressive event(s), with or without mixed features.

Safety Follow-up (SFU) Period: Patients who complete the study, or who prematurely discontinue from either the OL or DB periods, will be followed for 4 more weeks and will have 2 evaluations for safety assessments at Visits 32 and 33 during the SFU period. During the SFU, patients will receive treatment as usual at the discretion of the investigator or designee. Patients will not receive investigational product (IP) during the SFU period.

Study Treatment Groups: Cariprazine 3.0 mg/d and 1.5 mg/d

Controls: Matching placebo

Dosage/Dose Regimen: Investigational product (IP) in the form of capsules packaged in blister packs will be provided by the sponsor. No IP will be administered during the screening/washout period or the SFU period. During the OL treatment period (up to 16 weeks), patients will take 1 capsule daily. All patients will begin with cariprazine 1.5 mg on Day 1. Patients diagnosed with bipolar I disorder, current episode (ie, index episode) manic, with or without mixed features, will receive cariprazine 3.0 mg/d on Day 2 and continue on 3.0 mg/d until the end of the OL treatment period. Patients diagnosed with bipolar I disorder, current episode (ie, index episode) depressive with or without mixed features, will continue to receive cariprazine 1.5 mg/d from Days 2 to 7. On Day 8, the dose for these patients will be increased to 3.0 mg/d and continue until the end of the OL treatment period. For the 39-week DB treatment period, patients will be supplied with identically appearing

capsules of either cariprazine 3.0 mg, cariprazine 1.5 mg, or placebo. During the DB treatment period patients will take 1 capsule daily.

Randomization: After completing the OL treatment period, eligible patients will be randomized in a 1:1:1 ratio to cariprazine 3.0 mg/d, cariprazine 1.5 mg/d, or placebo.

Visit Schedule: There are a total of up to 33 visits including screening/washout (up to 7 days), the OL treatment period (up to 16 weeks), the DB treatment period (up to 39 weeks), and the SFU period (4 weeks) as shown in Table 1.

Patients meeting remission and stability criteria and subsequent randomization criteria will be eligible for early randomization beginning at Week 12 (Visit 10) and will move forward to the DB treatment period without requiring all visits in the OL treatment period.

If no tolerability issues arise, all patients will receive at least 6 weeks of OL treatment. Some patients will be discontinued from the study after 6 or 8 weeks of OL treatment if remission or stability criteria, respectively, have not been achieved.

Study Population Characteristics

Number of Patients: Approximately 378 patients are planned to be randomized (126 per treatment arm). It is anticipated that approximately 1245 patients will be screened and approximately 822 will enter the OL treatment period. In the event that screening or randomization failure rates are higher than projected, enrollment will continue until approximately 126 patients per treatment arm are randomized. Screened patients who have not reached the randomization visit at the time the randomization target is met, will not be discontinued from the study. These patients will be allowed to continue in the study until they either complete the study, prematurely discontinue, or otherwise fail to meet randomization criteria.

Condition/Disease: Bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive, with or without mixed features.

Key Inclusion Criteria: Male or female 18 to 65 years of age; meeting DSM-5 criteria for bipolar I disorder, current episode manic, with or without mixed features; and having a total YMRS score ≥ 20 and a score of at least 4 on 2 of the following YMRS items: irritability, speech, content, and disruptive/aggressive behavior, or bipolar I disorder, current episode depressive, with or without mixed features; and having a MADRS total score ≥ 23 and a score of at least 3 on 2 of the following MADRS items: apparent sadness, reported sadness, inner tension or inability to feel.

Key Exclusion Criteria: diagnosis of another psychiatric disorder other than bipolar disorder with the exception of specific phobias.

Efficacy Measures

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

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

- YMRS total score ≥ 17
- MADRS total score ≥ 20
- CGI-S ≥ 4
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms as judged by the clinical impression of the investigator
- Psychiatric hospitalization
- Exacerbation of illness as judged by the clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

For patients who meet relapse criteria, the investigator will categorize the relapse event(s) as manic or depressive event(s), with or without mixed features.

Pharmacokinetics: Samples will be collected for determination of the plasma concentrations of cariprazine and its metabolites. A total of 12 blood samples will be collected at the visits shown in Table 1.

Pharmacogenetic Sampling: Blood samples will be collected at any time point between Visit 2/Baseline and Visit 7 (Week 6) to determine individual genotype status and for pharmacogenetic biobanking. Participation is optional.

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

General Statistical Methods and Types of Analyses:

The OL safety population will consist of all screened patients who took at least 1 dose of cariprazine during the OL period of the study. The OL intent-to-treat (ITT) population will consist of all patients in the OL safety population who had at least 1 postbaseline assessment of the YMRS, MADRS, or CGI-S scores during the OL period of the study. The randomized population will consist of all patients in the OL safety population who were randomized to a treatment group during the DB treatment period of the study. The DB safety population will consist of all randomized patients who took at least 1 dose of DB IP. The DB ITT population will consist of all patients in the DB safety population who had at least 1 post-randomization assessment of the YMRS, MADRS, or CGI-S scores during the DB period of the study.

The primary efficacy analysis will compare the time to first relapse of any mood episode between each cariprazine group and the placebo group using the log-rank test stratified by modified index episode (manic or depressive) for the DB ITT Population. The modified index episode is derived as following: manic index episode(s) with or without mixed features will be classified as manic episode(s); depressive index episode(s) with or without mixed features will be classified as depressive episode(s). The comparison of cariprazine 3.0 mg/d versus placebo will be tested first at the two-sided 0.05 significance level, only when it is significant, the comparison of cariprazine 1.5 mg/d versus placebo will be tested also at the two-sided 0.05 significance level. This testing strategy controls the overall Type I error rate at the 0.05 significance level. Estimates of the hazard ratio (HR) and 95% confidence intervals will be based on the Cox proportional hazards model, with treatment group as covariates stratified by modified index episode (manic or depressive). The Kaplan-Meier estimates for cumulative distribution function of relapse rate for each treatment group will be presented.

All safety parameters will be analyzed descriptively for the OL and DB safety populations.

Sample Size Calculation: The sample size is based on several considerations. Assuming that the relapse rate is approximately 35% in the placebo group and the relapse HR is assumed to be 0.42, the study would have to observe 75 events to have at least 85% statistical power to detect that at least 1 dose is significant. The statistical method for the power calculation is based on the log-rank 2-sided test at a 5% significance level to compare the difference of each of the 2 survival curves of the cariprazine treatment groups versus that of placebo. Based on the assumed event rates, and considering the 26% of patients who may discontinue early from the DB treatment period for other reasons, approximately 378 patients should be randomized to cariprazine 3.0 mg/d, cariprazine 1.5 mg/d, and placebo, or approximately 126 patients per treatment group. It should be noted that this study is designed to test the 3.0 mg/d dose of cariprazine versus placebo first at the 0.05 significance level and, if significant, then the 1.5 mg/d dose of cariprazine will be tested at the 0.05 significance level. Given this sequential testing strategy, the higher dose of 3.0 mg/d has 85% statistical power to show significance versus placebo, and the 1.5 mg/d dose, if it is as effective as the 3.0 mg/d dose, and the 3.0 mg/d dose is statistically significant, would also have 85% statistical power at the 0.05 significance level.

Figure 1 Study Schema

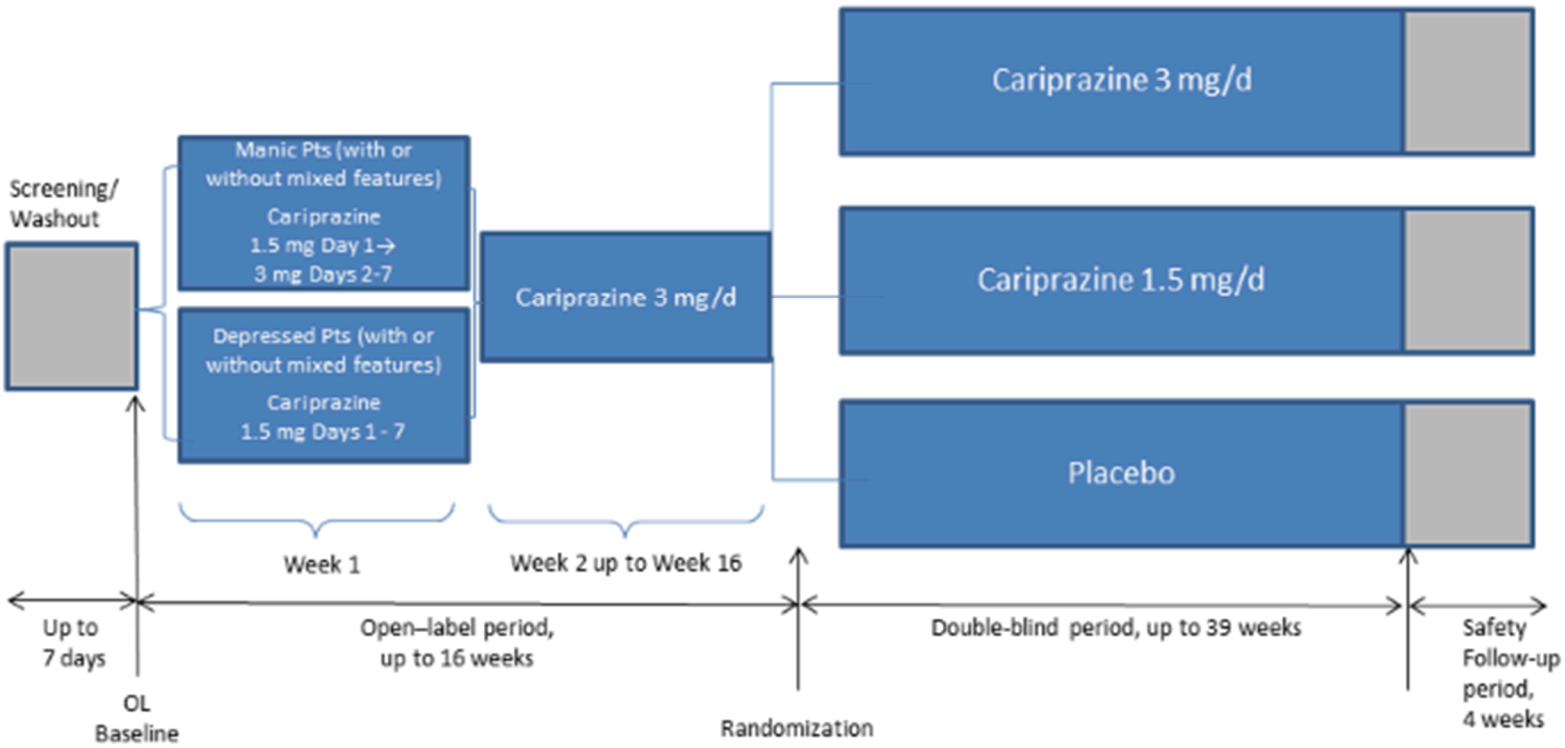

Table 1 Schedule of Visits and Procedures

Screening/Washout Period and Open-Label Treatment Period

Trial Period	Screening/Washout Period		Open-label Treatment Period									
Visit Number/Visit Title	**1/Screening**	**2/Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/End of OL**
End of Trial Week (Day)	**Up to 7 days (Days -7 to -1)**	**0 (1)**	**1 (8)**	**2 (15)**	**3 (22)**	**4 (29)**	**6 (43)**	**8 (57)**	**10 (71)**	**12 (85)**	**14 (99)**	**16 (113)**
Visit Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Informed Consent	X											
Verified Clinical Trials check[a]	X											
Inclusion/Exclusion Criteria	X	X										
Assessment of Remission Criteria[b]				X	X	X	X					
Assessment of Stability Criteria[c]					X	X	X	X				
Maintenance of stability[d]						X	X	X	X	X	X	X
Assessment of Randomization Criteria[e]										X	X	X
Randomization												X
IP Dispensing		X	X	X	X	X	X	X	X	X	X	X
IP Return: Compliance and Accountability			X	X	X	X	X	X	X	X	X	X
Medical and Psychiatric History	X											
SCID-5	X											
Hepatitis Screen	X											
Urine Drug Screen/BloodAlcohol Concentration by Breathalyzer	X											X
Serum Pregnancy Test	X						X					X
Clinical Laboratory	X						X					X
Hemoglobin A1c	X											X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	X	X	X	X
MADRS	X	X	X	X	X	X	X	X	X	X	X	X
CGI- S	X	X	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
PSP		X				X						X
WPAI-BD	X											X

Trial Period	Screening/Washout Period		Open-label Treatment Period									
Visit Number/Visit Title	**1/Screening**	**2/Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/End of OL**
End of Trial Week (Day)	**Up to 7 days (Days -7 to -1)**	**0 (1)**	**1 (8)**	**2 (15)**	**3 (22)**	**4 (29)**	**6 (43)**	**8 (57)**	**10 (71)**	**12 (85)**	**14 (99)**	**16 (113)**
Visit Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Extrapyramidal Symptoms (AIMS/BARS/SAS)		X	X		X		X		X		X	X
Vital Signs and Weight[f]	X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference	X						X					X
Height	X											
Physical examination	X											
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X											X
[redacted]	X[g]											X[h]
PK sample (taken at any time during visit)						X		X		X		X
Pharmacogenetic consent[i]	X	X	X	X	X	X	X					
Pharmacogenetic sampling[j]		X	X	X	X	X	X					

Note: Visit 2/Baseline is expected to occur within 7 days of Visit 1; if required, it may be conducted up to 3 days after the scheduled visit. Visits 3 to 12 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.

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impressions-Improvement Scale; CGI-S = Clinical Global Impressions-Severity Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; DB = double-blind; ECG = electrocardiogram; ET = Early Termination; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; OL = open-label; PK = pharmacokinetic; PSP = Personal and Social Performance scale; SAE = serious adverse event; SAS = Simpson-Angus Scale; SCID-5 = Structured Clinical Interview for DSM-5; WPAI-BD = Work Productivity and Activity Impairment: Bipolar Disorder questionnaire; YMRS = Young Mania Rating Scale.

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

[b] Assess remission criteria (per Section 4.5). Patients who do not meet remission criteria by Visit 7/Week 6 must be discontinued and will undergo procedures for Visit 31/ET and subsequently complete the SFU period.

[c] Assess stability criteria (per Section 4.5). If remission criteria are met but stability criteria are not met at the subsequent visit, the patient must be re-assessed for remission at the following visit. Patients who do not meet stability criteria by Visit 8/Week 8 must be discontinued and will undergo procedures for Visit 31/ET and subsequently complete the SFU period.

[d] Assess YMRS, MADRS and CGI-S during the 8-week period following achievement of stability criteria (per Section 4.5) to ensure YMRS total score ≤ 12 and MADRS total score ≤ 12 and CGI-S ≤ 3. During the 8 weeks, 1 excursion in YMRS and/or MADRS score (ie, YMRS > 12 [cannot meet or exceed 17] and/or MADRS > 12 [cannot meet or exceed 20]) is allowed (see Section 4.6)

[e] Patients who have previously met stability criteria (per Section 4.5) should be assessed for fulfillment of randomization criteria (per Section 4.6). Patients who meet randomization criteria should undergo Visit 12/End of OL procedures and be randomized to DB treatment. Patients eligible for early randomization will skip any remaining visits in the OL treatment period.

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

[g] [redacted]

h [redacted]

i Pharmacogenetic consent may be obtained at any time between Visit 1/Screening and Visit 7 (Week 6).

j Pharmacogenetic sampling (one sample) may be obtained at any time between Visit 2/Baseline and Visit 7 (Week 6).

Double-blind Treatment Period

Trial Period	Double-blind Treatment Period																		Safety Follow-up Period	
Visit Number/ Visit Title	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31/ET**	**32**	**33**
End of Trial Week (Day)	**18 (127)**	**20 (141)**	**22 (155)**	**24 (169)**	**26 (183)**	**28 (197)**	**30 (211)**	**32 (225)**	**34 (239)**	**36 (253)**	**38 (267)**	**40 (281)**	**42 (295)**	**44 (309)**	**46 (323)**	**48 (337)**	**50 (351)**	**52 (365)**	**55 (386)**	**57 (400)**	**59 (414)**
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Serum Pregnancy test						X						X							X		X
Clinical Laboratory						X						X							X		
Hemoglobin A1c																			X		
IP Dispensing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
IP Return (Compliance and Accountability)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MADRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-I	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSP				X						X									X		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
WPAI-BD				X															X		
Extrapyramidal Symptoms (AIMS/BARS/SAS)		X		X		X		X		X		X		X		X		X	X		
Assess relapse criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference						X						X							X		
Physical examination																			X		
ECG																			X		
[redacted]																			X		X

Trial Period	Double-blind Treatment Period																			Safety Follow-up Period	
Visit Number/ Visit Title	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31/ET**	**32**	**33**
End of Trial Week (Day)	**18 (127)**	**20 (141)**	**22 (155)**	**24 (169)**	**26 (183)**	**28 (197)**	**30 (211)**	**32 (225)**	**34 (239)**	**36 (253)**	**38 (267)**	**40 (281)**	**42 (295)**	**44 (309)**	**46 (323)**	**48 (337)**	**50 (351)**	**52 (365)**	**55 (386)**	**57 (400)**	**59 (414)**
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sample[c]	X	X			X			X			X			X			X		X		

Note: If necessary, Visits 13 to 33 may be conducted up to 3 days before or after the scheduled visits. The visit windows for each scheduled visit are relative to Visit 12 for Visits 13 through 31/ET and relative to Visit 31/ET for Visits 32 and 33.

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; ET = Early Termination; IP = investigational product; MADRS = Montgomery-Åsberg Depression Rating Scale; PK = pharmacokinetic; PSP = Personal and Social Performance scale; SAE = serious adverse event; SAS = Simpson-Angus Scale; WPAI-BD = Work Productivity and Activity Impairment: Bipolar Disorder questionnaire; YMRS = Young Mania Rating Scale.

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

[b] [redacted]

[c] Collected at any time during visit.

1. Background and Clinical Rationale

Bipolar disorder is a severe chronic mood disorder characterized by episodes of mania or hypomania alternating or commingling with episodes of depression (Vieta 2013). It affects more than 1% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status and represents one of the leading causes of disability among young people (Grande 2016). In the United States, it affects 5.7 million adults or about 2.6% of the population 18 years of age and older in any given year (Kessler 2005). Bipolar disorder causes substantial psychosocial morbidity that frequently affects the patient's marriage, children, occupation, and other aspects of the patient's life (Zarate 2000). The World Health Organization has ranked bipolar disorder as the seventh leading cause of worldwide nonfatal disease burden (World Health Organization 2001). Bipolar disorder confers the highest risk of suicide among major psychological disorders (Costa 2015).

Bipolar mania accounts for 1 in 7 psychiatric emergencies. Acute manic and mixed episodes are frequently associated with severe behavioral, physical, functional, and cognitive disturbances, all of which can have important personal and social consequences. For the most part, bipolar mania constitutes a medical emergency requiring a hospital admission to ensure the immediate safety of the patient or others and rapid symptomatic relief (Keck 2003).

The depressive phase of bipolar disorder causes significantly more morbidity and mortality than the manic or hypomanic phase. Patients with bipolar disorder experience depressive symptoms much more frequently than manic or hypomanic symptoms (Hlastala 1997; Judd 2002; Judd 2003; Keller 1986; Post 2005; Post 2003). In addition, compared with bipolar mania, bipolar depression is associated with an increased risk of suicide and psychosocial impairment (Altshuler 2002; Calabrese 2003; Calabrese 2004; Dilsaver 1997; Leverich 2003; MacQueen 2001).

A variety of pharmacologic agents are currently available for the management of acute mania, including mood stabilizers, anticonvulsants, and antipsychotics, all of which can be used as monotherapy or in combination regimens. For bipolar depression, pharmacotherapeutic options are limited. At present, only Seroquel (quetiapine), Seroquel XR (quetiapine XR), Symbyax (olanzapine and fluoxetine), and Latuda (lurasidone HCl) are approved by the FDA for the treatment of patients with bipolar depression. Other common pharmacotherapies include lithium, anticonvulsants (eg, valproate, lamotrigine), antidepressants, atypical antipsychotics, or combinations of these. Fewer treatment options are available for the maintenance of bipolar disorder, particularly as monotherapy.

In recent years, atypical antipsychotics (eg, olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole, cariprazine) have been approved for bipolar disorder. First- and second-generation antipsychotics are used in the acute setting in combination with mood stabilizers to achieve a more rapid control of symptoms in severely agitated patients whose treatment also necessitates hospitalization.

Only quetiapine and cariprazine have data demonstrating efficacy for the acute treatment of both mania and depressive episodes associated with bipolar I disorder.

Compared with conventional agents, the side-effect profile of atypical antipsychotics is more favorable. However, the atypicals have been associated with an increased risk of metabolic side effects, including weight gain, dyslipidemia, glucose intolerance, and type II diabetes mellitus. Due to this increased risk, the FDA requires a warning label for diabetes on all atypical antipsychotics.

The optimum long-term treatment strategies for bipolar disorder I are not yet established. More effective therapies with improved side-effect profiles are still needed to enhance long-term, outcomes in these patients while preventing recurrences of mood episodes.

Cariprazine is an orally active and potent dopamine (DA) D_3/D_2 receptor functional antagonist developed by Gedeon Richter Plc., and AbbVie Sales, LLC. It is approved in the US for the treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder. For bipolar mania, the starting dose is 1.5 mg/d with a recommended dose of 3 to 6 mg/d. In addition to efficacy in mania, cariprazine has also been shown to be effective in Bipolar I patients with most recent episode depressed.

Study RGH-MD-54 was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in 488 patients with bipolar depression. Two cariprazine treatment groups (1.5 or 3.0 mg/day) were evaluated. This study met its primary endpoint, demonstrating a statistically significant improvement in change from baseline to Week 6 in MADRS total score in both the cariprazine 1.5 mg and cariprazine 3.0 mg groups compared with placebo in the treatment of patients with bipolar depression. For the key secondary efficacy endpoint of change from baseline to Week 6 in CGI-S, numerically larger reductions compared with placebo were observed in both cariprazine dose groups but these differences did not reach statistical significance after adjusting for multiplicity.

Study RGH-MD-56 was an 8-week, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study in 578 patients with bipolar depression. Three cariprazine dose groups (0.75, 1.5, or 3.0 mg/day) were evaluated. For the primary efficacy parameter, the change

from baseline to the end of Week 6 in MADRS total score, statistically significant improvement was demonstrated for the cariprazine 1.5 mg dose relative to placebo. Nominally significant improvement was shown for cariprazine 3.0 mg, which did not remain statistically significant after adjusting for multiplicity. No statistically significant treatment effect was shown for the 0.75 mg dose at Week 6.

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

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 and the degree of its apparent partial agonist activity is greater than aripiprazole.

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.

Cariprazine has low potency at other receptor sites, such as the 5-HT_{2C}, histamine H_1, and adrenergic receptor sites, suggesting a lower potential for side effects such as extrapyramidal symptoms (EPS) and body weight gain. Cariprazine displays potent in vivo oral activity in various animal models of psychosis and mania and shows antidepressant- and anxiolytic-like activity as well as procognitive-like effects.

Discussion of Study Design, Including the Choice of Control Groups

[redacted]

[redacted]

[redacted]

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

1) To evaluate the efficacy and safety of cariprazine at a target dose of 3.0 mg/d compared with placebo in prevention of relapse in patients with bipolar I disorder whose current episode (ie, index episode) is manic or depressive, with or without mixed features;

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

2.2 Clinical Hypotheses

1) In bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive with or without mixed features, cariprazine at 3.0 mg/d is safe and effective in preventing relapse when compared to placebo.

2) In bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive, with or without mixed features, and who were initially stabilized on a target dose of 3.0 mg/d, cariprazine at 1.5 mg/d is safe and effective in preventing relapse when compared to placebo.

3. Study Design

This is a multicenter, multinational, DB, placebo-controlled, randomized withdrawal study evaluating the safety and efficacy of cariprazine compared with placebo in the prevention of relapse in bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive, with or without mixed features.

Screening/Washout Period: Patients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for bipolar I disorder whose current episode (ie, index episode) is manic or depressive, with or without mixed features will undergo a screening and washout period of up to 7 days, during which consent, eligibility assessment, and withdrawal of prior psychiatric and additional prohibited medications will occur. The length and timing of the washout of prior psychiatric medications during the 7 days allotted for the screening period is at the discretion of the investigator. Prior medications should be gradually withdrawn such that the washout is completed by Visit 2/Baseline. Please note that during the screening/washout period, psychotropic medications, other than those listed as rescue (Section 4.8.3), may not be newly initiated or reinstated. In order to ensure the safe transition of patients into the study, based upon the clinical judgment of the investigator, patients may be hospitalized during initiation of the study. This hospitalization can be for up to 14 days during the screening and OL periods (with the end of hospitalization no later than Visit 3 [Day 8] of the OL treatment period). This 14-day allowance for hospitalization may include all or part of the screening period. Hospitalization beyond the initial 14 days allowed will require consultation with the AbbVie medical monitor. Following the protocol-allowed 14 days of hospitalization (and any sponsor-allowed extension), patients should be treated as outpatients.

Open-label Treatment Period: Patients who continue to meet eligibility criteria at Visit 2/Baseline will enter an OL treatment period for up to 16 weeks. Note that, since patients need to respond to initial treatment and subsequently meet stability criteria and maintain it for 8 weeks before being randomized, there will be some patients who will meet the criteria earlier than others.

Patients will be started on cariprazine 1.5 mg/d with a target dose of 3.0 mg/d. During the initial 8 weeks of the OL treatment period, patients will be assessed for remission of symptoms, defined as Young Mania Rating Scale (YMRS) total score ≤ 12 and Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≤ 12 and Clinical Global Impressions-Severity (CGI-S) ≤ 3. Per protocol, the earliest any patient can achieve remission is Day 15 (Visit 4). This is to ensure all patients are on cariprazine 3.0 mg/d for at least one week. The patient is considered stabilized once remission (ie, YMRS and MADRS total scores are both ≤ 12 and CGI-S ≤ 3) has been established and maintained at the subsequent visit. The earliest any patient can achieve stability

is Day 22 (Visit 5). Stabilized patients will then be treated for an additional 8 weeks of OL cariprazine 3.0 mg/d. Patients who do not achieve remission by Week 6 or stability by Week 8 will be discontinued from the study. Additionally, patients who require hospitalization (excluding protocol-specified allowed hospitalization) or who require the initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms as judged by the clinical impression of the investigator, at any time during the OL treatment period, will be discontinued.

Following the attainment of stability, YMRS total score ≤ 12 and MADRS total score ≤ 12 and CGI-S ≤ 3 must be maintained for an additional 8 weeks, with the exception of allowing 1 excursion (YMRS > 12 and/or MADRS > 12). If an excursion occurs, the YMRS and MADRS scores must return to the remission threshold (ie, ≤ 12) at the subsequent visit. The excursion (YMRS > 12 and/or MADRS > 12) may occur at any time during the 8-week stability period with the exception of Visit 12/End of OL, but must be followed by a return to remission threshold at the next visit. In the event the excursion occurs in the 8th week of stability but prior to Visit 12/End of OL, patients should be assessed at the following visit to confirm whether randomization criteria have been met. Previously stabilized patients whose efficacy scores increase to YMRS ≥ 17, MADRS ≥ 20, or CGI-S ≥ 4 during OL treatment will be discontinued from the study. Once stabilization has occurred and been maintained as described above, the patient will be randomized.

Patients who meet remission and stability criteria and subsequent randomization criteria will be eligible for early randomization beginning at Week 12 (Visit 10) and will move forward to the DB treatment period without requiring all visits in the OL treatment period.

If no tolerability issues arise, all patients will receive at least 6 weeks of OL treatment. Some patients will be discontinued from the study after 6 or 8 weeks of OL treatment if remission or stability criteria, respectively, have not been achieved.

Randomization/DB Treatment Period: OL patients who are able to maintain stability criteria for at least 8 weeks with no more than 1 excursion above the remission threshold will be randomized 1:1:1 to receive cariprazine at the same dose (3.0 mg/d), cariprazine at a reduced dose (1.5 mg/d), or placebo for up to 39 weeks. Patients will continue to receive study drug until a relapse event (manic or depressive) occurs or until completion of the 39 weeks of randomized treatment. Relapse will be defined as the occurrence of any 1 of the following:

- YMRS total score ≥ 17
- MADRS total score ≥ 20
- CGI-S ≥ 4
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms as judged by the clinical impression of the investigator,
- Psychiatric hospitalization
- Exacerbation of illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

For patients who meet relapse criteria, the investigator will categorize the relapse event(s) as manic or depressive event(s), with or without mixed features.

Safety Follow-up Period: Patients who complete the study, or who prematurely discontinue from either the OL or DB periods, will be followed for 4 more weeks and will have 2 evaluations for safety assessments at Visit 32 and 33 during the SFU period. During the SFU, patients will receive treatment as usual at the discretion of the investigator or designee. Patients will not receive IP during the SFU period.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 378 patients are planned to be randomized (126 per treatment arm). It is anticipated that approximately 1245 patients will be screened and approximately 822 will enter the OL treatment period. In the event that screening or randomization failure rates are higher than projected, enrollment will continue until approximately 126 patients per treatment arm are randomized. Screened patients who have not reached the randomization visit at the time the randomization target is met, will not be discontinued from the study. These patients will be allowed to continue in the study until they either complete the study, prematurely discontinue, or otherwise fail to meet randomization criteria.

4.2 Study Population Characteristics

The study population will include bipolar I disorder patients whose current episode (ie, index episode) is manic or depressive, with or without mixed features. The diagnosis will be based upon *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria, approached through a structured clinical interview (Structured Clinical Interview for DSM-5 [SCID-5]).

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent has been obtained.
2. Patients are male or female, 18 to 65 years of age, inclusive.
3. Patients meet DSM-5 criteria at both screening and baseline for one of the following:
    a. DSM-5 criteria for bipolar I disorder current episode manic with or without psychotic features; with or without mixed features, or
    b. DSM-5 criteria for bipolar I disorder current episode depressive with or without psychotic features; with or without mixed features
4. Patients meet one of the following at both screening and baseline (note: the same criterion must be met at both visits):
    a. YMRS total score ≥ 20 and a score of at least 4 on 2 of the following YMRS items: irritability, speech, content, and disruptive/aggressive behavior, or
    b. MADRS total score ≥ 23 and a score of at least 3 on 2 of the following MADRS items: apparent sadness, reported sadness, inner tension or inability to feel
5. Normal physical examination results, vital signs, clinical laboratory test results, and electrocardiogram (ECG) results or abnormal results that are judged not clinically significant by the investigator.
6. 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]).
7. Ability to follow study instructions, complete study assessment tools with minimal assistance and no alteration to the assessment tools, and likely to complete all required visits.
8. Continue to meet all Visit 1 (Screening) inclusion criteria at Visit 2 (Baseline); to be assessed at Visit 2.
9. Each patient must have an identified external contact person or an identified responsible person (eg, family member, friend, social worker, case worker, or nurse) who is considered reliable by the investigator and who will provide support to the patient and act as an external contact in the event the site is having difficulty reaching the patient during the trial and to ensure observation of patient's wellbeing.

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

11. Women of childbearing potential only must have a negative qualitative serum β-human chorionic gonadotropin (β-hCG) pregnancy test prior to enrollment.

4.4 Exclusion Criteria

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

Psychiatric Criteria

1. Four or more episodes of a mood disturbance within the 12 months before Visit 1.

2. Another psychiatric disorder other than bipolar disorder with the exception of specific phobias.

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

    a. Major/minor neurocognitive disorder, amnestic, or other neurocognitive disorders

    b. Schizophrenia, schizoaffective disorder, and other psychotic disorders

    c. Intellectual development disability

4. Known or suspected borderline or antisocial personality disorder or other DSM-5 personality disorders of sufficient severity to interfere with participation in this study.

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

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

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

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

    c. A repeat UDS must be performed prior to Visit 2 and must be negative, except benzodiazepine use as described in 6(b).

7. History of intolerance or hypersensitivity to cariprazine or rescue medications.

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

9. 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 before Visit 1

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

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

Treatment-Related Criteria:

10. Patient had electroconvulsive therapy in the 3 months prior to Visit 1.

11. Patient received treatment with depot antipsychotic within 6 months prior to Visit 1.

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

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

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 Section 4.8).

15. Previous treatment with vagus nerve stimulation or transcranial magnetic stimulation within 6 months before Visit 1.

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

17. Initiation or termination of phototherapy within the 2 weeks before Visit 1, or plans to initiate same during the course of the study.

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

Other Medical Criteria:

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

20. Any concurrent medical condition that, in the judgment of the investigator, might interfere with the conduct of the study, confounds the interpretation of the study results, or endangers the patient's well-being.

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

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

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 toward a risk of seizure.

24. Patients who meet any of the following ophthalmologic criteria:

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

        1. Opacification ≥ AREDS standard photo #2

           OR

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

           OR

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

    b. Any clinically significant ocular trauma or complications of ocular trauma, or history of retinal detachment, intraocular surgery (with the exception of cataract surgery to remove or replace lenses bilaterally) or laser treatment

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

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

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

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

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

26. Known human immunodeficiency virus infection.

27. Positive hepatitis C antibody on screening.

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

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

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

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

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

Other Criteria:

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

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

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

4.5 Remission and Stability Criteria During the OL Treatment Period

Remission is defined as meeting all of the following on or after Visit 4: a YMRS total score ≤ 12 and MADRS total score ≤ 12 and a CGI-S ≤ 3. **Note:** Patients who do not meet remission criteria by Visit 7 (Week 6) will be discontinued and undergo early termination (ET) procedures and subsequently complete the SFU period.

Stability is defined as confirmation of remission criteria at the visit following the study visit during which remission criteria were met. **Note:** If remission criteria are met, but stability criteria are not met at the subsequent visit, the patient must be reassessed for remission at the following visit. **For this subset of patients only, discontinue patient if remission criteria are met at Visit 6, but stability criteria are not met at Visit 7.** All other patients who do not meet criteria for stability by Visit 8 (Week 8) will be discontinued and undergo ET procedures and subsequently complete the SFU period.

4.6 Randomization Criteria

Randomization requirement:

- Ability to safely tolerate cariprazine 3.0 mg/d
- Maintenance of stability criteria (ie, YMRS total score ≤ 12 and MADRS total score ≤ 12 and CGI-S ≤ 3 for 8 weeks)
- During the 8 weeks, 1 excursion in YMRS and/or MADRS score (ie, YMRS > 12 [cannot meet or exceed 17] and/or MADRS > 12 [cannot meet or exceed 20]) is allowed. In the event the excursion occurs in the 8th week of stability, but prior to Visit 12/End of OL, patients should be assessed at the following visit to confirm whether randomization criteria have been met
    - If during the 8 weeks there is an excursion in YMRS ≥ 17 or MADRS ≥ 20 or CGI ≥ 4, the patient should be discontinued from the study and have ET procedures performed and subsequently enter the SFU period
    - If the excursion occurs on Visit 12/end of OL, the patient is not eligible for randomization and should be discontinued from the study and have ET procedures performed and subsequently enter the SFU period

4.7 Relapse Criteria in the Double-blind Treatment Period

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

- YMRS total score ≥ 17
- MADRS total score ≥ 20
- CGI-S ≥ 4
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms as judged by the clinical impression of the investigator,
- Psychiatric hospitalization
- Exacerbation of illness as judged by clinical impression of the investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

For patients who meet relapse criteria, the investigator will categorize the relapse event(s) as manic or depressive event(s), with or without mixed features.

4.8 Permissible and Prohibited Medications/Treatments

4.8.1 Permissible Medications/Treatments

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

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

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

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

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

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

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

investigator must document the outcome of the pregnancy and provide a copy of the documentation to AbbVie.

4.8.2 Prohibited Medications/Treatments

Medications that are moderate or strong CYP3A4 inhibitors or are CYP3A4 inducers 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 7 days prior to the start of open-label IP dosing with cariprazine. Patients who cannot or should not be taken off of the CYP 3A4 inhibitor or inducer should not be enrolled. If a patient requires sustained concomitant treatment with either a moderate or strong CYP3A4 inhibitor or with a CYP3A4 inducer at any time during the study, he/she must be discontinued.

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

Psychotropic medications include the following:

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

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

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

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

4.8.3 Rescue Medications

Medically appropriate episodic use (up to 3 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/d)
- Zolpidem extended release (maximum of 12.5 mg/d)
- Zaleplon (maximum of 20 mg/d)
- Eszopiclone (maximum of 3.0 mg/d)
- Zopiclone (maximum of 7.5 mg/d)
- Chloral hydrate (maximum of 1000 mg/d) may be used acutely with approval from the AbbVie medical monitor
- Suvorexant (maximum of 20 mg/d)

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

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

For EPS or akathisia that emerge or worsen during the study, the rescue medications listed below will be allowed. However, each of the 3 EPS scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson-Angus Scale [SAS]) should be administered first to support the decision to dispense these rescue medications. The only exception to administering the EPS scales before dispensing rescue medication is medical urgency (eg, dystonia, severe akathisia, etc).

- Benztropine
- Diphenhydramine
- Propranolol
- Biperiden
- Trihexyphenidyl

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

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

Rescue medications for agitation, restlessness, and hostility:

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

The medication use and 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

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

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

5.4 Method for Assignment to Treatment Groups/Randomization

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

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 3.0 or 1.5 mg/d, or placebo. Stratified randomization will be used for this study with strata defined by two factors: index episode (manic, manic with mixed features, depressive, depressive with mixed features) and region (US and non-US).

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

The IWRS system will also be used to ensure an appropriate distribution of bipolar types (manic or depressed). If the study begins to skew towards one bipolar pole, adjustments to allow enrollment of the other bipolar type may occur.

IP will be labeled with medication kit numbers. The IWRS will provide the site with the specific medication kit number(s) for each patient in the OL treatment period (cariprazine 3.0 mg/d or 1.5 mg/d,) and for each randomized patient during the DB treatment period (cariprazine 3.0 or 1.5 mg/d, 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

Table 2 Treatment Regimen and Dosing

Drug/Dose	Investigational Product Frequency	Route of Administration
Open-Label Treatment Period (Week 1)		
Index Episode: Manic (with or Without Mixed Features)		
Cariprazine 1.5 mg Day 1 / Cariprazine 3.0 mg Days 2-7	Once daily	Oral (capsule)
Index Episode: Depressive (with or without Mixed Features)		
Cariprazine 1.5 mg Days 1-7	Once daily	Oral (capsule)
Open-Label Treatment Period (Weeks 2 to 16)[a]		
Cariprazine 3.0 mg	Once daily	Oral (capsule)
Double-Blind Treatment Period (Weeks 17 to 55)		
Placebo	Once daily	Oral (capsule)
Cariprazine 1.5 mg	Once daily	Oral (capsule)
Cariprazine 3.0 mg	Once daily	Oral (capsule)

All investigational products will be taken orally as a single daily dose at approximately the same time of day (morning or evening). The dosing time can be switched if there are tolerability problems. Any switch must allow at least 24 hours between 2 consecutive doses and must be documented in the eCRF.

[a] Patients meeting randomization criteria (Section 4.6) on or after Week 12 (Visit 10) are eligible for early randomization and will skip any remaining visits in the OL period.

5.6 Treatment Compliance

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

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

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

5.7 Storage of Study Medications/Treatments

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

6. Response Measures and Summary of Data Collection Methods

6.1 Diagnostic Assessments

The Structured Clinical Interview for DSM-5 (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 the investigator, subinvestigator, or rater who has extensive professional training and experience in the diagnosis of mental illness. The SCID-5 will be considered a source document for this study.

6.2 Efficacy Assessments

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

6.2.1 Primary Efficacy Assessments

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

6.2.1.1 Young Mania Rating Scale

The YMRS (Young 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; scoring between listed points is encouraged. Possible scores range from 0 to 60.

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

6.2.1.2 Montgomery-Åsberg Depression Rating Scale

The MADRS (Montgomery 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 will be scored on a 7-point scale with a score of 0 reflecting no symptoms and a score of 6 reflecting symptoms of maximum severity.

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

6.2.1.3 Clinical Global Impressions–Severity

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

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

6.2.2 Additional Efficacy Assessments

6.2.2.1 Clinical Global Impressions–Improvement

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

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

6.2.2.2 Personal and Social Performance Scale

The Personal and Social Performance (PSP) scale is a 100-point, single-item, clinician-rated scale, which is subdivided into 10 equal intervals (Morosini 2000) (Attachment 12.9). The ratings are based mainly on the assessment of functioning in the following 4 domains: a) social useful activities; b) personal and social relationships; c) self-care; d) disturbing and aggressive behaviors. Ratings from 91 to 100 show excellent functioning in all 4 domains; from 71 to 90 refer only to mild difficulties; from 70 to 31 to manifest disabilities of various degrees, while under 30 the person's functioning is so poor that intensive support or supervision is needed.

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

6.3 Pharmacokinetics Measures

Samples for determination of the plasma concentrations of cariprazine and its metabolites desmethyl cariprazine and didesmethyl cariprazine will be collected at 12 time points during the study: Visit 6 (Week 4), Visit 8 (Week 8), Visit 10 (Week 12), Visit 12 (Week 16), Visit 13 (Week 18), Visit 14 (Week 20), Visit 17 (Week 26), Visit 20 (Week 32), Visit 23 (Week 38), Visit 26 (Week 44), Visit 29 (Week 50), and Visit 31 (Week 55). 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 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.

6.4 Pharmacogenetic Sampling

Pharmacogenetic sampling is to be conducted only at study centers where the institutional review board (IRB)/independent ethics committee (IEC) has approved the pharmacogenetic portion of the study. Participation in the pharmacogenetic portion of the study is optional and will require a separate informed consent form (ICF). The pharmacogenetic ICF must be signed before the pharmacogenetic blood sample is taken. Pharmacogenetic consent may be obtained at any time between Visit 1/Screening and Visit 7 (Week 6). Pharmacogenetic sampling can be conducted at any time point between Visit 2 (Baseline) and Visit 7 (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 trials conducted by AbbVie.

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

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

6.5 Medical Resource Utilization and Health Economics

Exploratory analyses of medical resource utilization and health economics data will include time to psychiatric hospitalization. Quality-of-life will be assessed via Work Productivity and Activity Impairment: Bipolar Disorder (Attachment 12.12; Reilly 1993), which is a 6-item patient-rated questionnaire used to quantify health-related work productivity loss for the employed population. It is used to evaluate patient's employment status and productivity loss, as well as evaluate impairment in the domains of work and regular daily activities other than work.

The scale (Attachment 12.12) will be administered at Visits 1, 12, 16, and 31/ET.

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, (Schedule of Visits and Procedures).

6.6.1 Adverse Events

Adverse events (AEs) will be collected throughout the study. For all AEs, the investigator must provide an assessment of the severity, causal relationship to the IP, start and stop date, and seriousness of the event (eg, serious adverse event [SAE]), document all actions taken with regard to the IP, and detail any other treatment measures taken for the AE. For events noted as

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

[redacted]

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 Screening	1	Hepatitis C virus antibody, hepatitis B surface antigen, and hepatitis B core antibody total. Reflex hepatitis B core antibody immunoglobulin M will be performed for all hepatitis B core antibody total positive or reactive results
Hematology	1, 7, 12, 18, 24, 31, or ET	Absolute and differential white blood cell count, erythrocyte count, hemoglobin, hematocrit, platelet count, and red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)
Hemoglobin A1c	1, 12, 31, or ET	--
Chemistry	1, 7, 12, 18, 24, 31, or ET	Sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, Free T3, free T4, TSH, lactate dehydrogenase, creatine phosphokinase, γ-glutamyl transpeptidase, uric acid, phosphate, lipid panel (total cholesterol, triglycerides, low density lipoproteins, high density lipoproteins), prolactin, insulin, and magnesium
Urine myoglobin	1, 7, 12, 18, 24, 31, or 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, 7, 12, 18, 24, 31, or ET	Specific gravity, pH, protein, glucose, ketones, blood, nitrite, bilirubin, and microscopy (red blood cell count [high-power field], white blood cell count [high-power field], casts [low-power field], and crystals).
Serum β-hCG (women of childbearing potential only)	1, 7, 12, 18, 24, 31/ET, 33	--
Urine drug screen	1, 12	Benzoylecgonine (cocaine), barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, methadone, phencyclidine
Blood alcohol concentration as measured by breathalyzer	1, 12	--
Repeat urine drug screen, blood alcohol concentration as measured by breathalyzer, 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; 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 only.

Waist circumference will be measured at Visits 1, 7, 12, 18, 24, and 31/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 Screening (Visit 1), Visit 12 and Visit 31 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.

[redacted]

6.6.7 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.

6.6.7.1 Extrapyramidal Symptom Scales

The following 3 scales will be used to systematically assess EPS side effects at Visits 2, 3, 5, 7, 9, 11, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 31, 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. The AIMS will be administered by a trained and experienced rater. The same rater should assess the patient at each visit.

Barnes Akathisia Rating Scale

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

Simpson-Angus Scale

The SAS (Simpson 1970) is a 10-item rating scale for assessment of antipsychotic-induced parkinsonism in both clinical practice and research settings. 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. The SAS will be administered by a trained and experienced rater. The same rater should assess the patient at each visit.

6.6.7.2 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. At all other visits the C-SSRS will be completed for ideation and behavior since the previous visit.

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

6.7 Summary of Methods of Data Collection

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

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

7. Statistical Procedures

7.1 Analysis Populations

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

7.1.1 Screened Population

The screened population will consist of all patients who underwent a Screening Visit and received a PID number.

7.1.2 Open-label Safety Population

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

7.1.3 Open-label Intent-to-Treat Population

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

7.1.4 Open-label Safety-Follow-up Population

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

7.1.5 Randomized Population

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

7.1.6 Double-blind Safety Population

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

7.1.7 Double-blind Intent-to-Treat Population

The DB ITT population will consist of all patients in the DB safety population who had at least 1 post-randomization assessment of the YMRS, MADRS, or CGI-S scores during the DB period of the study.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

7.2.1 Primary Efficacy Variable

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

Relapse criteria include any of the following:

- YMRS total score ≥ 17
- MADRS total score ≥ 20
- CGI-S ≥ 4
- Initiation of treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms as judged by the clinical impression of the investigator,
- Psychiatric hospitalization
- Exacerbation of illness as judged by clinical impression of investigator (eg, clinically significant agitation, suicidal or homicidal ideations)

For patients who meet relapse criteria, the investigator will categorize the relapse event(s) as manic or depressive event(s), with or without mixed features.

7.2.2 Secondary Efficacy Variable

None.

7.2.3 Other Efficacy Variables

Additional efficacy parameters include:

- Change from baseline in YMRS total score by visit during OL and DB period
- Change from baseline in MADRS total score by visit during OL and DB period
- Change from baseline in CGI-S score by visit during OL and DB period
- CGI-I score by visit during OL and DB period
- Change from baseline in PSP score by visit during OL and DB period

Additional efficacy parameters only for the DB treatment period include:

- Time to manic episode
- Time to depressive episode

Manic episode with mixed features or depressive episode with mixed features are classified as manic or depressive episodes, respectively.

7.3 Hypothesis and Methods of Analysis

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

7.3.1 Primary Efficacy Analyses

The primary efficacy analysis is to evaluate the time to first relapse of any mood episode in bipolar I disorder patients who responded to OL treatment with cariprazine.

The primary null hypothesis is that the distribution of the time to first relapse for each of the cariprazine 3.0 mg/d and 1.5 mg/d treatment groups is not different from that for the placebo treatment group. The alternative primary hypothesis is that the distribution of the time to first relapse for each of the cariprazine 3.0 mg/d and 1.5 mg/d treatment group is different from that for the placebo treatment group.

The hypothesis testing will compare the time to relapse between each cariprazine group and placebo group using the log-rank test stratified by modified index episode (manic or depressive) for the DB ITT population. To derive the modified index episode, the manic index episode(s) with or without mixed features will be classified as manic episode(s); depressive index episode(s) with or without mixed features will be classified as depressive episode(s). Estimates of the hazard ratio (HR) and 95% confidence intervals will be based on the Cox proportional hazards model with treatment group as covariates stratified by modified index episode (manic or depressive). The Kaplan-Meier estimates for the cumulative distribution of the relapse rate for each treatment group will be provided.

The primary hypotheses for cariprazine 3.0 mg/d and 1.5 mg/d treatment groups versus placebo will be tested sequentially in order to control the overall Type I error rate. The comparison of cariprazine 3.0 mg/d versus placebo will be tested first at the two-sided 0.05 significance level, only when it is significant, the comparison of cariprazine 1.5 mg/d versus placebo will be tested also at the two-sided 0.05 significance level. This testing strategy controls the overall Type I error rate at the 0.05 significance level.

Two sensitivity analyses will be performed to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption. The first sensitivity analysis will be based on the delta-adjusted method examined by Zhao et al. (2014), which specifies that the hazard of having an event for subjects who discontinued before the time point is increased relative to the hazard for subjects who continued beyond the time point for the experimental treatment group. The delta-adjustment will be gradually increased from zero until reaching the tipping point when the statistical significance of the primary efficacy endpoint is overturned, and the plausibility of the magnitude of delta-adjustment needed for reaching the tipping point will be subject to clinical scrutiny.

The second sensitivity analysis is an extension of the placebo-based pattern mixture model (Lu 2014; Lu 2015). The placebo-based pattern mixture model assumes that patients who discontinued from the cariprazine treatment groups would have disease progression after discontinuation similar to that of placebo. The extended placebo-based pattern mixture model uses a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analysis toward the informative censoring underlying the placebo-based pattern mixture model. The extended placebo-based pattern mixture model sensitivity analysis for time-to-event data is described as follows:

Let $h_0(t)$ denote the baseline hazard function associated with the placebo group. Let β_1 and β_2 denote the treatment effects in terms of log HRs under noninformative censoring for cariprazine 1.5 mg/d versus placebo and cariprazine 3.0 mg/d versus placebo, respectively. The hazard functions associated with the cariprazine 1.5 and 3.0 mg/d groups under noninformative censoring are thus given by $h_1(t) = h_0(t) \exp(\beta_1)$ and $h_2(t) = h_0(t) \exp(\beta_2)$, respectively. Consider the extended placebo-based pattern mixture model sensitivity analysis. For the placebo group, we assume that patients with premature discontinuation would have comparable experience after discontinuation to their counterparts without premature discontinuation. For the cariprazine treatment groups, each dropout time point for cariprazine patients defines a missing data pattern, and we assume that patients with premature discontinuation would have disease progression after discontinuation somewhere between their counterparts without premature discontinuation and patients in the placebo group. Specifically, we assume that $h_1(t) = h_0(t) \exp((1- \phi)\beta_1)$ and $h_2(t) =$

$h_0(t) \exp((1- \phi)\beta_2)$ for $t > C$, where C denotes the time of premature discontinuation. The sensitivity parameter $\phi \in [0,1]$ characterizes the gradual deviation from the noninformative censoring with $\phi = 0$ toward the informative censoring underlying the placebo-based pattern mixture model with $\phi = 1$. A multiple imputation approach will be used to implement the extended placebo-based pattern mixture model.

7.3.2 Secondary Efficacy Analyses

None.

7.3.3 Other Efficacy Analyses

The overall relapse rate, as well as the relapse rates for sub-categories of interest including manic episode and depressive episode will be presented.

Time to early discontinuation for any reason during the DB treatment period for the ITT population will be analyzed.

These efficacy parameters will be analyzed using the same method used to analyze the primary efficacy variable.

The following continuous efficacy variables will be summarized by visit for the OL and DB treatment periods separately for the corresponding ITT populations. For the DB treatment period, the variables for YMRS, MADRS, CGI-S, and CGI-I will be analyzed by using a mixed-effects model for repeated measures (MMRM) with treatment group, region (US and non-US), modified index episode strata (manic or depressive), visit, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Descriptive statistics will be provided at each assessment time point by treatment group for the change from baseline in PSP score.

For Open-label Treatment Period

- Change from baseline in YMRS total score by visit
- Change from baseline in MADRS total scores by visit
- Change from baseline in CGI-S score by visit
- CGI-I score by visit
- Change from baseline in PSP score by visit

For Double-blind Treatment Period

- Change from DB baseline in YMRS total score by visit
- Change from DB baseline in MADRS total score by visit
- Change from DB baseline in CGI-S score by visit
- CGI-I score by visit
- Change from DB baseline in PSP score by visit

7.3.4 Safety Analyses

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

Safety parameters will include AEs, clinical laboratory parameters, vital signs, ECG parameters, [redacted], C-SSRS, EPS scales (AIMS, BARS, and SAS), and prolactin level.

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

7.3.4.1 Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

The number and percentage of patients with any EPS TEAEs during the OL period and DB period will be summarized separately. The number and percentage of patients with EPS SAEs, and the number and percentage of patients with EPS AEs leading to premature discontinuation of IP will also be summarized.

The number and percentage of patients reporting TEAEs of ocular AESIs will be summarized overall for the OL treatment period in the OL safety population and the OL SFU period in the OL

SFU population, and by treatment for the DB treatment period and the DB SFU period in the DB safety population. The listing of all reported ocular AESIs will be provided.

7.3.4.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline values at each assessment time point will be presented for each clinical laboratory parameter, and for selected clinical laboratory parameters in conventional units.

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

7.3.4.3 Vital Signs

Descriptive statistics for vital signs (ie, supine radial pulse rate, supine systolic and diastolic BP, body weight, waist circumference, temperature, and body mass index) and changes from baseline values at scheduled postbaseline visits and at end of study will be presented.

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 Statistical Analysis Plan. The percentages will be calculated relative to the number of patients with baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive listing of patients with postbaseline PCS values will be provided, including the PID number, baseline and postbaseline values. A listing of all AEs occurring in patients who have PCS vital sign values will also be provided. The number and percentage of patients with orthostatic hypotension will be provided by treatment group. Orthostatic hypotension is defined as a reduction of $\geq$ 20 mm Hg in systolic BP or a reduction of $\geq$ 10 mm Hg in diastolic BP when the patient changes from the supine position to the standing position. A supportive listing will be provided including the PID number, study center number, and baseline and postbaseline systolic and diastolic BP values (supine and standing).

7.3.4.4 Electrocardiogram

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

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

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

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

7.3.4.5 Other Safety Parameters

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

[redacted]

[redacted]

7.3.4.5.2 Columbia-Suicide Severity Rating Scale

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

7.3.4.5.3 Extrapyramidal Symptom Scales

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

values. Listings of all AEs for patients with treatment-emergent parkinsonism or akathisia will also be provided.

7.3.5 Pharmacokinetic Analysis

Plasma concentrations of cariprazine, desmethyl cariprazine, and didesmethyl cariprazine will be listed for each subject with PK samples collected. Plasma concentration data will be used in population PK and/or PK-PD analyses to be reported separately. A detailed description of the population PK analysis and/or population PK-PD analysis will be specified in a separate prospective analysis plan.

7.3.6 Medical Resource Utilization and Health Economics Analyses

A detailed description of the analysis for the medical resource utilization and health economics assessments will be specified in a separate prospective analysis plan.

7.4 Subgroup Analyses

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

- Age group (< 55 years, ≥ 55 years)
- Sex (male, female)
- Race (white, all other races)
- Region (US, Non-US)
- Modified index episode (manic or depressive)

7.5 Sample Size Calculation

The sample size and power calculations are based on the analysis of time to relapse of any mood episode in the DB treatment period to compare each cariprazine dose group versus placebo based on a log-rank test. The trial will have a fixed follow-up design. Patients are followed from randomization until dropout, relapse, or a fixed duration of 39 weeks.

The relapse HR is assumed to be 0.42, supported by the final primary endpoint analysis result for the cariprazine maintenance study RGH-MD-06 in patients with schizophrenia (HR = 0.45) [redacted] The cumulative relapse rate at Week 39 for the placebo group is assumed to be 35%, [redacted]

[redacted]

Using these assumptions, the study would observe approximately 75 events to have at least 85% statistical power to detect a significant treatment effect in at least 1 dose. The statistical method for the power calculation is based on the log-rank 2-sided test at the 5% significance level to compare the difference of each of the 2 survival curves of the cariprazine treatment groups versus that of placebo. Based on the assumed event rates and considering the 26% of patients who may discontinue early from the study due to other reasons, approximately 378 patients should be randomized to cariprazine 1.5 mg/d, cariprazine 3.0 mg/d, and placebo, or approximately 126 patients per treatment group.

It should be noted that this study is designed to test 3.0 mg/d of cariprazine versus placebo first at the 0.05 significance level and, if the results are significant, then the 1.5 mg/d dose of cariprazine will be tested at the 0.05 significance level. Given this sequential testing strategy, the higher dose of 3.0 mg/d has 85% statistical power to show significance versus placebo and the 1.5 mg/d dose, if as effective as the 3.0 mg/d dose, and the 3.0 mg/d dose is statistically significant, would also have 85% statistical power at the 0.05 significance level.

7.6 Interim Analyses

No formal interim analysis is planned.

8. Study Visit Schedule and Procedures

See Table 1 for a schematic of the schedule of visits and procedures and Figure 1 for a schema of the study design.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Section 4.3 and Section 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/or the patient's legally authorized representative, and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization (US only), data protection consent (Europe only), and other written documentation in accordance with the

relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

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

Where applicable, a central vendor will be used to verify patients' current and past research study status in order to mitigate safety concerns associated with duplicate enrollment and protocol deviations associated with multiple trial enrollment. Following proper informed consent and after issuing a patient number, each patient will be checked in the Verified Clinical Trials (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 be enrolled without documented approval from the Sponsor.

8.2 Washout Intervals/Run-in

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

8.3 Procedures for Final Study Entry

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

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

8.4 Visits and Associated Procedures

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

Visit 2/Baseline is expected to occur within 7 days of Visit 1; however, if required, it may be conducted up to 3 days after the scheduled visit. Visits 3 to 33 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 12, relative to Visit 12 for Visits 13 through 31/ET, and relative to Visit 31/ET for Visits 32 and 33.

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

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

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

- Obtain informed consent and patient privacy; consent for pharmacogenetic sampling may also be obtained
- Access IWRS to register the patient and assign a PID number
- Verified Clinical Trials database check to be performed, where applicable
- Assess inclusion/exclusion criteria
- Collect and assess medical and psychiatric history
- Administer and assess SCID-5
- Collect blood sample for hepatitis screening
- Collect samples for UDS; assess blood alcohol concentration via breathalyzer
- Collect blood samples for serum pregnancy test (women of child-bearing potential only)
- Collect blood samples for clinical laboratory determinations
- Collect blood sample for Hemoglobin A1c
- Review prior and concomitant medications
- Assess YMRS, MADRS, CGI-S, and C-SSRS
- Collect vital signs measurements, including weight, waist circumference, and height
- Perform physical examination

- Perform ECG
- Have patient complete the WPAI-BD QoL questionnaire
- [redacted]
- Review and assess AEs and SAEs

8.4.2 Baseline (Visit 2)

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

- Assess inclusion/exclusion criteria
- Review concomitant medications
- Assess YMRS, MADRS, CGI-S, PSP, and C-SSRS
- Evaluate EPS symptoms (AIMS/BARS/SAS)
- Collect vital signs measurements (including weight)
- Obtain consent for and/or collect blood for pharmacogenetic sampling (a single sample can be obtained any time between Visit 2 and Visit 7, inclusive)
- Review and assess AEs and SAEs
- Access IWRS to dispense IP

8.4.3 Open-label Treatment Period (Visits 3 to 11)

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

- Collect blood samples for serum pregnancy test (women of child-bearing potential only) (Visit 7)
- Collect blood samples for clinical laboratory determinations (Visit 7)
- Obtain consent and/or collect blood for pharmacogenetic sampling (a single sample can be obtained any time between Visit 2 and Visit 7, inclusive)
- Review concomitant medications
- Assess CGI-I and C-SSRS
- Assess YMRS, MADRS, and CGI-S

- Assess PSP (Visit 6)
- Evaluate remission criteria (Section 4.5; Visits 4 to 7)
- Evaluate stability criteria (Section 4.5; Visits 5 to 8)
- If remission and stability criteria (Section 4.5) have both been met at Visit 5, 6, 7, or 8, evaluate randomization criteria (Section 4.6) to determine whether patient qualifies for randomization (Visits 10 to 12)

  Note: Patients meeting randomization criteria (Section 4.6) prior to Visit 12 are to undergo procedures specified for Visit 12/End of OL period (any remaining visits in the OL Treatment period will be skipped).

  Patients who have not achieved remission by Visit 7 (Week 6) or stability by Visit 8 (Week 8) are to be discontinued from the study and should undergo Visit 31/ET procedures and subsequently enter the SFU period.
- Evaluate EPS symptoms (AIMS/BARS/SAS) (Visits 3, 5, 7, 9, 11)
- Collect vital signs measurements (including weight at every visit)
- Collect waist circumference measurement (Visit 7)
- Review and assess AEs and SAEs
- Collect blood for PK evaluation at any time during the visit (Visits 6, 8, and 10)
- Collect IP blister card(s) and perform IP compliance and accountability
- Access IWRS to dispense IP

8.4.4 End of OL Period/Randomization Visit (Visit 12)

The following procedures will be carried out at Visit 12:

- Collect samples for UDS; assess blood alcohol concentration via breathalyzer
  - Collect blood samples for serum pregnancy test (women of child-bearing potential only)
- Collect blood samples for clinical laboratory determinations
- Collect blood sample for Hemoglobin A1c
- Review concomitant medications
- Evaluate EPS symptoms (AIMS/BARS/SAS)
- Collect vital signs measurements, including weight and waist circumference (not height)

- Perform ECG
- [redacted]
- Review and assess AEs and SAEs
- Collect blood for PK evaluation
- Assess CGI-I, PSP, and C-SSRS
- Have patient complete the WPAI-BD QoL questionnaire
- Assess YMRS, MADRS, CGI-S and determine whether randomization criteria (Section 4.6) have been met
    - Eligible Patients: Access IWRS to randomize patient and dispense DB IP
    - Patients not meeting randomization criteria are to undergo procedures as for Visit 31/ET and be scheduled to return for 2 safety follow-up visits (Visit 32 and Visit 33)
- Collect IP blister cards and perform drug compliance and accountability

8.4.5 Double-blind Treatment Period (Visits 13 to 30)

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

- Collect blood samples for serum pregnancy test (women of child-bearing potential only) (Visits 18 and 24)
- Collect blood samples for clinical laboratory determinations (Visits 18 and 24)
- Review concomitant medications
- Assess YMRS, MADRS, CGI-S, CGI-I, and C-SSRS
- Assess PSP (Visit 16 and Visit 22)
- Have patient complete the WPAI-BD QoL questionnaire (Visit 16)
- Evaluate EPS symptoms (AIMS/BARS/SAS) (Visits 14, 16, 18, 20, 22, 24, 26, 28, 30)
- Assess patient for relapse (per Section 4.7)

- Collect vital signs measurements (including weight)
- Collect waist circumference measurement (Visits 18 and 24)
- Review and assess AEs and SAEs
- Collect blood for PK evaluation (Visits 13, 14, 17, 20, 23, 26, and 29)
- Collect IP blister cards and perform drug compliance and accountability
- Access IWRS to dispense IP

8.4.6 Final or Early Termination Visit (Visit 31)

The following procedures will be carried out at the Final Visit at the end of the DB treatment period (Visit 31) or at ET:

- Collect blood sample for serum pregnancy test (women of child-bearing potential only)
- Collect blood samples for clinical laboratory determinations
- Collect blood sample for Hemoglobin A1c
- Review concomitant medications
- Assess YMRS, MADRS, CGI-S, CGI-I, PSP, C-SSRS
- Assess patient for relapse (per Section 4.7)
- Have patient complete the WPAI-BD QoL questionnaire
- Evaluate EPS symptoms (AIMS/BARS/SAS)
- Collect vital signs measurements, including weight and waist circumference
- Perform physical examination
- Perform ECG
- [redacted]
- Review and assess AEs and SAEs
- Collect blood for PK evaluation
- Collect IP blister card(s) and perform drug compliance and accountability

8.4.7 Safety Follow-up Visits 32 and 33

Patients who complete the study, and those who prematurely discontinue from either the OL or DB treatment periods, will enter a 4-week SFU period (2 visits, 1 at the end of every 2 weeks). During the SFU period, patients will be stabilized on appropriate medications, and additional evaluations (laboratory studies, ECG, etc) may be performed as deemed necessary by the investigator. This period may also be used for follow-up and management of all abnormal findings and AEs observed during OL or DB treatment periods. No IP will be administered during the SFU period.

- Collect blood sample for serum pregnancy test (women of child-bearing potential only [Visit 33 only])
- Review concomitant medications
- Collect vital signs measurements (including weight)
- [redacted]
- Review and assess AEs and SAEs

8.5 Instructions for the Patients

Patients are to be instructed to take their study medication daily around the same clock time; study medication should not be taken with grapefruit juice. Patients are to be reminded to return used/partially used blister cards at every study visit. The investigator (or designee) is to ensure that concomitant medications are reviewed against the prohibited and allowed rescue medications detailed in Section 4.8.2 and Section 4.8.3 and patients are counseled accordingly. If the permissibility of a specific medication/treatment is in question, the investigator should consult the AbbVie medical monitor.

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

Patients are to be asked to fast for at least 10 hours before blood and urine samples are collected at Screening (Visit 1), Visits 7, 12, 18, 24, and 31 or at ET.

8.6 Unscheduled Visits

Additional examinations and laboratory assessments may be performed as necessary to ensure the safety and well-being of the patients during the study period. Unscheduled visit eCRF pages

will be completed for each unscheduled visit. For all parameters not measured, indicate "not done".

8.7 Compliance with Protocol

All assessments will be conducted at the appropriate visits as outlined in Table 1, and the timing of the visits should occur as close as possible to the specified day. Visit 2/Baseline is expected to occur within 7 days of Visit 1. If required, Visit 2/Baseline assessments may be conducted up to 3 days after the scheduled visit. If necessary, Visits 3 to 33 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 12, relative to Visit 12 for Visits 13 through 31/ET, and relative to Visit 31/ET for Visit 32 and 33. Every attempt should be made to complete the postbaseline ophthalmological examinations (Visit 12 and Visit 31/ET, and Visit 33 if required) on the same date as all other study procedures for that visit.

At each visit, the patient will be asked if the patient changed the dose/regimen of any existing concomitant medications or initiated the use of any new concomitant medications since the last visit to ensure compliance with the protocol.

8.8 Early Discontinuation of 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 for one of the following reasons:

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

Notification of early patient discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate eCRF page. Patients who take IP during the study (OL treatment period or the DB treatment period) and who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment. A final assessment will be defined as completion of the evaluations scheduled for Visit 31/ET. If the patient discontinues after IP is taken, the patient is also expected to return for 2 safety follow-up visits, Visit 32 (2 weeks after completion of the ET visit) and Visit 33 (4 weeks after completion of the ET visit).

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

1. The reason the patient discontinued;

2. The date of the last dose of test products from the trial;

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

4. (S)AEs;

5. Compliance with the test product 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 31/ET and subsequently Visits 32 and 33 (SFU Period) are performed (Table 1, Schedule of Visits and Procedures).

7. Retrieve all IP(s) from the patient.

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

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 fails to achieve remission by Week 6 or stability by Week 8 of the OL treatment period;

2. After stability criteria (Section 4.5) have been met, if there is a lack of ongoing stability as evidenced by an excursion event of YMRS total score of ≥ 17 and/or MADRS total score of ≥ 20, or CGI-S ≥ 4;

3. The patient initiated treatment with a mood stabilizer, antidepressant, antipsychotic agent, or with a benzodiazepine that exceeds the protocol-specified allowance or duration (ie, more than 2 mg/d of lorazepam equivalent or for more than 3 consecutive days) to treat worsening mood symptoms;

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

5. At the end of the OL treatment period, the patient does not meet all criteria to enter the DB treatment period (eg, patient is unable to tolerate cariprazine 3.0 mg/d);

6. Positive UDS after enrollment, confirmed by retest at next scheduled visit; for exceptions see Exclusion Criterion 6(b) and Section 4.8.3;

7. The patient meets the criteria for relapse of a mood episode during the DB treatment period;

8. 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.

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

10. A female patient becomes pregnant during treatment.

8.10 Study Termination

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

9. Adverse Events

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

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event 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, adverse events will be assessed regardless of the administration of a pharmaceutical product.

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

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

Adverse events 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 adverse events 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 adverse events will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

A SAE is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, 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 a 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 a SAE.)

AbbVie considers all cancer adverse events as SAEs. Elective abortions and abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

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

Any pre-planned 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 entry into the study, then it should be documented as a SAE and reported to AbbVie.

9.1.3 Severity

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

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

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event 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 adverse event may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate case report form.

All adverse events 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 adverse event that is marked 'ongoing' at the exit visit must be followed up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

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

In the event of a SAE, the investigator must:

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

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

3. Provide AbbVie with a complete, written description of the adverse event(s) on the SAE/AESI form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(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 following the last dose of IP. Within 24 hours of learning of the pregnancy, the study site personnel must report the event to the sponsor's Global Patient Safety department on the clinical trial pregnancy form and fax/email it to the following SAE/pregnancy fax number/email address, even if no AE has occurred:

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

Email: IR-Clinical-SAE@abbvie.com.

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

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

9.5 Potential Hy's Law Cases

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

- ALT or AST $\geq 3 \times$ ULN AND
- Total bilirubin $\geq 2 \times$ ULN AND
- Alkaline phosphatase $< 2 \times$ ULN

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

A lab alert for potential Hy's Law cases will be in place, and will notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's Law case must be faxed to the sponsor on the SAE/AESI form as soon as possible (within 24 hours of learning of the potential Hy's Law) to the following SAE/pregnancy fax number/email address even if no AE has occurred:

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

Email: IR-Clinical-SAE@abbvie.com

The eCRF pages for potential Hy's Law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring must be initiated in conjunction with the study physician and in accordance with the FDA "Guidance for Industry: Drug-Induced Liver Injury-Pre-Marketing Clinical Evaluation" July 2009.

9.6 Procedures for Unmasking of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the sponsor (AbbVie medical safety physician) should be notified prior to unmasking study medication. The investigator should inform the sponsor (AbbVie 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 logging into the IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

10. Administrative Items

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

10.1 Protection of Human Patients

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

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

10.1.2 Compliance with IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. AbbVie 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 AbbVie.

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

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

10.2 Changes to the Protocol

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

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient’s name will not be disclosed in these documents. The patient's name may be disclosed to the sponsor of the study, AbbVie, 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, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements

(eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ["EU Directive"]).

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

10.4 Documentation

10.4.1 Source Documents

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

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

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

- The results of laboratory tests performed by the site (eg, results of urine pregnancy tests).
- Key study variables.

Source documentation practices must follow ALCOA-C principles (ie, records must be **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal, **A**ccurate, and **C**omplete).

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 AbbVie within a short time after the completion of the study, or as designated by AbbVie. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

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

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

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

AbbVie 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, and instructions to take the capsules as directed. The card will also include the medication number. Immediately before dispensing the blister card, the investigator or designee will write the study center number, patient's initials (if applicable), patient number, visit number, and dispensing date on the blister card.

10.5.2 Investigational Product Supply Inventory

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

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

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

10.6 Monitoring by the Sponsor

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

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

10.7 Handling of Biological Specimens

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

Blood samples obtained for analysis of plasma concentrations of cariprazine and its metabolites (desmethyl cariprazine and didesmethyl cariprazine) will be stored at the central clinical laboratory until ready for analysis by the Sponsor's bioanalytical Clinical Research Organization using validated bioanalytical methods. All samples not used for analyses will be destroyed by the Sponsor's bioanalytical Clinical Research Organization. AbbVie 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 which may influence how patients respond to a drug or may explain the pathophysiology of the disease. Blood samples will be stored to provide a resource for potential future trials conducted by AbbVie.

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

10.8 Publications

AbbVie as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators and sites and AbbVie 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 AbbVie.

10.9 Coordinating Investigator

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

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12. Attachments

12.1 Elements of Informed Consent

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

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; the Sponsor; the IRB; or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the investigator as the contact. The guidance of the IRB/EC may be required)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable
- The expected circumstances for which the patient's participation may be terminated by the investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of consent (eg , "I agree to participate . . .")
- A place for the patient's signature and date of signing
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

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

12.2 Young Mania Rating Scale

1. ELEVATED MOOD

0 Absent
1 Mildly or possibly increased on questioning
2 Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
3 Elevated, inappropriate to content; humorous
4 Euphoric; inappropriate laughter; singing

2. INCREASED MOTOR ACTIVITY - ENERGY

0 Absent
1 Subjectively increased
2 Animated; gestures increased
3 Excessive energy; hyperactive at times; restless (can be calmed)
4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. SEXUAL INTEREST

0 Normal; not increased
1 Mildly or possibly increased
2 Definite subjective increase on questioning
3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
4 Overt sexual acts (toward patients, staff, or interviewer)

4. SLEEP

0 Reports no decrease in sleep
1 Sleeping less than normal amount by up to one hour
2 Sleeping less than normal by more than one hour
3 Reports decreased need for sleep
4 Denies need for sleep

5. IRRITABILITY

0 Absent
2 Subjectively increased
4 Irritable at times during interview; recent episodes of anger or annoyance on ward
6 Frequently irritable during interview; short, curt throughout
8 Hostile, uncooperative; interview impossible

6. SPEECH (RATE AND AMOUNT)

0 No increase
2 Feels talkative
4 Increased rate or amount at times, verbose at times
6 Push; consistently increased rate and amount; difficult to interrupt
8 Pressured; uninterruptible, continuous speech

7. LANGUAGE -THOUGHT DISORDER

0 Absent
1 Circumstantial; mild distractibility; quick thoughts
2 Distractible; loses goal of thought; changes topics frequently; racing thoughts
3 Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
4 Incoherent; communication impossible

8. CONTENT

0 Normal
2 Questionable plans, new interests
4 Special project(s); hyperreligious
6 Grandiose or paranoid ideas; ideas of reference
8 Delusions; hallucinations

9. DISRUPTIVE - AGGRESSIVE BEHAVIOUR

0 Absent, co-operative
2 Sarcastic; loud at times, guarded
4 Demanding; threats on ward
6 Threatens interviewer; shouting; interview difficult
8 Assaultive; destructive; interview impossible

10. APPEARANCE

0 Appropriate dress and grooming
1 Minimally unkempt
2 Poorly groomed; moderately disheveled; overdressed
3 Disheveled; partly clothed; garish make-up
4 Completely unkempt; decorated; bizarre garb

11. INSIGHT

0 Present; admits illness; agrees with need for treatment
1 Possibly ill
2 Admits behavior change, but denies illness
3 Admits possible change in behavior, but denies illness
4 Denies any behavior change

12.3 Montgomery-Åsberg Depression Rating Scale (MADRS)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

It is important to remember that it is only on rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

Item List

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

1. Apparent sadness

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

0 No sadness.

1

2 Looks dispirited but does brighten up without difficulty.

3

4 Appears sad and unhappy most of the time.

5

6 Looks miserable all the time. Extremely despondent.

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances.

1

2 Sad or low but brightens up without difficulty.

3

4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.

5

6 Continuous or unvarying sadness, misery or despondency.

3. Inner tension

Representing feeling of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension.

1

2 Occasional feelings of edginess and ill-defined discomfort.

3

4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.

5

6 Unrelenting dread or anguish. Overwhelming panic.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared with the subject's own normal pattern when well.

0 Sleeps as usual.

1

2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.

3

4 Sleep reduced or broken by at least two hours.

5

6 Less than two or three hours sleep.

5. Reduced appetite

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

0 Normal or increased appetite.

1

2 Slightly reduced appetite.

3

4 No appetite. Food is tasteless.

5

6 Needs persuasion to eat at all.

6. Concentration difficulties

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating.

1

2 Occasional difficulties in collecting one's thoughts.

3

4 Difficulties in concentration and sustaining thought which reduces ability to read or hold a conversation.

5

6 Unable to read or converse without great difficulty.

7. Lassitude

Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness.

1

2 Difficulties in starting activities.

3

4 Difficulties in starting simple routine activities which are carried out with effort.

5

6 Complete lassitude. Unable to do anything without help.

8. Inability to feel

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people.

1

2 Reduced ability to enjoy usual interests.

3

4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.

5

6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. Pessimistic thoughts

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts.

1

2 Fluctuating ideas of failure, self-reproach or self-depreciation.

3

4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.

5

6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. Suicidal thoughts

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes.

1

2 Weary of life. Only fleeting suicidal thoughts.

3

4 Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention.

5

6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

12.4 Clinical Global Impressions–Severity

SEVERITY OF ILLNESS

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

Check one:

1 = Normal, not at all ill

2 = Borderline ill

3 = Mildly ill

4 = Moderately ill

5 = Markedly ill

6 = Severely ill

7 = Among the most extremely ill patients

12.5 Clinical Global Impressions–Improvement

GLOBAL IMPROVEMENT

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

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

Check one:

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

12.6 Barnes Akathisia Rating Scale

Rating scale for drug-induced akathisia (Barnes Akathisia Rating Scale)

Patient name:
Patient research no.:
Hospital No.:
Ward:
Rater:

Instructions

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

Objective

0 Normal, occasional fidgety movements of the limbs
1 Presence of characteristic restless movements: shuffling or tramping movements of the legs/feet, or swinging of one leg while sitting, and/or rocking from foot to foot or "walking on the spot" when standing, but movements present for less than half the time observed
2 Observed phenomena, as described in (1) above, which are present for at least half the observation period
3 Patient is constantly engaged in characteristic restless movements, and/or has the inability to remain seated or standing without walking or pacing, during the time observed

Subjective

Awareness of restlessness

0 Absence of inner restlessness
1 Non-specific sense of inner restlessness
2 The patient is aware of an inability to keep the legs still, or a desire to move the legs, and/or complains of inner restlessness aggravated specifically by being required to stand still
3 Awareness of intense compulsion to move most of the time and/or reports strong desire to walk or pace most of the time

Distress related to restlessness

0 No distress
1 Mild
2 Moderate
3 Severe

Global clinical assessment of akathisia

0 Absent. No evidence of awareness of restlessness. Observation of characteristic movements of akathisia in the absence of a subjective report of inner restlessness or compulsive desire to move the legs should be classified as pseudoakathisia
1 Questionable. Non-specific inner tension and fidgety movements
2 Mild akathisia. Awareness of restlessness in the legs and/or inner restlessness worse when required to stand still. Fidgety movements present, but characteristic restless movements of akathisia not necessarily observed. Condition causes little or no distress
3 Moderate akathisia. Awareness of restlessness as described for mild akathisia above, combined with characteristic restless movements such as rocking from foot to foot when standing. Patient finds the condition distressing
4 Marked akathisia. Subjective experience of restlessness includes a compulsive desire to walk or pace. However, the patient is able to remain seated for at least five minutes. The condition is obviously distressing
5 Severe akathisia. The patient reports a strong compulsion to pace up and down most of the time. Unable to sit or lie down for more than a few minutes. Constant restlessness which is associated with intense distress and insomnia

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

12.7 Abnormal Involuntary Movement Scale

EXAMINATION PROCEDURE

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

1. Ask patient whether there is anything in his/her mouth (ie, gum, candy, etc.) and if there is, to remove it.
2. Ask patient about the current condition of his/her teeth. Ask patient if he/she wears dentures. Do teeth or dentures bother patient now?
3. Ask patient whether he/she notices any movements in mouth, face, hands or feet. If yes, ask to describe and to what extent they currently bother patient or interfere with their activities.
4. Have patient sit in chair with hands on knees, leg slightly apart, and feet flat on floor. (Look at entire body for movements while in this position.)
5. Ask patient to sit with hands hanging unsupported. If male, between legs, if female and wearing a dress, hanging over knees. (Observe hands and other body areas.)
6. Ask patient to open mouth. (Observe tongue at rest within mouth.) Do this twice.
7. Ask patient to protrude tongue. (Observe abnormalities of tongue movement.) Do this twice.
8. Ask patient to tap thumb, with each finger, as rapidly as possible for 10-15 seconds; separately with right hand. (Observe facial and leg movements.)*
9. Flex and extend patient's left and right arms (one at a time).
10. Ask patient to stand up. (Observe profile. Observe all body areas again, hips included.)
11. Ask patient to extend both arms outstretched in front with palms down. (Observe trunk, legs and mouth.) *
12. Have patient walk a few paces, turn, and walk back to chair. (Observe hands and gait.) Do this twice. *

* Activated movements

AIMS -SCORE SHEET

FACIAL AND ORAL MOVEMENTS

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

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

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

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

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

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

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

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

EXTREMITY MOVEMENTS

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

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

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

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

TRUNK MOVEMENTS

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

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

GLOBAL JUDGMENTS

8. Severity of abnormal movements

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

9. Incapacitation due to abnormal movements

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

10. Patient's awareness of abnormal movements

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

DENTAL STATUS

11. Current problems with teeth and/or dentures

0 No
1 Yes

12. Does patient usually wear dentures?

0 No
1 Yes

12.8 Simpson-Angus Scale

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9. TREMOR
Patient is observed walking into examining room and is then reexamined for this item:

0 Normal
1 Mild finger tremor, obvious to sight and touch
2 Tremor of hand or arm occurring spasmodically
3 Persistent tremor of one or more limbs
4 Whole body tremor

10. SALIVATION

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

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

12.9 Personal and Social Performance Scale

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

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

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

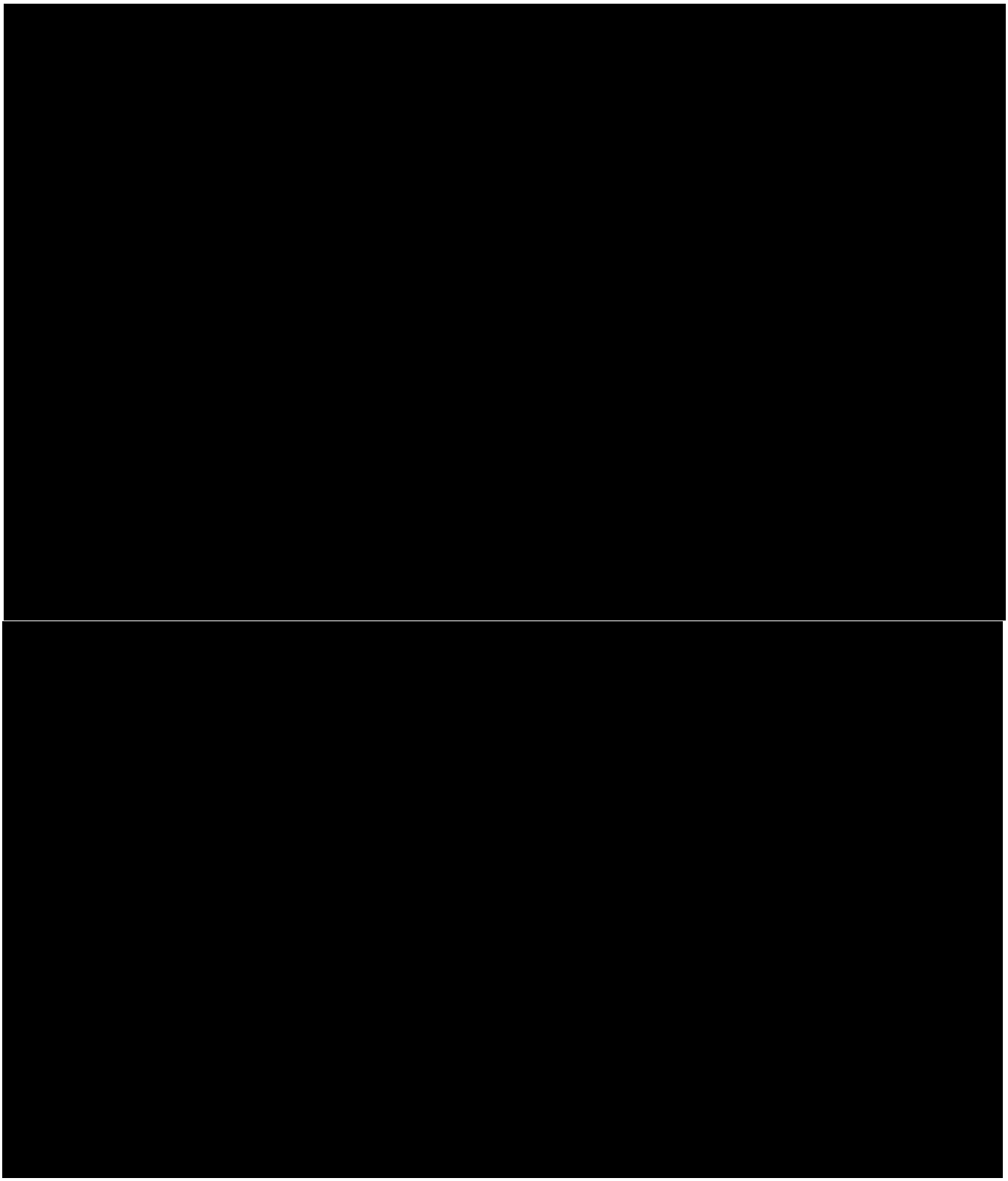
Occasional is defined as occurring three or more times in the reference period or occurring even less than three times but in circumstances and/or with such a previous history to convince the rater that there is a risk of recurrence in the near future. If the aggressive behavior has been present occasionally, the rating may be decreased by one degree, eg, from severe to marked.
*Main areas: a=socially useful activities, including work and study; b=personal and social relationships; c=self-care; d=disturbing and aggressive behaviors.

Guidelines for PSP Total Score

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

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

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



12.11 Columbia-Suicide Severity Rating Scale

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline Version 1/14/09

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

Disclaimer:

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

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE

Since Last Visit Version 1/14/09

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

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

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

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

12.12 Work Productivity and Activity Impairment Questionnaire: Bipolar Disorder (WPAI-BD)

The following questions ask about the effect of your bipolar disorder on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1) Are you currently employed (working for pay)? ____NO ___YES
If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2) During the past seven days, how many hours did you miss from work because of problems associated with your bipolar disorder? *Include hours you missed on sick days, times you went in late, left early, etc. because of bipolar disorder. Do not include time you missed to participate in this study.*
_____HOURS

3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
_____HOURS

4) During the past seven days, how many hours did you actually work?
_____HOURS *(If "0", skip to question 6)*

5) During the past seven days, how much did bipolar disorder affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If bipolar disorder affected your work only a little, choose a low number. Choose a high number if bipolar disorder affected your work a great deal.*

Bipolar disorder had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Bipolar disorder completely prevented me from working

CIRCLE A NUMBER

6) During the past seven days, how much did bipolar disorder affect your ability to do your regular daily activities, other than work at a job? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If bipolar disorder affected your activities only a little, choose a low number. Choose a high number if bipolar disorder affected your activities a great deal.*

Bipolar disorder had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Bipolar disorder completely prevented me from doing my daily activities

CIRCLE A NUMBER

12.13 Protocol Modifications for COVID-19

The following modifications to the Global Protocol are being instituted in response to the novel coronavirus disease (COVID-19) pandemic and are intended to provide guidance for the safe conduct of Study RGH-MD-25 in light of the restrictions imposed on patients and clinical sites during the COVID-19 pandemic. These measures can be followed for active patients in Study RGH-MD-25, who have completed all assessments through Visit 2 (inclusive) per the Global Protocol and are continuing in the study. The instructions and procedures specified herein will supersede those specified in the Global Protocol 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 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. The following procedures apply in cases where patients are either unable or unwilling to attend study visits as a result of the pandemic.

12.13.1 Planned Changes in Research

In response to the impact of COVID-19 to study patients and site staff, the Sponsor is proposing a change in research to Study RGH-MD-25 that would allow the following options 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
  - 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

Any procedures completed in accordance with this addendum should be clearly denoted in the source document(s) and in the electronic case report forms (eCRFs) as having been completed remotely due to COVID-19.

12.13.2 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.

- Young Mania Rating Scale (YMRS)
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Clinical Global Impression-Severity scale (CGI-S)
- Clinical Global Impression-Improvement scale (CGI-I)
- Personal and Social Performance scale (PSP)

For patients in the Open-label Period (OLP) of the study, the following assessments are also required:

- Visits 4 through 7 (as applicable): Assessment of remission criteria (Global Protocol Section 4.5)
- Visits 5 through 8 (as applicable): Assessment of stability criteria (Global Protocol Section 4.5)
- Visits 6 through 12 (as applicable): Maintenance of stability (Global Protocol Section 4.6)
- Visits 10 through 12 (as applicable): Assessment of randomization criteria (Global Protocol Section 4.6)

For patients in the Double-blind Period (DBP) of the study (Visits 13 through 31/ET), the following assessment is also required:

- Assess relapse criteria (Global Protocol Section 4.7)

12.13.3 Remote Assessment of Health Outcome Measures

In the event that visits 12, 16, or 31/Early Termination (ET) are being conducted remotely (eg, by telephone, telemedicine virtual visit, video call), study staff should verbally administer the Work Productivity and Activity Impairment: Bipolar Disorder (WPAI-BD) questionnaire to the patient and record the patient's responses in the source. The source document should capture the name

of study personnel administering the WPAI-BD, 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 WPAI-BD per the Global Protocol.

12.13.4 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 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.
- Movement scales (Abnormal Involuntary Movement Scale (AIMS); Barnes Akathisia Rating Scale (BARS); Simpson-Angus Scale (SAS)) – Telemedicine virtual visits or video calls (without recording) are the preferred methods 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.

12.13.4.1 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. If specimen processing cannot be completed within the time specified in the central laboratory manual for any 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 #5) or Country-Specific Protocol, if applicable.)
- Serum pregnancy testing
- Urine drug screen/blood alcohol concentration assessment
- Electrocardiogram (ECG)
- Vital signs (with or without weight)
- Physical examination

12.13.4.2 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 #5) 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. The Principal Investigator (PI) must determine whether the patient can safely continue in the study if a laboratory assessment is not completed. 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. For patients allowed to continue in the study, all attempts should be made to have patients complete laboratory assessments at the next scheduled timepoint, or earlier, at an Unscheduled Visit.

12.13.4.3 Electrocardiogram (ECG)

If visit is being performed remotely, this assessment may be omitted at the protocol-specified timepoint. The PI must determine whether the patient can safely continue in the study if an ECG is not performed. For patients allowed to continue in the study, all attempts should be made to have patients undergo an ECG at the next scheduled timepoint, or earlier, at an Unscheduled Visit. 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.

12.13.4.4 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 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.

12.13.4.5 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.

[redacted]

12.13.5 Visit 31/ET- End of Double-Blind and Early Termination Visit

Every attempt should be made to complete the Visit 31/ET efficacy and safety assessments on the same date. In the event that a remote visit for Visit 31/ET is not possible at the scheduled timepoint, all Visit 31/ET efficacy assessments should be completed within 2 weeks of last dose of IP. If Visit 31/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 31/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 31/ET procedures are being completed more than 2 weeks after the last dose of IP, efficacy assessments should be omitted.

12.13.6 Treatment Compliance

Investigational Product compliance is to be assessed at every visit. 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.

Patients who take less IP or more IP than the prescribed regimen must be counseled on the importance of taking study medication as instructed. If a patient demonstrates poor compliance during the study (< 80% or > 120% overall), the investigator should evaluate whether the patient should be discontinued from the study. It is recognized that patients may miss doses 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.

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 Modified Schedule of Visits and Procedures-Open-Label Treatment Period (Applicable to active Patients who have completed visit 2)

Trial Period	**Screening/Washout Period**		**Open-label Treatment Period**									
Visit Number/Visit Title	**1/Screening**	**2/Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/End of OL**
End of Trial Week (Day)	**Up to 7 days (Days -7 to -1)**	**0 (1)**	**1 (8)**	**2 (15)**	**3 (22)**	**4 (29)**	**6 (43)**	**8 (57)**	**10 (71)**	**12 (85)**	**14 (99)**	**16 (113)**
Visit Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
COVID-19 Informed Consent/Reconsent (where applicable)	Refer to Global or Country-Specific Amendment for Visit 1 Procedures	Refer to Global or Country-Specific Amendment for Visit 2 Procedures	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Assessment of Remission Criteria				X	X	X	X					
Assessment of Stability Criteria					X	X	X	X				
Maintenance of stability						X	X	X	X	X	X	X
Assessment of Randomization Criteria										X	X	X
Randomization												X
Access IWRS for IP assignment			X	X	X	X	X	X	X	X	X	X
Dispense IP[a]			X	X	X	X	X	X	X	X	X	X
IP Compliance and Accountability[b]			X	X	X	X	X	X	X	X	X	X
IP Return[c]			X	X	X	X	X	X	X	X	X	X
Urine Drug Screen/Blood Alcohol Concentration by Breathalyzer[d]												X
Serum Pregnancy Test[e]							X					X
Clinical Laboratory[e]							X					X
Hemoglobin A1c[e]												X
Prior and Concomitant Medications			X	X	X	X	X	X	X	X	X	X
YMRS			X	X	X	X	X	X	X	X	X	X
MADRS			X	X	X	X	X	X	X	X	X	X
CGI-S			X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X	X	X
C-SSRS[f]			X	X	X	X	X	X	X	X	X	X
PSP						X						X
WPAI-BD[g]												X
Extrapyramidal Symptoms (AIMS/BARS/SAS)[h]			X		X		X		X		X	X
Vital Signs and Weight[i]			X	X	X	X	X	X	X	X	X	X
Waist Circumference[j]							X					X
AEs/SAEs			X	X	X	X	X	X	X	X	X	X
ECG[k]												X
[redacted]												X
PK sample (taken at any time during visit)[m]						X		X		X		X

Trial Period	Screening/Washout Period		Open-label Treatment Period									
Visit Number/Visit Title	**1/Screening**	**2/Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12/End of OL**
End of Trial Week (Day)	**Up to 7 days (Days -7 to -1)**	**0 (1)**	**1 (8)**	**2 (15)**	**3 (22)**	**4 (29)**	**6 (43)**	**8 (57)**	**10 (71)**	**12 (85)**	**14 (99)**	**16 (113)**
Visit Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Pharmacogenetic consent[n]			X	X	X	X	X					
Pharmacogenetic sampling[o]			X	X	X	X	X					

Note: If necessary, Visits 3 to 12 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 12. **In extenuating circumstances, the visit window for Visits 4 to 12 (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. Visit 3 should occur within the original ± 3 day window.**

AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression-Improvement scale; CGI-S = Clinical Global Impression-Severity scale; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; HbA1c = glycated hemoglobin; IP = investigational product; IWRS = interactive web response system; MADRS = Montgomery-Åsberg Depression Rating Scale; OP = Open-label; PI = Principal Investigator; PK = pharmacokinetic; PSP = Personal and Social Performance scale; SAE = serious adverse event; SAS = Simpson-Angus Scale; WOCBP = women of childbearing potential; WPAI-BD = Work Productivity and Activity Impairment: Bipolar Disorder questionnaire; YMRS = Young Mania Rating Scale.

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

[b] 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.

[c] 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.

[d] If visit is being performed remotely, this assessment may be omitted at this timepoint. A urine drug screen and assessment of blood alcohol concentration by breathalyzer should be obtained as an unscheduled assessment at the next in-home visit (where possible) or in-person visit.

[e] Clinical laboratory assessments, including serum pregnancy testing (WOCBP only) and HbA1c, may be performed at an off-site laboratory facility if needed. Results of these tests will be recorded in the source document only. 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 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. For all omitted laboratory assessments, the PI must determine whether the patient can safely continue in the study if a laboratory assessment is not completed. For patients allowed to continue in the study, patient should have laboratory assessments performed at the next scheduled timepoint, or earlier, at an Unscheduled Visit.

[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] If visit is being performed remotely, study staff should verbally administer the WPAI-BD questionnaire to the patient and record the patient's responses in the source.

[h] 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. In the event a rater is not available, these assessments may be omitted and assessed at the next scheduled timepoint, or earlier, at an Unscheduled Visit.

[i] If visit is being performed remotely, this assessment may be omitted at this timepoint. Blood pressure and pulse rate will be measured both standing and supine. Vital signs, including weight, should be obtained at the next scheduled in-home (where possible) or in-person visit.

[j] If visit is being performed remotely, this assessment may be omitted at this timepoint. Waist circumference should be assessed at the next scheduled in-home (where possible) or in-person visit.

[k] If visit is being performed remotely, this assessment may be omitted at this timepoint. The PI must determine whether the patient can safely continue in the study if an ECG is not performed. For patients allowed to continue in the study, patient should have an ECG performed at the next scheduled timepoint, or earlier, at an Unscheduled Visit.

[l] [redacted]

[m] 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.

[n] Pharmacogenetic consent may be obtained at any time between Visit 1/Screening and Visit 7/Week 6. Pharmacogenetic consent may not be obtained remotely.

[o] Pharmacogenetic sampling (one sample) may be obtained at any time between Visit 2/Baseline and Visit 7/Week 6. To be omitted if sampling not possible due to remote visits being completed.

Table 5 Modified Schedule of Visits and Procedures-Double-Blind Treatment and Safety Follow-Up Periods

Trial Period	Double-blind Treatment Period																		Safety Follow-up Period	
Visit Number/ Visit Title	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31/ET**	**32**	**33**
End of Trial Week (Day)	**18 (127)**	**20 (141)**	**22 (155)**	**24 (169)**	**26 (183)**	**28 (197)**	**30 (211)**	**32 (225)**	**34 (239)**	**36 (253)**	**38 (267)**	**40 (281)**	**42 (295)**	**44 (309)**	**46 (323)**	**48 (337)**	**50 (351)**	**52 (365)**	**55 (386)**	**57 (400)**	**59 (414)**
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Serum Pregnancy test[a]						X						X							X[b]		X
Clinical Laboratory[a]						X						X							X[b]		
Hemoglobin A1c[a]																			X[b]		
Access IWRS for IP assignment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispense IP[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
IP Compliance and Accountability[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
IP Return[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MADRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-I	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PSP				X						X									X		
C-SSRS[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
WPAI-BD[g]				X															X		
Extrapyramidal Symptoms (AIMS/BARS/SAS)[h]		X		X		X		X		X		X		X		X		X	X		
Assess relapse criteria	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference[j]						X						X							X		
Physical examination[k]																			X		
ECG[k]																			X		
[redacted]																			X		X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sample[m]	X	X			X			X			X			X			X		X		

Note: If necessary, Visits 13 to 33 may be conducted up to 3 days before or after the scheduled visits. The visit windows for each scheduled visit are relative to Visit 12 for Visits 13 through 31/ET, and relative to Visit 31/ET for Visits 32 and 33. **In extenuating circumstances, the visit window for Visits 14 to 33 (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.**
AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impressions-Improvement scale; CGI-S = Clinical Global Impressions-Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; ET = Early Termination; HbA1c = glycated hemoglobin; IP = investigational product; IWRS = interactive web response system; MADRS = Montgomery-Åsberg Depression Rating Scale; OP = Open-label; PI = Principal Investigator; PK = pharmacokinetic; PSP = Personal and Social Performance scale; SAE = serious adverse event; SAS = Simpson-Angus Scale; WOCBP = women of childbearing potential; WPAI-BD = Work Productivity and Activity Impairment: Bipolar Disorder questionnaire; YMRS = Young Mania Rating Scale.

[a] Clinical laboratory assessments, including serum pregnancy testing (WOCBP only) and HbA1c, 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. For all omitted laboratory assessments, the PI must determine whether the patient can safely continue in the study if a laboratory assessment is not completed. For patients allowed to continue in the study, patient should have laboratory assessments performed at the next scheduled timepoint, or earlier, at an Unscheduled Visit.

[b] Clinical laboratory assessments scheduled for Visit 31/ET, 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.

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

[d] Assessment of compliance should be performed at each visit during the Double-blind Treatment period. 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.

[e] 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.

[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] If visit is being performed remotely, study staff should verbally administer the WPAI-BD questionnaire to the patient and record the patient's responses in the source.

[h] 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. In the event a rater is not available, these assessments may be omitted and assessed at the next scheduled timepoint, or earlier, at an Unscheduled Visit.

[i] Blood pressure and pulse rate will be measured both standing and supine. If visit is being performed remotely, this assessment may be omitted at this timepoint; however, vital signs, including weight, should be obtained at the next scheduled in-home (where possible) or in-person visit.

[j] If visit is being performed remotely, this assessment may be omitted. Every attempt should be made to have patient complete as an unscheduled assessment during the SFU period.

[k] 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.

[l] [redacted]

[m] 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.

12.14 Package Insert

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

12.15 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AREDS	Age-Related Eye Disease Study
AST	aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
β-hCG	β-human chorionic gonadotropin
BCVA	best-corrected visual acuity
BP	blood pressure
CGI-I	Clinical Global Impressions-Improvement scale
CGI-S	Clinical Global Impressions-Severity
CRF	case report form
C-SSRS	Columbia–Suicide Severity Rating Scale
DA	dopamine
DB	double-blind
DSM-5	*Diagnostic & Statistical Manual of Mental Disorders*, 5th Edition
ECG	electrocardiogram
eCRF	electronic CRF
EPS	extrapyramidal symptoms
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRR	Hardy Rand Rittler
ICD-10	International Classification of Diseases, Tenth Revision
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	intraocular pressure
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat

Term/Abbreviation	Definition
IWRS	interactive web response system
MADRS	Montgomery-Åsberg Depression Rating Scale
NEAE	newly emergent adverse event
OL	open-label
OL SFU	open-label safety-follow-up
PCS	potentially clinically significant
PID	patient identification number
PSC	posterior subcapsular
PSP	Personal and Social Performance scale
PK	pharmacokinetic
SAE	serious adverse event
SAS	Simpson-Angus Scale
SCID-5	Structured Clinical Interview for DSM-5
SFU	safety-follow-up
TEAE	treatment-emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal
WPAI-BD	Work Productivity and Activity Impairment: Bipolar Disorder
YMRS	Young Mania Rating Scale

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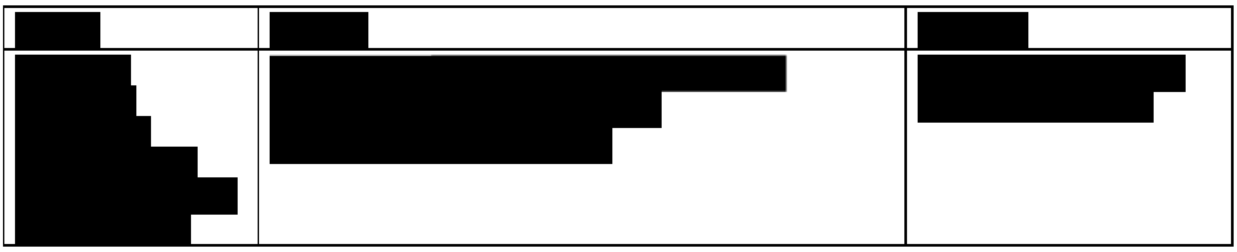

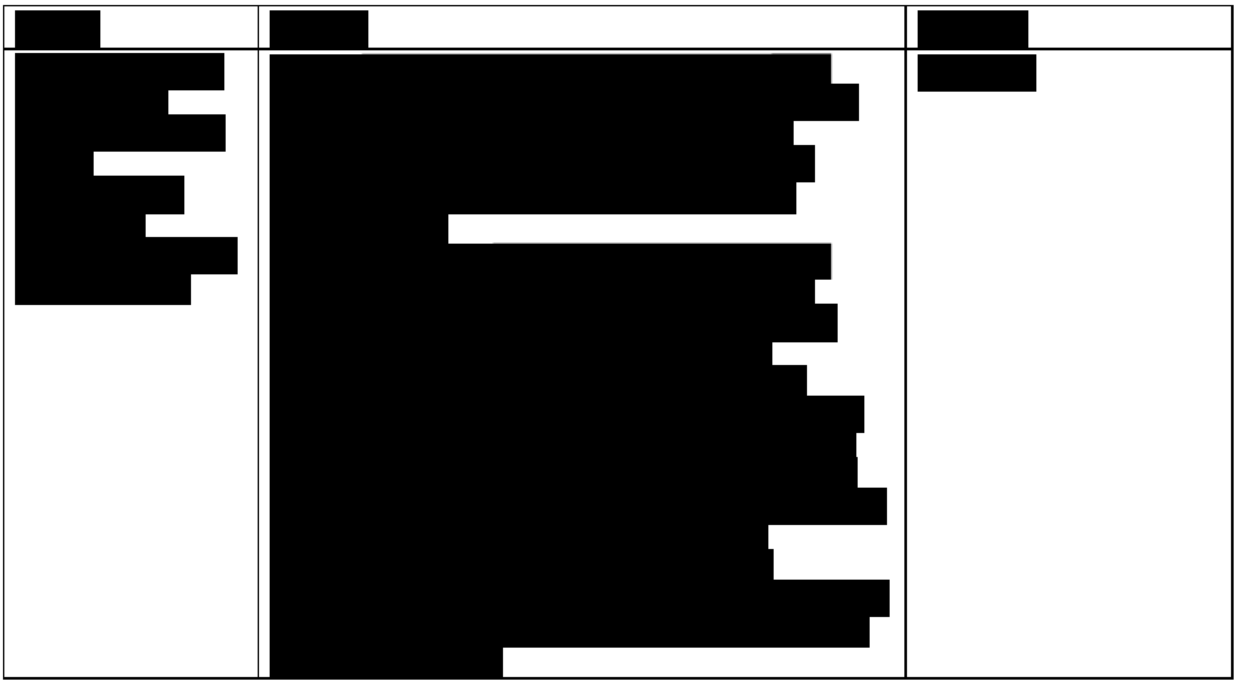

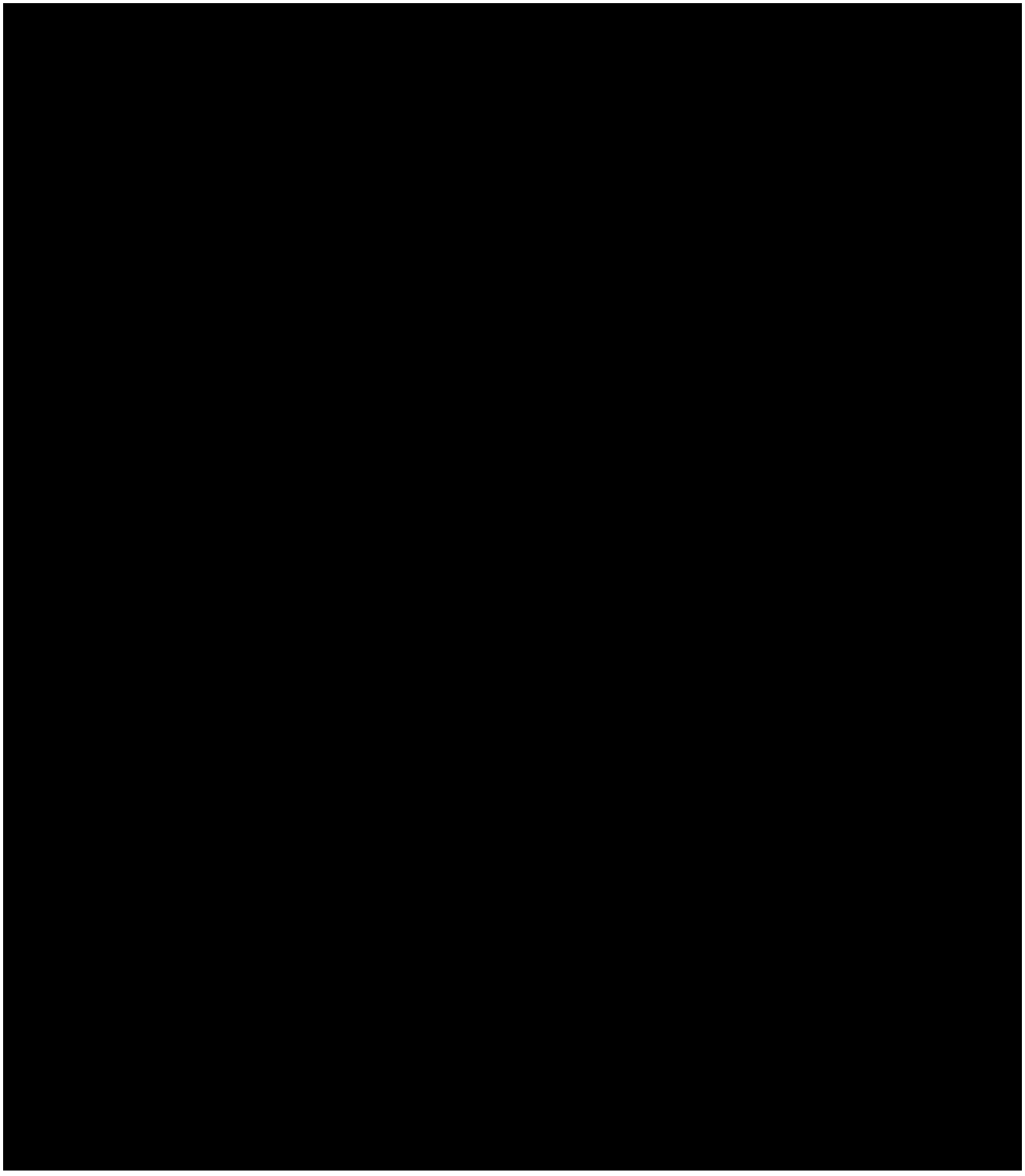

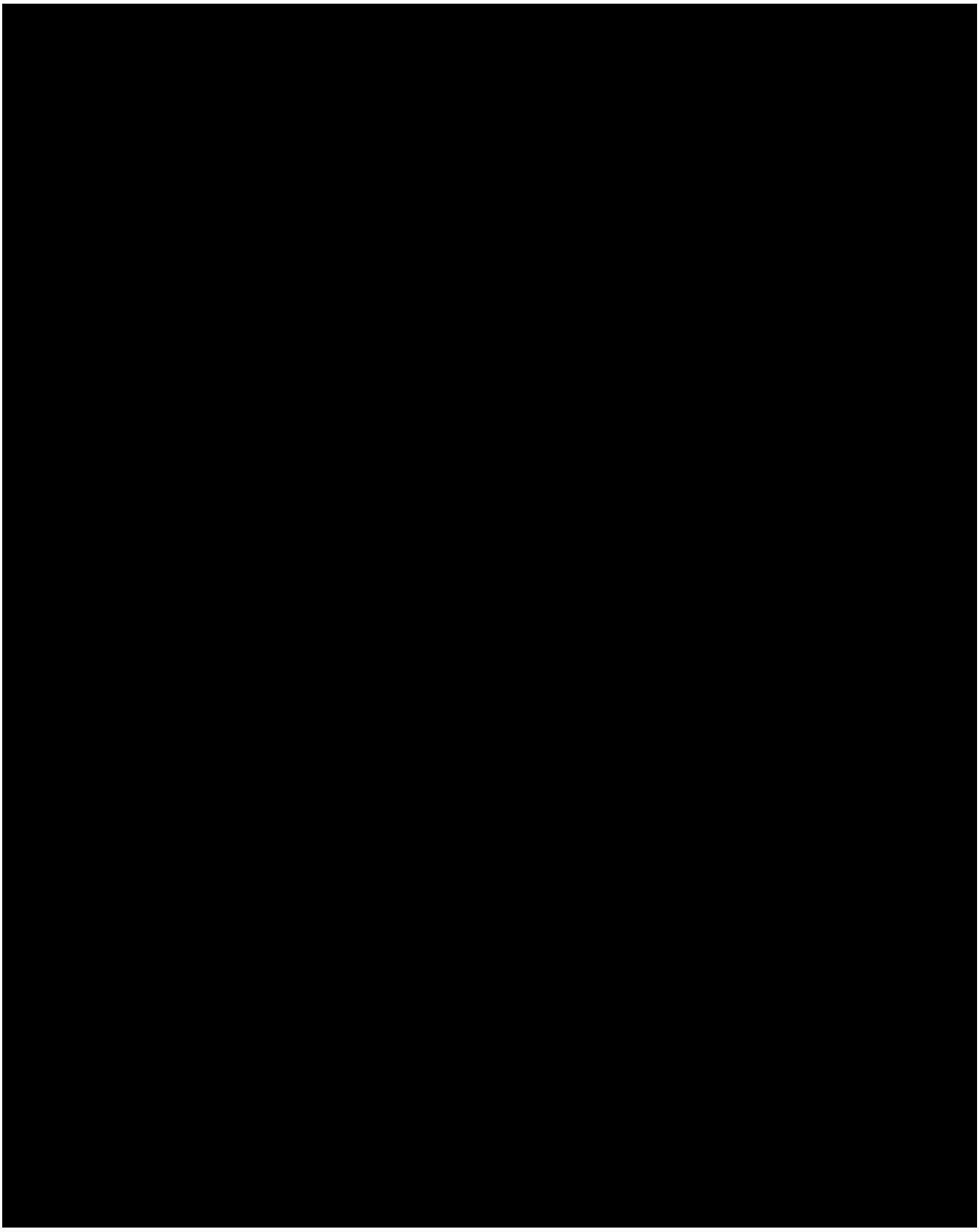

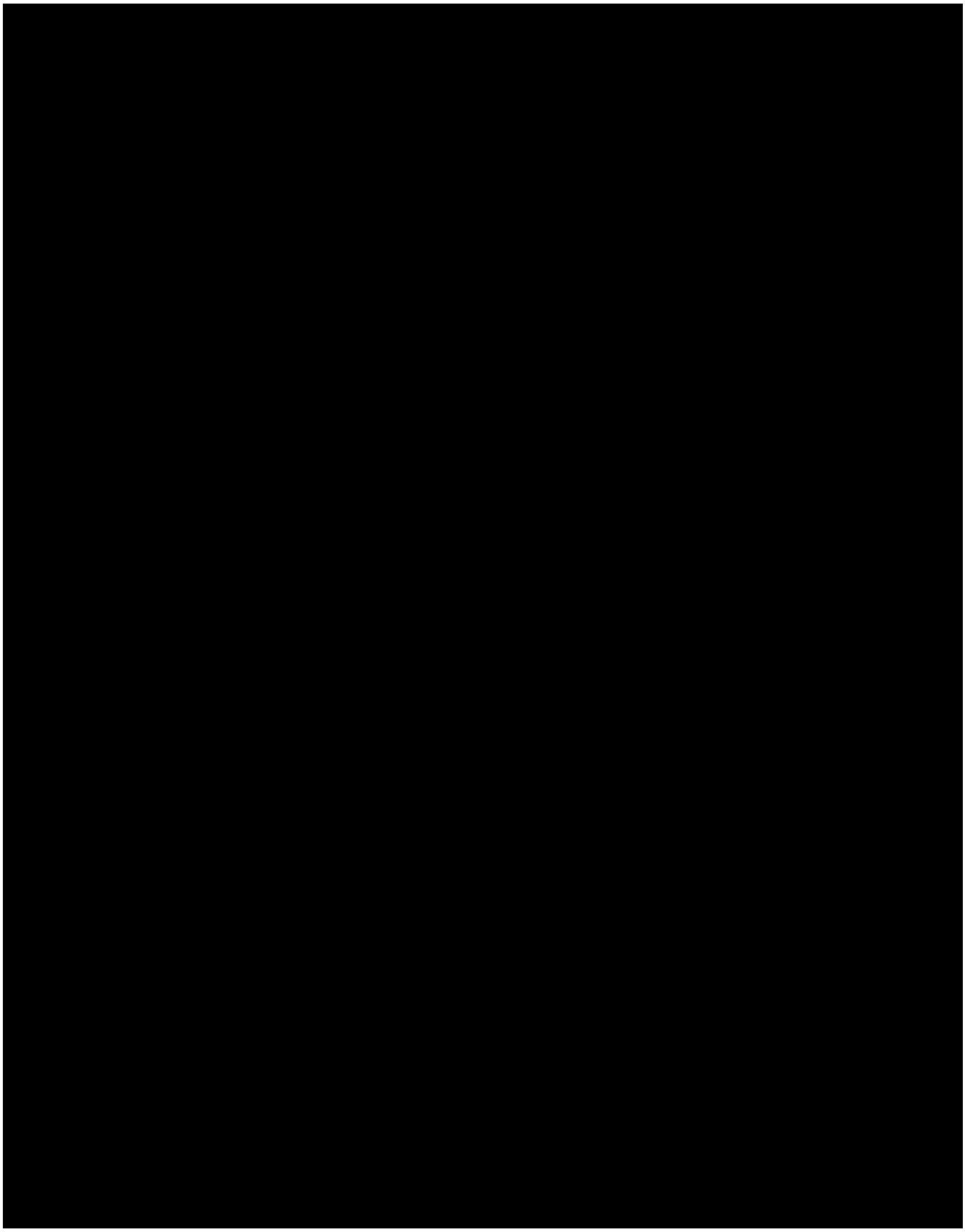

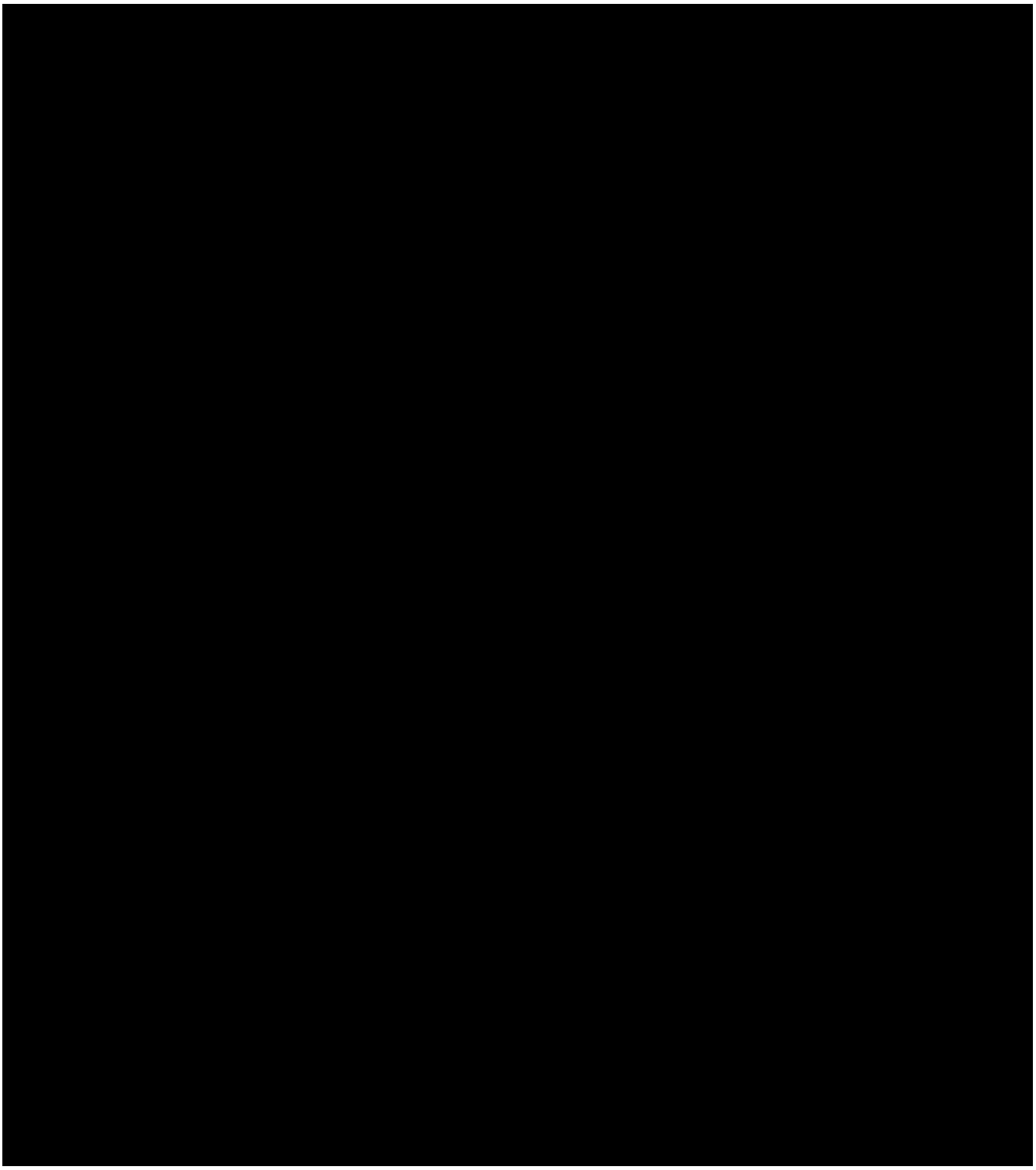

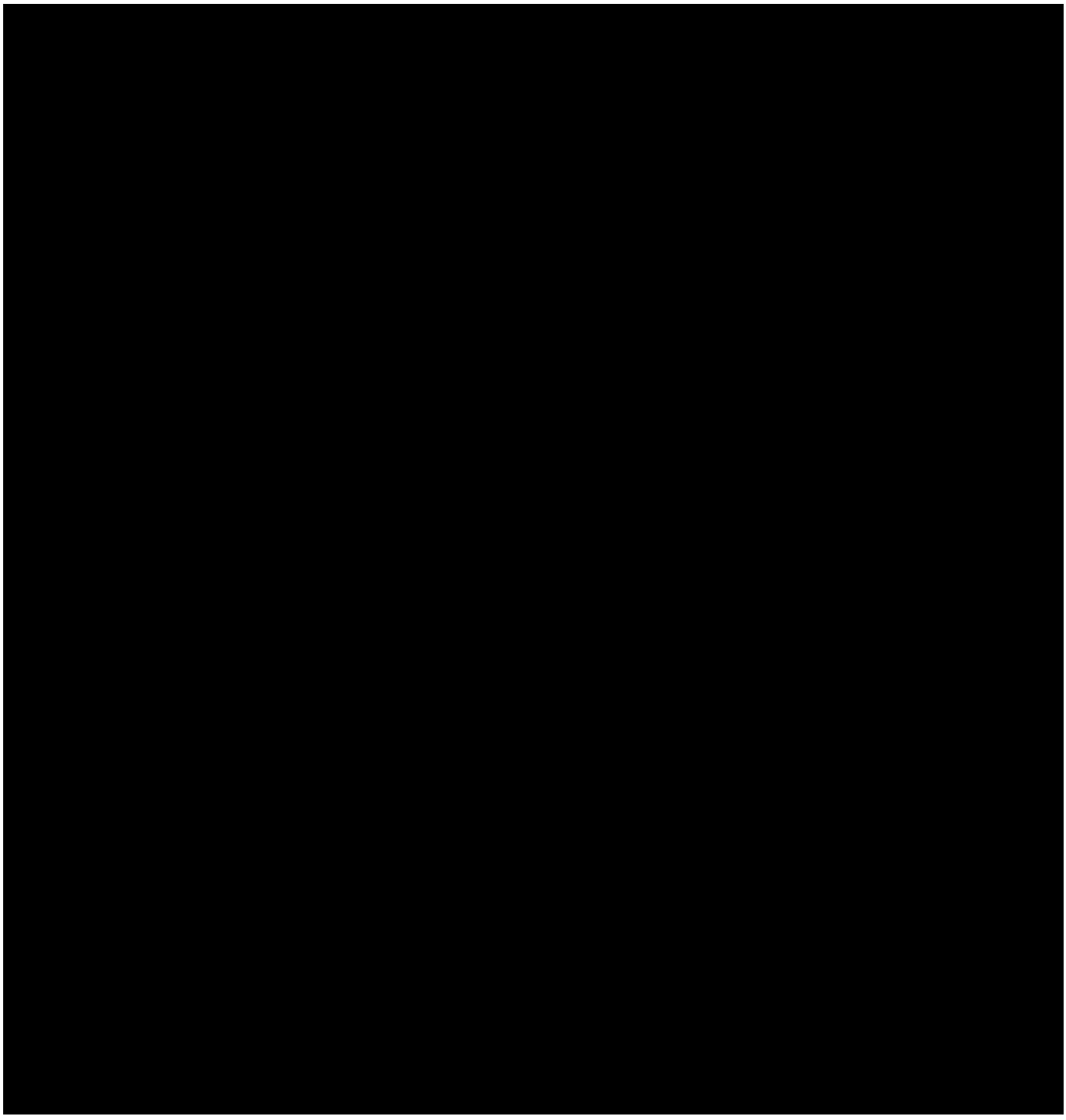

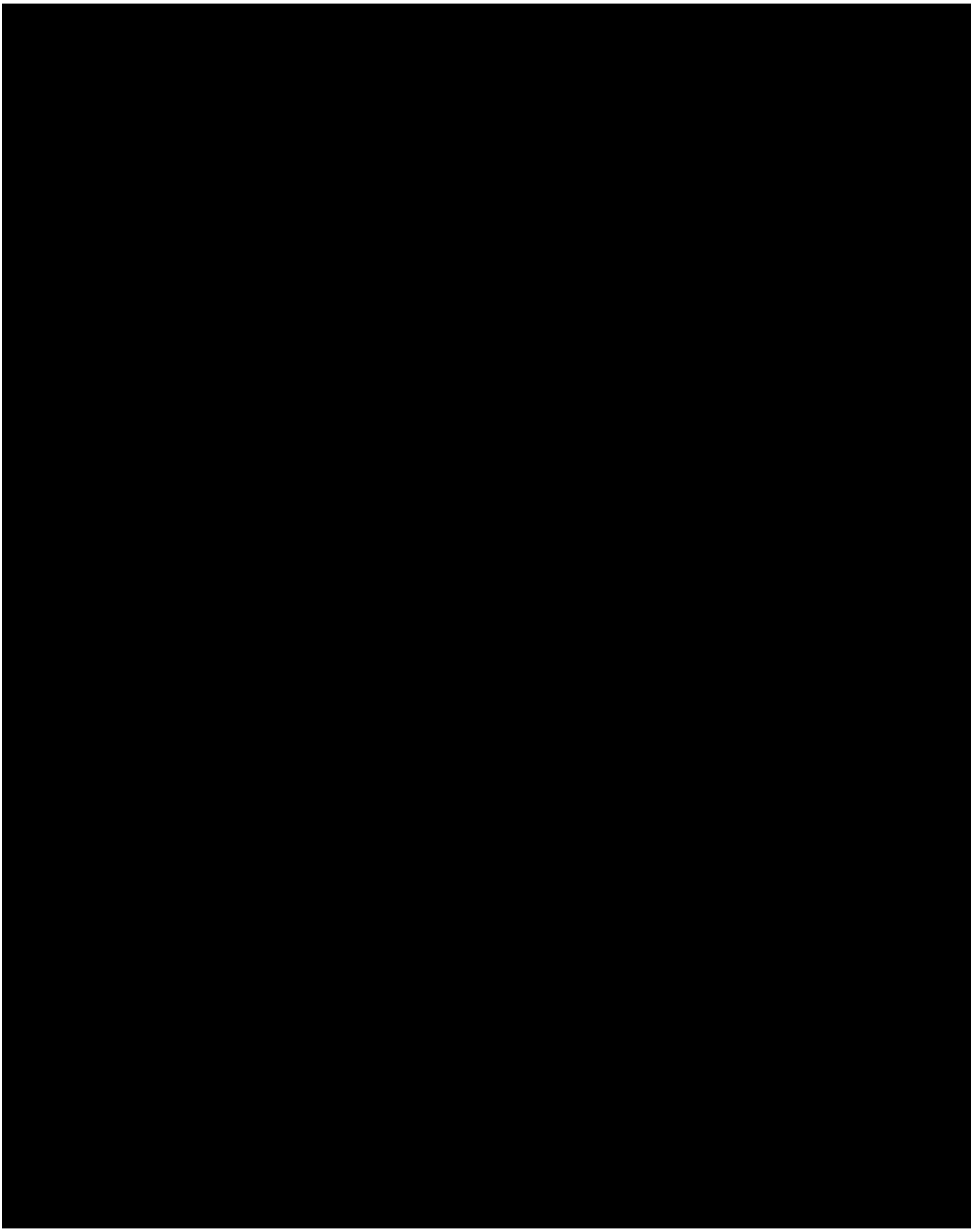

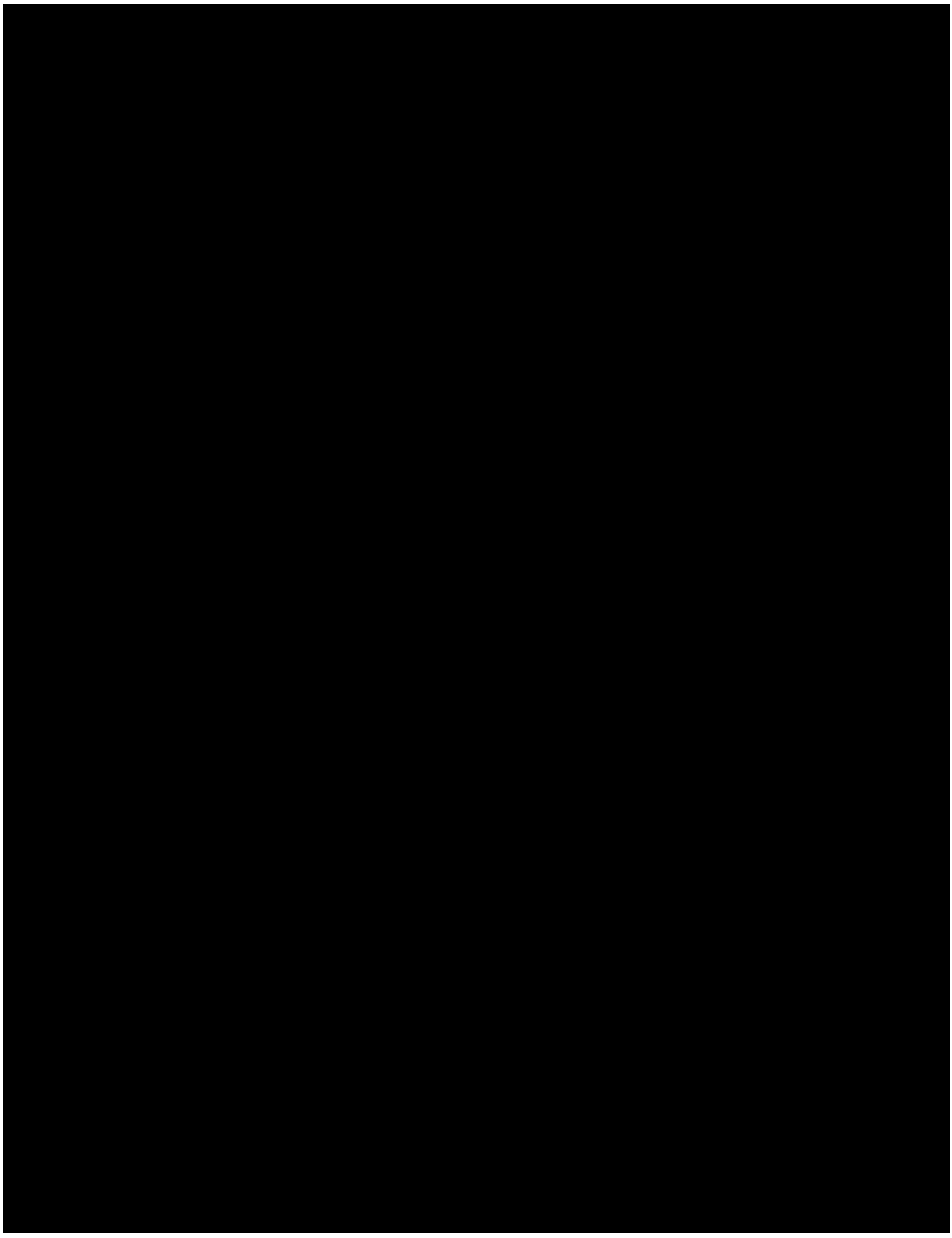

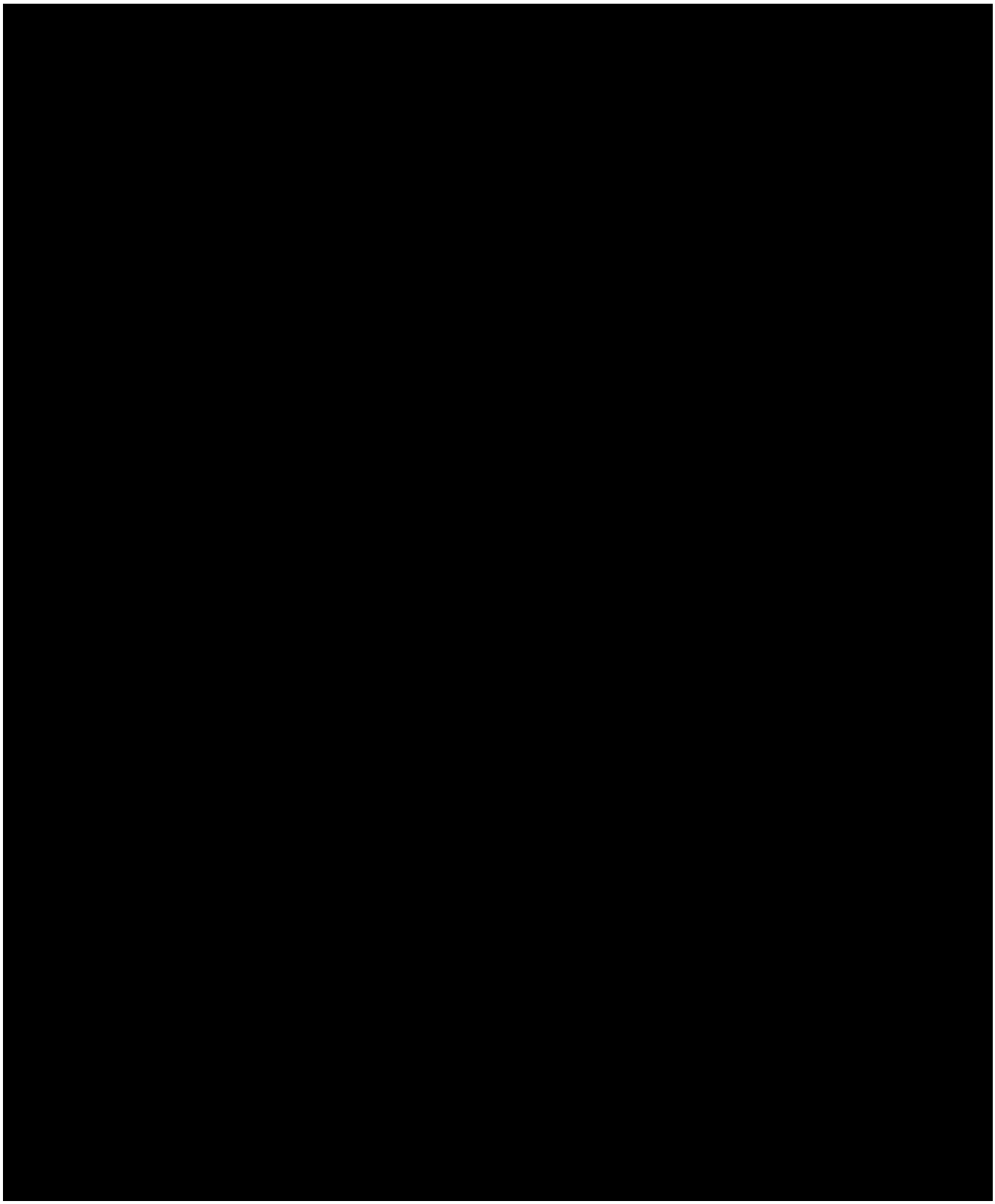

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