1.0 TITLE PAGE

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RGH-MD-25

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 IS MANIC OR DEPRESSIVE, WITH OR WITHOUT MIXED FEATURES

STATISTICAL ANALYSIS PLAN

Final: 11 October 2017

Amendment #1: 28 February 2019

Amendment #2: 13 June 2022

Amendment #3: 23 Nov 2022

2.0 TABLE OF CONTENTS

2.1 LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

Term/Abbreviation	Definition
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BCVA	Best corrected visual acuity
BMI	Body mass index
BP	Blood pressure
CGI-I	Clinical Global Impressions-Improvement scale
CGI-S	Clinical Global Impressions-Severity
CI	Confidence interval
CRF	Case report form
C-SSRS	Columbia–Suicide Severity Rating Scale
DB	Double-blind
DBTP	Double-blind treatment period
DSM-5	*Diagnostic & Statistical Manual of Mental Disorders*, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic CRF
EPS	Extrapyramidal symptoms
ET	Early Termination
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IOP	Intraocular pressure
IP	Investigational product
ITT	Intent to treat
IWRS	Interactive web response system
LOCF	Last-observation-carried forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MMRM	Mixed-effects model for repeated measures
OC	Observed cases
OL	Open-label
OLTP	Open-label treatment period
PCS	Potentially clinically significant
PID	Patient identification
PK	Pharmacokinetic
PSP	Personal and Social Performance scale
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SFU	Safety follow-up
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WPAI-BD	Work Productivity and Activity Impairment: Bipolar Disorder
YMRS	Young Mania Rating Score

4.0 INTRODUCTION

This statistical analysis plan (SAP) describes the methodology that will be used to summarize the statistical analyses of the efficacy and safety data for the final protocol of Study RGH-MD-25 (version dated 12 Dec 2016) and its most recent amendment #5 dated 09 June 2022.

This is a Phase 3B, multicenter, multinational, double-blind (DB), placebo-controlled, randomized withdrawal study 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.

The study is designed with four periods:

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 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. During the screening/washout period, psychotropic medications, other than those listed as rescue (Protocol 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 open-label treatment period [OLTP]). 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 OLTP 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 OLTP, patients will be assessed for remission of symptoms, defined as Young Mania Rating Score (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 Visit 4 (Day 15). 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 Visit 5 (Day 22). 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 Visit 7 (Week 6) or stability by Visit 8 (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 OLTP, 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 (Week 16)/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 (Week 16)/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 OLTP 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 (DBTP): 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 OLTP or DBTP, will be followed for 4 more weeks and will have 2 evaluations for safety assessments at Visit 32 (Week 57) and Visit 33 (Week 59) 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.

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 OLTP (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 OLTP. 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 Day 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 OLTP. For the 39-week DBTP, patients will be supplied with identically appearing capsules of either cariprazine 3.0 mg, cariprazine 1.5 mg, or placebo. During the DBTP, patients will take 1 capsule daily. The dosing regimen is presented in the Table 4-1.

Table 4-1. Treatment Regiment 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 on or after Visit 10 (Week 12) are eligible for early randomization and will skip any remaining visits in the OL period.

The schedule of evaluations is presented in Table 4-2.

Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic/pharmacodynamic parameters is prepared separately.

Table 4-2. 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 Protocol 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 Protocol 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 Protocol 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 Protocol Section 4.6)

[e] Patients who have previously met stability criteria (per Protocol Section 4.5) should be assessed for fulfillment of randomization criteria (per Protocol 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		

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**
[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[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.

5.0 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.

6.0 PATIENT POPULATIONS

6.1 SCREENED POPULATION

The Screened Population will consist of all patients who signed informed consent and received a Patient identification (PID) number.

6.2 OPEN-LABEL SAFETY POPULATION

The OL Safety Population will consist of all patients in the screened population who took at least 1 dose of OL cariprazine during the OLTP of the study.

6.3 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 OLTP of the study.

6.4 OPEN-LABEL SAFETY-FOLLOW-UP POPULATION

The OL SFU population will consist of patients in the OL safety population who were not randomized.

6.5 RANDOMIZED POPULATION

The Randomized Population will consist of all patients in the OL Safety Population who were randomized to a treatment group during the DBTP of the study.

6.6 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.

Patients will be included in the treatment group corresponding to the DB IP they actually received regardless of the treatment they were randomized to.

6.7 DOUBLE-BLIND INTENT-TO-TREAT POPULATION

The DB ITT Population will consist of all who took at least 1 dose of DB IP and had at least 1 post-randomization assessment of the YMRS, MADRS, or CGI-S scores during the DBTP of the study, or had a relapse event.

Patients will be included in the randomized treatment group for the DB ITT population.

7.0 STUDY PATIENTS

7.1 PATIENT DISPOSITION

The OLTP starts with the first dose of OLTP and ends with one of the following: the last scheduled assessment at Visit 12 (Week 16) or early termination (ET) before Visit 12 for patients who do not enter the DBTP; or 1 day before the date of the first dose of DBTP (or the date of the first dose of the DB IP if the last scheduled assessment date in the OLTP is on the date of the first dose of the DBTP) for patients who enter the DBTP.

The DBTP starts with the first day of randomization and ends with the last scheduled assessment at Visit 31 (Week 55) or ET.

The SFU period starts one day after the end of the previous period and ends with the last available assessment. For patients without Visit 32 (Week 57) or Visit 34 (Week 59) assessment, the SFU period would not be derived.

Screen-failure patients (ie, patients screened but not included in the OL Safety Population) and the associated reasons for failure will be tabulated overall for the Screened Population.

The number and percentage of patients in the Screened, OL Safety and OL ITT Populations will be summarized overall and by study center. The number and percentage of patients in the Randomized, DB Safety, and DB ITT Populations will be summarized overall by treatment group and by treatment group and study center.

The number and percentage of patients in the OL Safety Population, who prematurely discontinued from the OLTP, who completed the OLTP, who entered the DBTP, and who entered the SFU period will be summarized overall and by reasons for premature discontinuation as recorded on the OL disposition page of the electronic case report forms (eCRF).

Similarly, the number and percentage of patients in the DB Safety Population who completed the DBTP, who prematurely discontinued from the DBTP, and who entered the SFU period will be summarized overall, by DBTP treatment group and by reasons for premature discontinuation as recorded on the DB disposition page of the eCRF. Patients who relapse during the DBTP will also be summarized as completing the study.

7.2 PROTOCOL DEVIATIONS

The number and percentage of patients with important protocol deviations will be summarized overall for the OLTP**,** and by treatment group for the DBTP. Supportive listings will also be provided. At a minimum, deviations related to the following categories will be included:

- Inclusion or exclusion criteria
- Withdrawal criteria
- Treatment or dose
- Concomitant medications

These and any additional important protocol deviations will be reviewed and documented before database lock and unblinding of treatment codes.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters, including age; age group; region; race; ethnicity; sex; weight; height; and body mass index (BMI), calculated as weight [kg]/(height [m])^2 will be summarized descriptively overall for the OL Safety and OL ITT Populations and by treatment group for the DB Safety and DB ITT populations.

The baseline efficacy variables for OLTP, which is defined as the last available assessment at or prior to the first dose of OL IP, will be summarized descriptively overall for the OL ITT Population. The baseline efficacy variables for DBTP, which is defined at the last available assessment at or prior to the first dose of DB IP, will be summarized by treatment for the DB ITT Population.

The medical and surgical history, psychiatric disorders, and nondrug psychiatric treatment, will be summarized descriptively overall for the OL Safety Populations and by treatment group for the DB Safety Populations.

Continuous variables will be summarized by number of patients and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

Prior medication is defined as any medication started before the date of the first dose of OL IP. *Concomitant medication* during the OLTP is defined as any medication taken on or after the date of the first dose of OL IP during the OLTP. *Concomitant medication* during the DBTP is defined as any medication taken on or after the date of the first dose of DB IP during the DBTP.

The use of prior and concomitant medications during the OLTP will be summarized by the number and percentage of patients receiving each medication within each therapeutic class for the OL Safety Population. The use of concomitant medications during the DBTP and SFU period will be summarized by treatment group by the number and percentage of patients receiving each medication within each therapeutic class for the DB Safety Population. Multiple medication use by a patient will only be counted once.

The use of rescue medications during the OLTP and during the DBTP will be summarized by treatment group and generic terms for the following rescue medication categories in the safety population:

- Insomnia
- Extrapyramidal symptoms (EPS) or akathisia
- Agitation, Restlessness, and Hostility

The *WHO Drug Dictionary Enhanced*, version March 2017 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to the OL IP for the OL Safety Population will be summarized for treatment duration, calculated as the number of days from the date of the first dose of OL cariprazine taken to the date of the last dose taken during the OLTP, inclusive. Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be presented.

Exposure to the DB IP for the DB Safety Population during the DBTP will be summarized for treatment duration, calculated as the number of days from the date of the first dose of DB IP to the date of the last dose of DB IP, inclusive. Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be presented by treatment group.

Exposure to cariprazine during the entire study (OLTP and DBTP) will be summarized by intervals for the OL Safety Population. Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be presented.

By design, patients will take a fixed dose of cariprazine and there is no titration period during the DBTP. Mean daily dose, final dose will not be provided during the DBTP.

Patient-years, defined as exposure to the IP in years, will be summarized for the OLTP for the OL Safety Population. Patient-years will also be summarized by treatment group for the DBTP for the DB Safety Population. Patient years of exposure to cariprazine during the entire study (OLTP and DBTP) will also be summarized for the OL Safety Population.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the total number of capsules actually taken by a patient during that period divided by the number of capsules prescribed that were expected to be taken during the same period multiplied by 100. The total number of capsules actually taken during a specific period is calculated as the number of days in that period multiplied by the number of capsules taken each day during that period. The number of capsules expected to be taken for a specific treatment period will be calculated by multiplying the number of days in that period by the number of capsules to be taken per day. This information will be obtained from the IP record of the patient's eCRF. Descriptive statistics for IP compliance will be presented by treatment for each period between 2 consecutive visits, as well as for the period from the first dose of DB IP actually taken to the last dose of DB IP actually taken from the Safety Population.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for OL IP compliance will be presented overall for each period between 2 consecutive visits, as well as for the entire OLTP for the OL Safety Population. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for DB IP compliance will be presented by treatment group for each period between 2 consecutive visits, as well as for the entire DBTP for the DB Safety Population.

10.0 EFFICACY ANALYSES

All efficacy analyses for the OLTP will be performed using the OL ITT Population, unless stated otherwise. Baselines for efficacy parameters in the OLTP will be defined as the last nonmissing efficacy assessment before the first dose of OL IP.

All efficacy analyses for the DBTP will be performed using the DB ITT Population, unless stated otherwise. Baselines for the additional efficacy parameters in the DBTP 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 (CIs) will be 2-sided 95% CIs, unless stated otherwise.

To accommodate the flexible duration of the OLTP, the derived visits in the DBTP will be named as Week *i* post randomization (or DB Week *i*) for a specific Week *i* after the first dose of the DB study medications. The total exposure to IPs for patients in Week *i* post randomization will vary because of the flexible OLTP. The detailed week-mapping windows is provided in Section 16.1.

10.1 PRIMARY EFFICACY PARAMETER

The primary efficacy parameter is the time to first relapse of any mood episode during the DBTP. The time to first relapse is defined as the number of days from the randomization date to the first relapse date. Relapse during the DBTP will be defined as meeting 1 or more of the following criteria:

- 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 the above relapse criteria will categorize the relapse event(s) as manic or depressive event(s), with or without mixed features. Patients who did not meet the above relapse criteria will be censored at the time of completion or discontinuation from the DBTP.

The primary efficacy analysis is to evaluate the time to first relapse of any mood episode in bipolar I disorder patients who responded to OLTP 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) and region (US, non-US) 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 the covariate stratified by modified index episode (manic or depressive) and region (US, non-US). The Kaplan-Meier estimates for the cumulative distribution of the relapse rate for each treatment group will be provided.

Per the protocol, relapses are collected within a double-blind treatment period that lasts with a maximum of 39 weeks (or 273 days + 3 days visit time window), hence all survival analyses will censor data at 276 days.

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 two-sided 0.05 significance level, and 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 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 proposed by Lu (2014, 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.

Sample SAS programs for primary efficacy analysis and sensitivity analyses are provided in Appendix I and Appendix II.

The analysis for primary efficacy parameter will be performed within each category of the following, and the corresponding Kaplan-Meier curves will be provided:

- Age group (< 45 years, ≥ 45 years).
- Sex (male, female)
- Race (white, all other races)
- Region (US, Non-US)
- Modified index episode (manic or depressive)

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

Kaplan-Meier curves of cumulative rate of first relapse with manic episode with or without mixed features during the DBTP, and Kaplan-Meier curves of cumulative rate of first relapse with depressive episode with or without mixed features during the DBTP will be generated.

Additional sensitivity analysis for the primary endpoint, time to first relapse of any mood episode, will be conducted for the DB ITT population, censoring ongoing participants in Russia and Ukraine as of 24Feb2022, and will be analyzed using the log-rank test stratified by modified index episode and region. Any relapse events in Russia and Ukraine on or after 24Feb2022 will not be included and all ongoing participants in those two countries will be considered 'lost' as of that date.

10.2 SECONDARY EFFICACY PARAMETER

None.

10.3 ADDITIONAL EFFICACY PARAMETERS

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

Time to early discontinuation with any reason (including relapse) during the DBTP for the DB ITT population will be analyzed using the same method used to analyze the primary efficacy variable.

For the following continuous efficacy variables, the change from baseline refers to the change from OL baseline during the OLTP, and the change from DB baseline during the DBTP, unless stated otherwise.

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 total score and sub-domain 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 total score and sub-domain score by visit

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) for additional efficacy parameters will be provided by visit for the OL ITT population and the DB ITT population using both last-observation-carried forward (LOCF) and observed cased (OC) approaches. LOCF approach will be used to impute missing postbaseline values. Imputation of missing values will be done for the OLTP and the DBTP separately.

For the DBTP, the additional efficacy parameters 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 (Kenward and Roger, 1997) will be used to estimate denominator degrees of freedom. The analysis will be performed based on post-DB baseline scores using only the OC without imputation of missing values. Least squares mean and their standard errors based on the MMRM analysis will be plotted by treatment group and visit.

The analysis for change from baseline in YMRS and MADRS total scores by visit will also be performed within modified index episode (manic or depressive).

Sub-domains for PSP are socially useful activities, personal and social relationships, self-care, disturbing and aggressive behaviors.

11.0 SAFETY ANALYSES

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

Safety parameters will include adverse events (AEs), clinical laboratory parameters, vital signs, Electrocardiogram (ECG) parameters, ophthalmology parameters, Columbia–Suicide Severity Rating Scale (C-SSRS), EPS scales, including Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (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. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

The derived visits in the DBTP will use the same strategy as described in Section 10.0. The detailed week mapping windows is provided in Section 16.1.

11.1 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 date of the first dose of OL IP. Per eCRF instructions, a new AE record will be created with a new AE onset date for any AE that worsens. Therefore, TEAEs can simply be identified as those Aes with recorded onset date (and time, if known) on or after the date of the first dose of IP.

The number and percentage of patients reporting TEAEs during the OLTP 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 DBTP 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 total number and percentage of TEAEs during the DBTP will also be summarized by severity and relationship to IP for each treatment group.

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

For OLTP, DBTP, 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.

An AE that occurs more than 30 days after the date of the last dose of DB IP or occurs after the last SFU visit (whichever comes last) will not be summarized except for Aes related to reported pregnancies. Aes associated with pregnancies reported in the protocol-required timeframe up to approximately 12 weeks following the last dose of DB IP will be summarized.

The number and percentage of patients with common (≥ 2% of patients in any treatment group) TEAEs will be summarized by preferred term for OLTP and be summarized by preferred term and treatment group for DBTP.

The number and percentage of TEAEs leading to premature discontinuation of IP during the OLTP will be summarized by preferred term. The incidence of Aes leading to premature discontinuation of IP during the DBTP will be summarized by preferred term and treatment group.

An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any serious adverse event (SAE) criterion.

Summary tables will be provided for patients with TESAEs if these occurred in 5 or more patients. The number and percentage of patients with TESAEs will be summarized for OLTP, DBTP, and SFU period.

For the Screened Population, listings will be presented for patients with SAEs, patients with Aes leading to premature discontinuation, and patients who die (if any). All patients with SAEs, including SAEs reported during the screening period and the SFU period, and patients discontinuing because of Aes occurring before the start of OLTP will be included in these listings.

The number and percentage of patients with EPS TEAEs, EPS SAEs, and EPS Aes leading to premature discontinuation of IP will be summarized overall for the OLTP in the OL safety population and by treatment for the DBTP in the DB safety population separately.

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

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values and change from baseline values at each assessment timepoint will be presented for the OLTP and by treatment group for the DBTP in International System of Units (SI units). There is a central lab transition (from Q2 to Covance) during the clinical trial. In addition, descriptive statistics for clinical laboratory values and changes from baseline values at each assessment timepoint will also be presented by central lab for the OLTP and by treatment group for the DBTP in SI units.

The descriptive statistics will be provided for the following laboratory parameters:

Hematology	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)
Fasting serum chemistry	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
Urinalysis	Specific gravity, pH, protein, glucose

Hemoglobin A_{1c}

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters listed in Appendix III. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of Appendix III. Only patients with selected clinical laboratory data at baseline and at least one postbaseline visit during the OLTP and DBTP will be included in the summary.

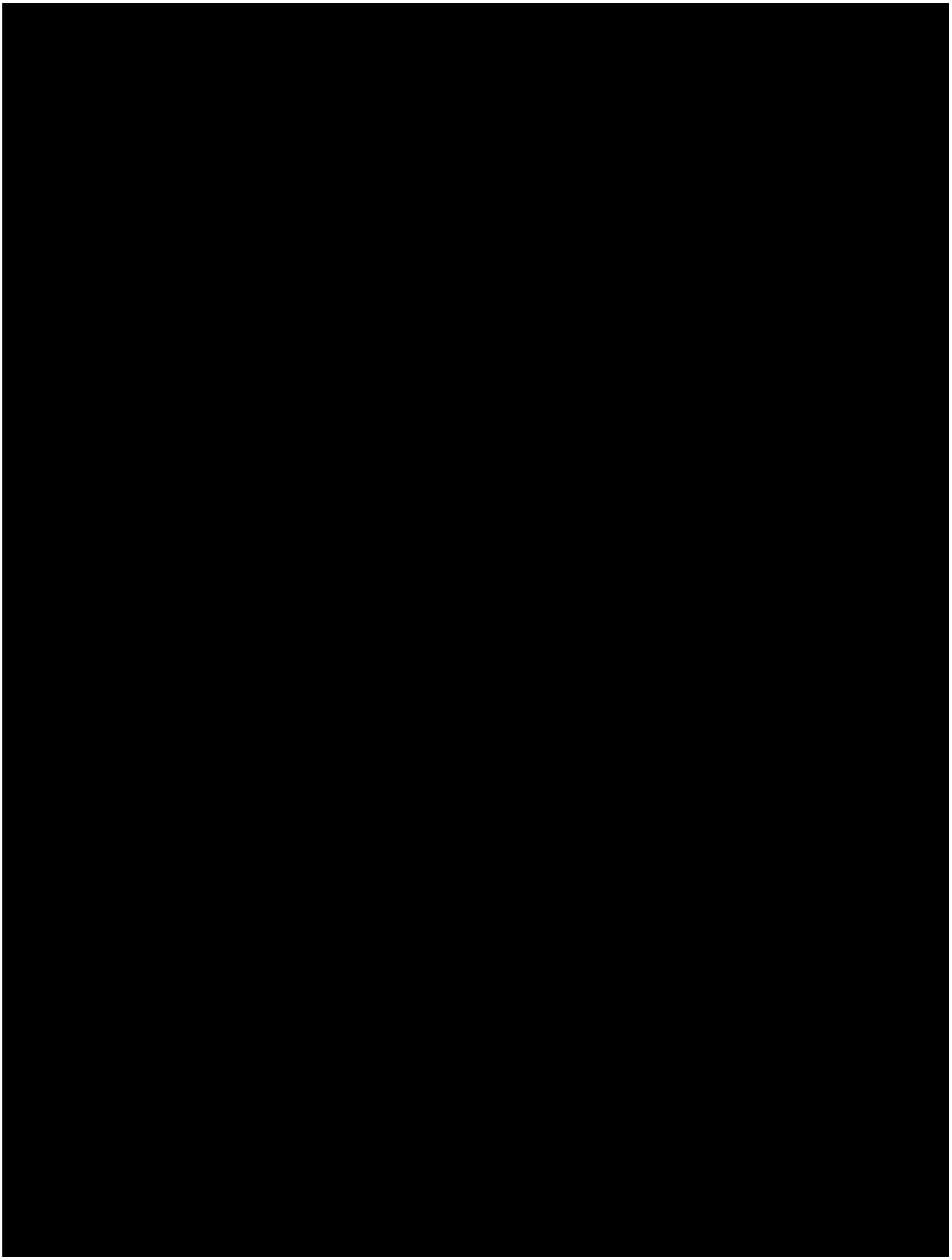
Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11.2-1. The number and percentage of patients who have PCS postbaseline clinical laboratory values will be tabulated overall for the OLTP, and by treatment group for the DBTP. 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 corresponding treatment periods (OLTP or DBTP). The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value for the corresponding treatment periods (OLTP or DBTP). A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and all postbaseline (including non-PCS) values.

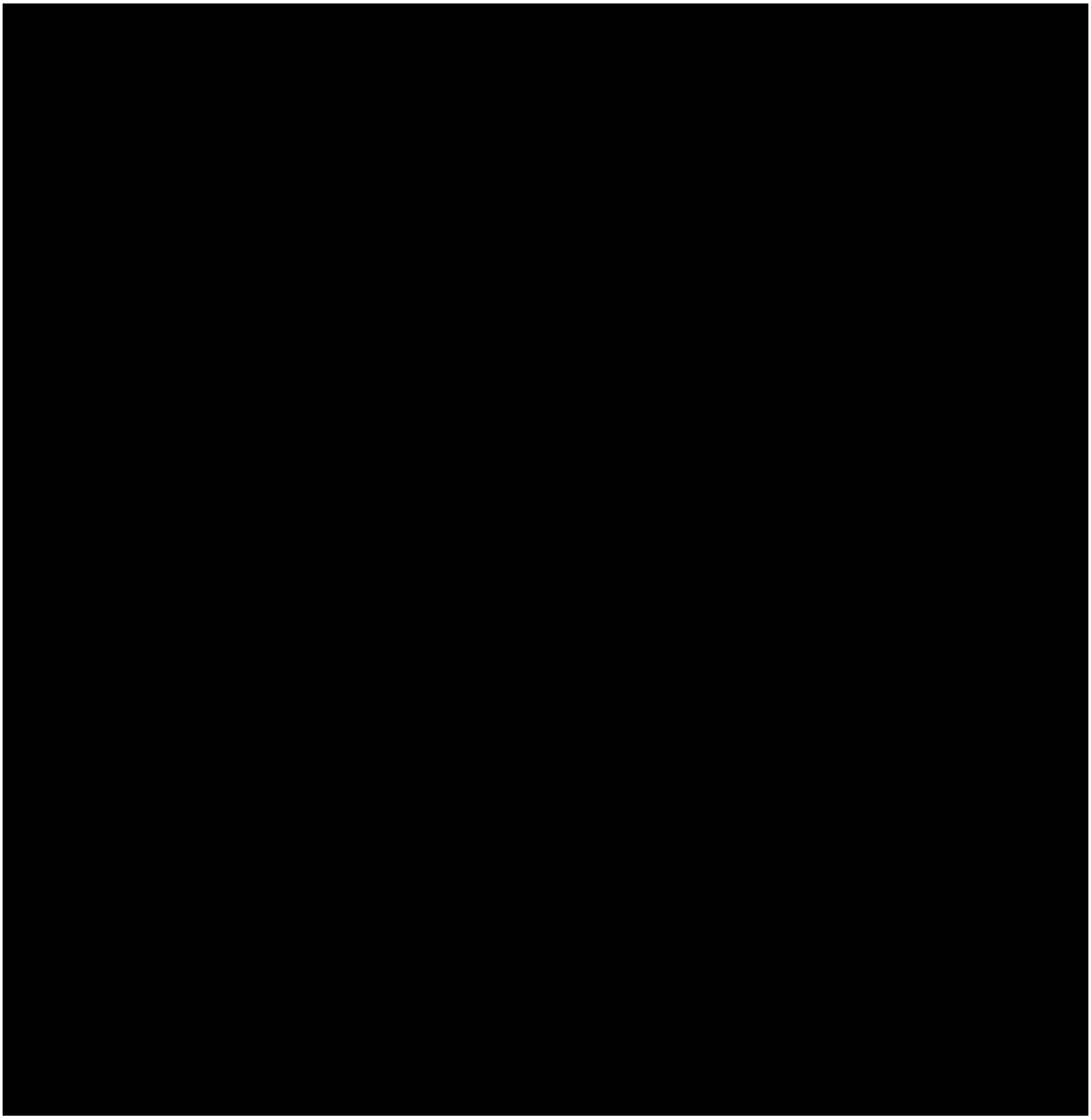
In addition, a tabular display showing all Aes that occurred in patients who had PCS postbaseline clinical laboratory values will be provided.

Potential Hy's Law criteria within a 24-hour window is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 3x ULN, along with total bilirubin (TBL) $\geq$ 2x ULN and a non-elevated alkaline phosphatase (ALP) < 2x ULN, all based on blood draws collected within a 24-hour period.

Patients who meet the potential Hy's Law criteria during the OLTP will be summarized for the OL Safety Population. Patients who meet the potential Hy's Law criteria from the first dose of DB IP to within 30 days after the last dose of DB IP will be summarized for the DB Safety Population. Supportive tabular displays will also be provided.

The number and percentage of patients with treatment-emergent significant changes in lipids parameters (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) and glucose will be tabulated by treatment group for the OLTP and the DBTP. The criteria for treatment-emergent significant changes in lipids and glucose are specified in Table 11.2-2 and Table 11.2-3. Percentages will be calculated relative to the number of patients with baseline values meeting the specified baseline criteria and with at least one postbaseline assessment during the specific period. The change in lipids and glucose from baseline to the highest (lowest for HDL cholesterol) postbaseline measurement during the specific period will be summarized. Supportive listings of patients with treatment-emergent changes in lipids and glucose values will be provided.





11.3 VITAL SIGNS

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for vital signs (supine systolic and diastolic blood pressures, supine pulse rate, weight, BMI, waist circumference, and temperature) and changes from baseline values at each visit and at the end of study will be presented overall for the OLTP and OL SFU period, and by treatment group for the DBTP and DB SFU period.

Vital sign values will be considered as PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11.3-1. The number and percentage of patients with PCS postbaseline values will be tabulated overall for the OLTP and by treatment group for the DBTP. The percentages will be calculated relative to the number of patients with available baseline values and at least 1 postbaseline assessment for the corresponding periods (OLTP or DBTP). The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value for the corresponding periods (OLTP or DBTP). A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all Aes that occurred in patients who had PCS postbaseline vital sign values will be provided.

The number and percentage of patients with orthostatic hypotension will be provided for OLTP and DBTP. Orthostatic hypotension is defined as a reduction of ≥ 20 mm Hg in systolic blood pressure or a reduction of ≥ 10 mm Hg in diastolic blood pressure while changing from the supine to standing position. A supportive listing of patients with orthostatic hypotension will be provided. A listing of all AEs for patients with orthostatic hypotension will also be provided.

Table 11.3-1. Criteria for Potentially Clinically Significant Vital Signs

Parameter	***Flag***	***Criteria***[a]	
		Observed Value	*Change From Baseline*
Supine systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Supine diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Supine pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute.

As specified in the Seventh Report for the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (NIH Publication No. 04-5230, 2004), hypertension status is defined in the following texts.

- Normotensive: systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg.

- Prehypertension: systolic BP 120 to 139 mm Hg or diastolic BP 80 to 89 mm Hg
- Stage I Hypertension: systolic BP 140 to 159 mm Hg or diastolic BP 90 to 99 mm Hg
- Stage II Hypertension: systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg

The number and percentage of patients with hypertension status changes from baseline will be provided for

- Shift of hypertension status from baseline to end of the OLTP in the OL Safety Population
- Shift of hypertension status from baseline to highest category during the OLTP in the OL Safety Population
- Shift of hypertension status from baseline to end of the DBTP in the DB Safety Population
- Shift of hypertension status from baseline to highest category during the DBTP in the DB Safety Population

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

11.4 ELECTROCARDIOGRAM

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and QTc) and changes from baseline values at each assessment time point to the end of study will be presented overall for the OLTP and by treatment group for the DBTP. The QTc will be calculated using both the Bazett and Fridericia corrections.

ECG parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria listed in Table 11.4-1. The number and percentage of patients with PCS postbaseline ECG values will be tabulated overall for the OLTP and by treatment group for the DBTP. 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 corresponding periods (OLTP or DBTP). The numerator is the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value for the corresponding periods (OLTP or DBTP). A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, study center 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 overall for the OLTP and by treatment group for the DBTP for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A listing of patients with postbaseline clinically significant ECG abnormalities according to the Investigator's or by the central cardiologist's overall interpretation will be provided.

The number and percentage of patients with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcB or QTcF will be tabulated. Patients will be counted only once for the most severe category. A supportive listing of patients with postbaseline QTcB or QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTc values (including changes from baseline). A listing of all AEs for patients with postbaseline QTcB or QTcF increases > 30 msec will also be provided.

Table 11.4-1. Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	*Unit*	*Higher Limit*
QRS duration	msec	≥ 150
PR interval	msec	≥ 250
QTcB	msec	> 500
QTcF	msec	> 500

QTcB = QT interval corrected for heart rate using the Bazett formula $QT/(RR)^{1/2}$; QTcF = QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$).

11.5 OTHER SAFETY PARAMETERS

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

[redacted]

[redacted]

11.5.2 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 overall for the OLTP and by treatment group for the DBTP. The distribution of response for most severe suicidal ideation and suicidal behavior during the lifetime history, the OLTP, and the DBTP will be presented overall for the OLTP and by treatment group for the DBTP. Supportive listings will be provided, including the PID number, treatment group (for DBTP only), 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. Listings of all AEs occurring in patients who have suicidal ideation or suicidal behavior during OLTP and DBTP will also be provided.

11.5.3 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 overall for the OLTP and by treatment group for the DBTP. Listings of patients with treatment-emergent parkinsonism or akathisia will be provided, including the PID number, baseline and postbaseline values. Listings of all AEs for patients with treatment-emergent parkinsonism or akathisia will also be provided.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for the total scores and the changes from baseline values at every assessment timepoint for each EPS scale (AIMS, BARS, and SAS) will be presented overall for the OLTP and by treatment group for the DBTP.

12.0 HEALTH OUTCOMES ANALYSES

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

The Health Outcome endpoint is change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to bipolar disorder at Week 16 for OLTP, and at Double-blind Weeks 8 and 39 for DBTP, as assessed by the WPAI-BD.

Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided by visit for the OL ITT population and the DB ITT populations.

Baseline for this HEOR endpoint during the DB treatment period for the DB ITT population will be defined as the last nonmissing efficacy assessment before the first dose of DB IP.

The change from baseline will be analyzed during the DB treatment period for the DB ITT population, by using an 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 analysis will be performed based on post-DB baseline using only the OC without imputation of missing values.

WPAI:BIPOLAR DISORDER Related Endpoints Derivation

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

- Q1 = Currently employed (working for pay).
- Q2 = During past 7 days, missed work hours because of problems associated with your bipolar disorder
- Q3 = During past 7 days, missed work hours due to other reason, such as vacation, holidays, time off to participate in this study
- Q4 = During past 7 days, how many hours actually worked
- Q5 = During past 7 days, how much bipolar disorder affected productivity while working

- Q6 = During past 7 days, how much bipolar disorder affected regular daily activity.

Scores:

Multiply scores by 100 to express in percentages.

- Percent work time missed due to bipolar disorder (absenteeism): Q2/(Q2 + Q4)
- Percent impairment while working due to bipolar disorder (presenteeism): Q5/10
- Percent overall work impairment due to bipolar disorder (overall work productivity loss): Q2/(Q2 + Q4) + (1- (Q2/(Q2 + Q4))) × (Q5/10)
- Percent activity impairment due to bipolar disorder (regular activity impairment): Q6/10

If the response to Q1 (“Currently employed?”) is No or missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 DETERMINATION OF SAMPLE SIZE

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

The relapse HR is assumed to be 0.42 based on cariprazine maintenance study in patients with schizophrenia (Durgam 2016) [redacted] compounds (asenapine and aripiprazone) in bipolar I disorder trials and schizophrenia maintenance trails were similar (Pigott 2003; Keck 2006; Kane 2011; Szegedi 2018). The cumulative relapse rate at Week 39 for the placebo group is assumed to be 35%, which is the average of the relapse rate in the placebo arm at Week 39 for the asenapine bipolar mania maintenance trial (Kane 2011) and the quetiapine bipolar I disorder maintenance trial (Suppes 2009).

Using these assumptions, the study would have to observe approximately 75 events to have 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 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 a total of 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 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 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.

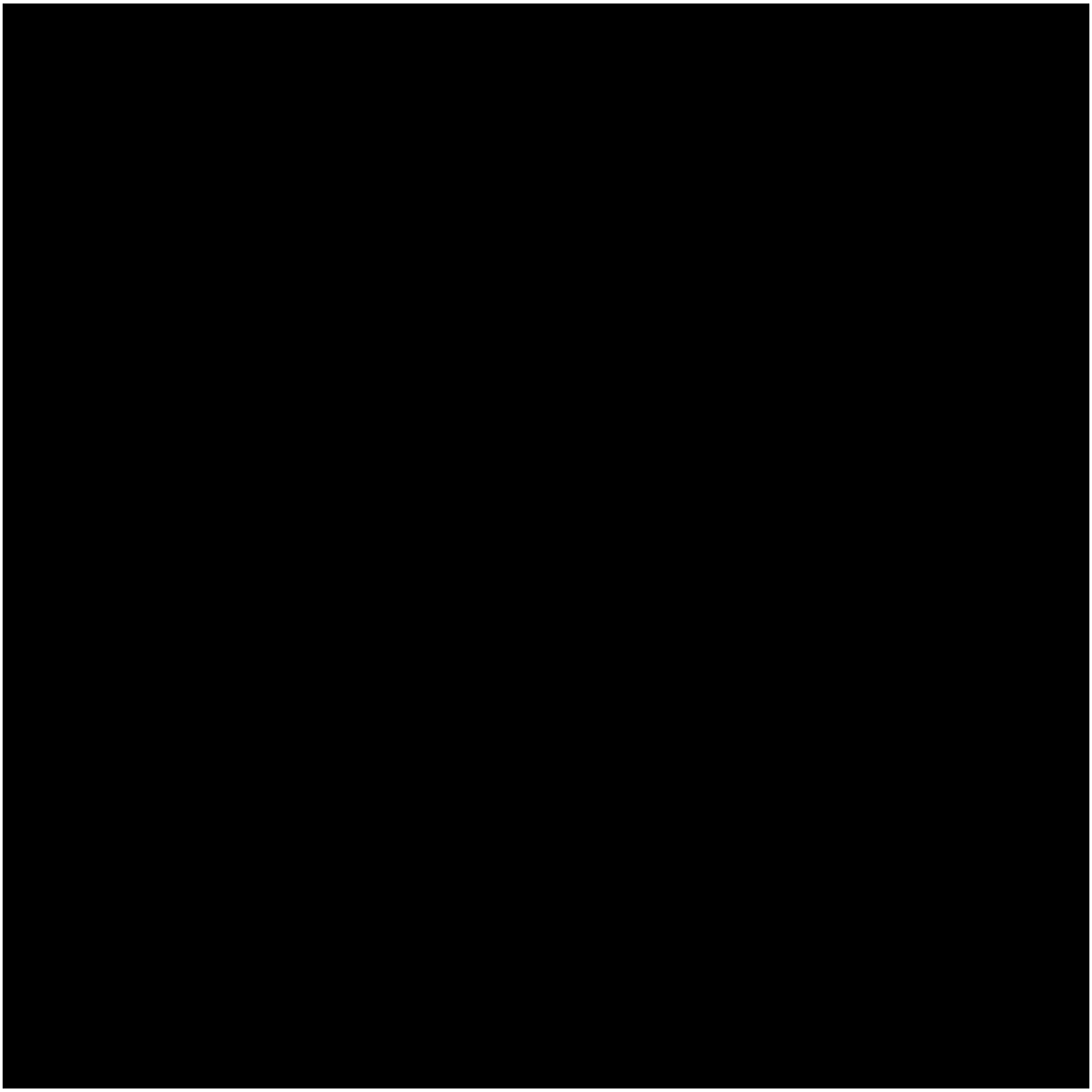
With the expectation that approximately 46% of patients will complete the OLTP period and will meet the randomization criteria, approximately 882 patients would be expected to enter and be treated with cariprazine in the OLTP.

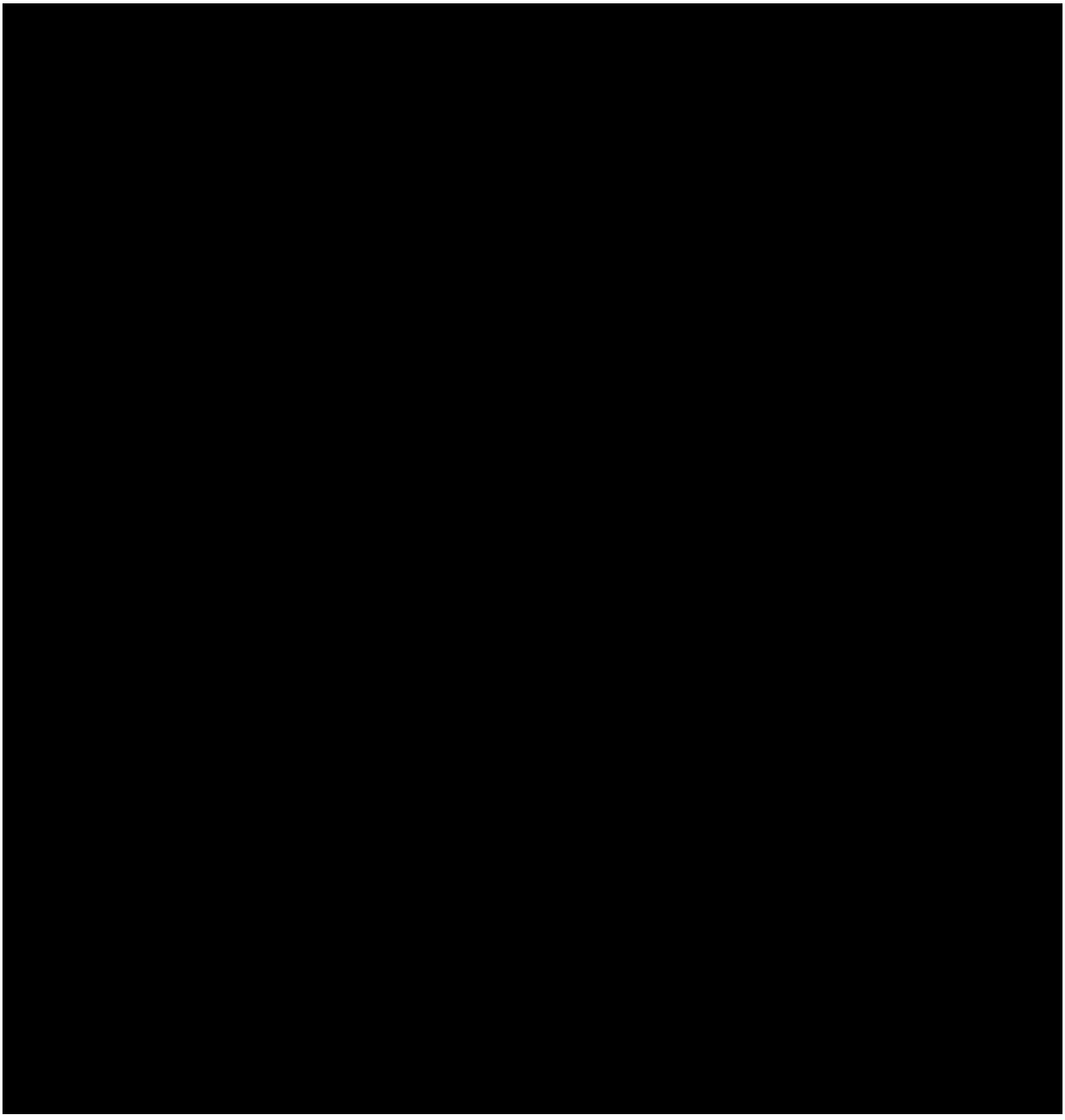
With the expectation of a 34% screening failure rate, approximately 1245 patients are expected to be screened. In the event that screening and/or randomization failure rates are higher than projected, enrollment will continue until approximately 126 patients per treatment arm are randomized. At the time the randomization target has been met, patients who have been screened, but are not yet randomized will be allowed to continue in the study until they complete the study, prematurely discontinue, or otherwise fail to meet randomization criteria.

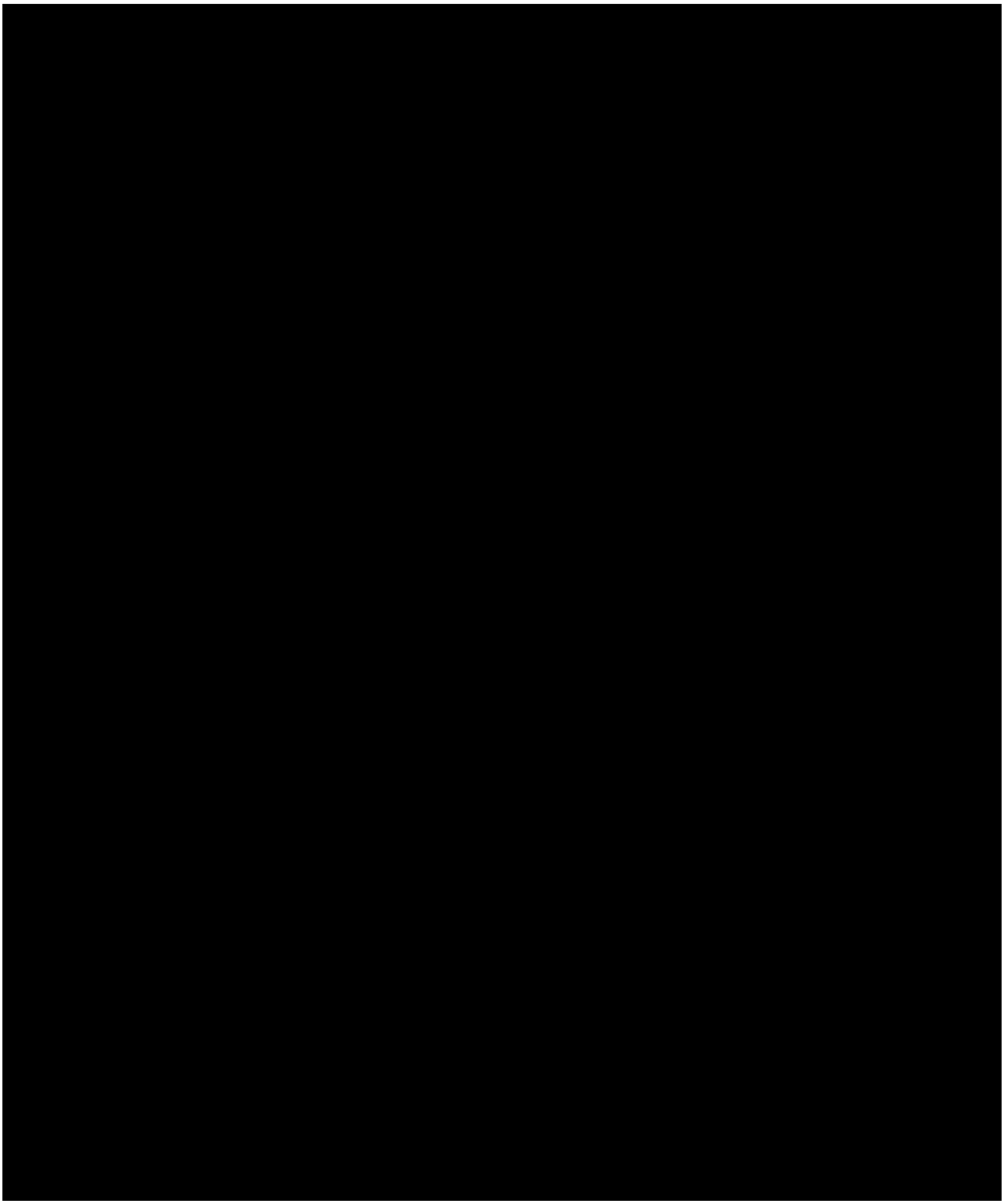
15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS on a Linux operating system.

16.0 DATA HANDLING CONVENTIONS







16.2 DERIVED EFFICACY VARIABLES AND SAFETY VARIABLES

If only a few item scores are missing, the total score will be calculated based on available item scores using the following formula: (total number of items in the scale) × (sum of nonmissing items / number of items with nonmissing values). The maximum number of missing items allowed for the total scores imputation is specified below.

- MADRS total score is the sum of the 10 items from the MADRS. If more than 2 items of the MADRS are missing, then the total score will be set to missing
- YMRS total score is the sum of the 11 items of the YMRS. If more than 1 item of the YMRS are missing, then the total score will be set to missing
- AIMS total score is the sum of the first 7 items of the AIMS. Possible range is 0 to 28, with each item ranging from 0 to 4. If more than 1 item of the first 7 AIMS items is missing, then the total score will be set to missing. Items 8 through 12 will be summarized separately (items 8-10 also range from 0-4 each, while items 11-12 are yes/no).
- SAS total score is the sum of the 10 items of the SAS. Possible range is 0 to 40, with each item ranging from 0 to 4. If more than 1 item for the SAS are missing, then the total score will be set to missing.
- BARS total score is the sum of the first 3 items (Q1, Q2a and Q2b) of the BARS. Possible range is 0 to 9, with each item ranging from 0 to 3. If any of these 3 BARS items is missing, then the total score will be set to missing. Q3 will be summarized separately as a single value score with possible range 0 to 5.

For the LOCF analysis, if a patient misses a postbaseline visit or if the postbaseline visit occurs outside the visit time window, a record for the scheduled visit will be imputed using the last nonmissing value immediately before the missing value. If the missing value occurs at Week 1, the baseline value will be carried forward for Week 1, provided that at least 1 subsequent postbaseline assessment is available. For a composite scale such as MADRS total score, individual items of a rating scale will not be carried forward. Only total scores will be carried forward using the last-observation-carried-forward approach.

Several ophthalmologic examinations were performed later than the visit dates of OLTP, hence the data will be reported by the examination dates within in the derived visit windows in the DBTP. Similarly, for the examination dates performed after the visit dates of DBTP, data will be reported in the SFU period according to the derived visit windows.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of OLTP, the results from the final nonmissing assessment made before the start of the OL IP will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.4 MISSING DATE OF THE LAST DOSE OF INVESTIGATIONAL PRODUCT

When the date of the last dose of OL IP is missing for a patient in the OL Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last visit date during the corresponding period will be used as the last dose date for the corresponding period.

When the date of the last dose of DB IP is missing for a patient in the DB Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last visit date will be used as the last dose date.

16.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of OL IP, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of OL IP, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.6 MISSING CAUSAL RELATIONSHIP TO INVESTIGATIONAL PRODUCT FOR ADVERSE EVENTS

If the causal relationship to the IP is missing for an AE that started on or after the date of the first dose of OL IP, a causality of yes will be assigned. The imputed values for causal relationship to OL or DB treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for Aes is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of OL IP, the month and day of the first dose of OL IP will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of OL IP, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of OL IP, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of OL IP, the day of the first dose of OL IP will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of OL IP or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of OL IP, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of OL IP or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of OL IP, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of OL IP, the date of the first dose of OL IP will be assigned to the missing start date

- If the stop date is before the date of the first dose of OL IP, the stop date will be assigned to the missing start date

16.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

16.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of OL IP, the month and day of the first dose of OL IP will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of OL IP, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of OL IP, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of OL IP, the day of the first dose of OL IP will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of OL IP or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of OL IP, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of OL IP or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of OL IP, the first day of the month will be assigned to the missing day

16.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date for a patient in the respective safety population (OL Safety Population or DB Safety Population). If the date of the last dose of IP in one of the periods is missing, replace it with the last visit date during the corresponding period in the imputations described below. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of IP, the month and day of the last dose of IP will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the last dose of IP, *December 31* will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the last dose of IP, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of IP, the day of the last dose of IP will be assigned to the missing day
- If either the year of the incomplete stop date is before the year of the date of the last dose of IP or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of IP, the last day of the month will be assigned to the missing day
- If either the year of the incomplete stop date is after the year of the date of the last dose of IP or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of IP, the first day of the month will be assigned to the missing day

16.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 16.9-1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 16.9-1. Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	***Possible Laboratory Results***	***Coded Value for Analysis***
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

SI = *Le Système International d'Unités* (International System of Units).

17.0 COVID-19 RELATED ANALYSIS

To eliminate immediate potential hazards to patients and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol clarification letter and corresponding protocol amendment were sent to sites during the pandemic to allow remote visits.

This section specifies analyses for evaluating the impact of COVID-19.

17.1 EFFICACY EVALUATION

For the assessment that are conducted remotely (eg, by telephone, telemedicine virtual visits, and video call) or in-home, the following assessments are required to be completed in the course of the remote visit: YMRS, MADRS, CGI-S, CGI-S, and PSP.

For patients in the OLTP of the study, the following assessments are also required:

- Visits 4 through 7 (as applicable): assessment of remission criteria
- Visit 5 through 8 (as applicable): assessment of stability criteria
- Visit 6 through 12 (as applicable): maintenance of stability
- Visits 10 through 12 (as applicable): assessment of randomization criteria

For patients in the DBTP of the study (Visit 13 through Visit 31/ET), assessment of relapse criteria is also required.

Minimal disruption is expected for the primary endpoint. To evaluate the missing rate for the additional endpoints at the end of OLTP and DBTP, the number of patients who missed the assessments due to COVID-19 will be summarized at each visit in the OL ITT or DB ITT population.

17.2 SAFETY AND OTHER EVALUATIONS

This section specifies analyses related to COVID-19 pandemic from the following aspects:

- Disposition
- Study visit (missing entire visit due to COVID-19 or missing assessments due to COVID-19)
- Protocol deviation
- Study drug disruption due to COVID-19

- TEAEs related with COVID-19 and supplemental signs and symptoms
- COVID-19 status (COVID-19 testing results or contact with a COVID-19 positive person)

OL Safety Population or DB Safety Population will be used for the planned analyses described above. The number of participants impacted by COVID-19 during the OLTP will be summarized overall and the number of participants impacted by COVID-19 during the DBTP will be summarized by treatment group and overall. In addition, the number of patients impacted by COVID-19 and their corresponding disposition status in the OLTP and DBTP will be summarized respectively.

The number of patients who missed at least one entire visit due to COVID-19 will be summarized overall for the OLTP and by treatment group and overall for the DBTP. Furthermore, the number of patients who missed at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, urine pregnancy test, vital signs, ECG, and ophthalmological assessments) and overall. Similar summaries will be provided by visit.

The number of patients with significant protocol deviation due to COVID-19 will be provided. The number of patients with study drug disruption due to COVID-19 will be provided as well. The number of participants with TEAEs related to coronavirus infection or coronavirus test positive will be provided. Supporting listings for the described analyses above will also be provided.

18.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

1. The definition of the DB ITT population in this document Section 6.7 was updated and overwrites the one specified in the Protocol Amendment 5, and reads as follows:

The DB ITT Population will consist of all who took at least 1 dose of DB IP and had at least 1 post-randomization assessment of the YMRS, MADRS, or CGI-S scores during the DBTP of the study, or had a relapse event.

2. The cutoff for the Age group in the SAP Section 7.4 was updated from 55 to 45 years old, due to imbalance between <55 and >=55 years based on the blinded data review. Now it reads as:

- Age group (< 45 years, ≥ 45 years).

19.0 REFERENCES

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20.0 APPENDICES

APPENDIX I. SAS PROGRAM FOR PRIMARY EFFICACY ANALYSIS

The primary efficacy analysis for time to relapse include (1) the log-rank test and (2) the Cox proportional hazards model with treatment group and modified index episode (manic or depressive) as the covariate. The sample SAS code for these analyses are provided below. Note in the dataset adtte (DB ITT population), variables trt02pn and trt02p are for the double-blind treatment group, episode is for the modified index episode, aval is for the time (days) to censor/relapse, and cnsr is for the status of censored (=0) or relapsed (=1).

(1) SAS program for log-rank test comparing treatment groups trt02pn=0 and =1:

```
proc lifetest data=adtte method=km;
   strata episode region/test=logrank group=trt02p diff=control('Placebo');
   time aval * cnsr(0);
   run;
```

(2) SAS program for Cox proportional hazard model:

```
proc phreg data=adtte;
   class trt02p (ref= 'Placebo') episode(ref='depressive') region;
   model aval * cnsr(0)= episode region trt02p/rl;
   contrast ' cariprazine 1.5 mg/d vs placebo Episode=depressive'    trt02p 1 0  episode 0/
estimate=exp e;
   contrast ' cariprazine 3.0 mg/d vs placebo Episode=depressive'    trt02p 0 1  episode 0/
estimate=exp e;
   contrast ' cariprazine 1.5 mg/d vs placebo Episode=manic'    trt02p 1 0  episode 1/ estimate=exp e;
   contrast ' cariprazine 3.0 mg/d vs placebo Episode=manic'    trt02p 0 1  episode 1/ estimate=exp e;
   ods output parameterestimates=pvval;
   run;
```

APPENDIX II. SAS PROGRAM FOR SENSITIVITY ANALYSES I AND II

The SAS program for Sensitivity Analyses II (delta-adjusted method) and III (placebo based pattern-mixed model) are presented as below. Note the program is for comparison of two treatment groups (eg. Dose1 vs. placebo):

```
/*************************************************************************************************************
Name:            Sensi.sas
Date:            18April2019
Description:     This analysis program performs the below sensitivity analyses for the primary
                 Efficacy parameter (time to relapse):

                 1. Delta-adjusted method (Zhao 2014)
                 2.  Placebo-based pattern mixture model (Lu, 2014 and 2015)


Datasets used:   (Note: This SAS program is for comparison between two treatment groups.)
                 adsl(AdaM), with the below variables:
                 Variable    Type    Len    Format       Informat    Label
                 ------------------------------------------------------------------------------------
                 AP02EDT     Num       8    YYMMDD10.                Period 02 End Date - DB
                 AP02SDT     Num       8    YYMMDD10.                Period 02 Start Date - DB
                 -
                 EOPH3STT    Char     20                             End of DB status
                 ITTDBFL     Char      1                             DB Intent-To-Treat Population
                 RANDDT      Num       8    YYMMDD10.                Date of Randomization
                 SUBJID      Char     20                $7.         Subject Identifier for the Study
                 RELAPSE     Char      8                             Relapse event
                 EPISODE     Char     20                             Index episode


                 adtte(AdaM), with the below variables:
                 Variable    Type    Len    Format       Informat    Label
                 ------------------------------------------------------------------------------
                 AVAL        Num       8                             Analysis Value, time to event
                 CNSR        Num       8                             Censor
                 PARAMN      Num       8                             Parameter (N)
                 SUBJID      Char     20                $7.         Subject Identifier for the Study
                 TRT02PN     Num       8                             Planned Treatment for DB
                 EPISODE     Char     20                             Index episode

Macro(s) called: (none)
Output files:    (none)
Revision:

*************************************************************************************************************/
libname ad '/sasdata/rgh/rgh25';

%let fllow=39;  ***planned minimum follow-up time***;
%let flhigh=39; ***planned maximum follow-up time***;

* obtain the planned follow-up time for each subject;

data a1;
set ads.adsl(keep=subjid randdt tr02sdt tr02edt eoph3stt relapse ittdbfl episode region
where=(ittdbfl='Y'));
durdb=tr02edt-randdt+1;
if index(upcase(EOPH3STT), 'COMPLETE')>0 then COMPDBFL="Y";
else COMPDBFL="N";
run;

proc freq data=a1;
    tables compdbfl*eoph3stt/list missing;    *patient disposition status;
run;

proc univariate data=a1 noprint;
    where COMPDBFL="N";
    var durdb;
    output out=b1 max=maxdurb;  *max duration for discontinued;
run;
```

```
proc sort data=a1 out=a2;
    by randdt;
run;

data b2;
    set a2 end=eof;
    retain franddt;
    format franddt yymmdd10.;
    if _n_=1 then do;
        franddt = randdt;
        set b1;
    end;
    if eof then do;
        lranddt = randdt;
        ta = lranddt - franddt; * duration of enrollment period;
        tfmin = %eval(&fllow.*7);
        tfmax = %eval(&flhigh.*7);
        output;
    end;
    keep franddt ta tfmin tfmax;
    label franddt="Randomization Date for First Randomized Subject"
          ta="Duration of Enrollment Period (days)"
          tfmin="Minimum Follow-up Time (days)"
          tfmax="Maximum Follow-up Time (days)";
run;

proc print data=b2 label;
    var franddt ta tfmin tfmax;
run;

data a3;
    set a1;
    if _n_=1 then set b2;
    e = randdt - franddt;   * enrollment time for the current subject;
    *if compynfl="Y" or index(upcase(trmspc),"26 WEEK")>0 then do; /* completed the study */
    if compdbfl="Y" then do;
        tf = durdb;
        complete=1;
    end;
    else do;   * relapsed or discontinued for other reasons;
        tf = min(ta - e + tfmin, tfmax);
        complete=0;
    end;
run;

data raw1;
    merge a3
          ad.adtte(keep=aval cnsr paramn subjid trt03pn where=(paramn=0));    ***paramn=0 corresponds
to time to relapse***;
    by subjid;
    status=(cnsr=0);
    rename subjid=subj trt03pn=treated aval=time tf=followup;
    keep subjid trt03pn cnsr status aval complete tf episode;
run;

* check number of events per treatment group;
proc freq data=raw1;
    tables treated*status/norow nocol nopercent;
run;

ods listing close;

* examine Bayesian analysis results to determine thinning;
proc phreg data=raw1;
    class episode;
    model time*status(0)=episode region treated;
    bayes piecewise=hazard;
run;

* ==> thin=10 is enough to achieve approx. indep. posterior samples;
%let thin=10; * thinning;
%let ninterval=8; * number of time intervals for piecewise exponential;
%let nimps=200; * number of imputations;
%let seed=314;
```

```
* obtain sample size in raw data;
proc sql noprint;
    select count(*) into :n from raw1;
quit;

data raw;
    set raw1(drop=subj);
    subj = _n_;
run;

options nonotes nosource;
ods noresults;
ods html close;
ods graphics off;

data bootid;    * dummy data set to store bootstrapped subject numbers;
    seed=123;
    do boot=0 to 100;
    do i=1 to &n;
        if boot=0 then subj=i;
        else do;
            call ranuni(seed, u);
            subj=ceil(&n*u); * bootstrapped subject number;
        end;
        output;
    end;
    end;
    call symput("seed", strip(put(seed,12.)));
    keep boot subj;
run;

* match the subject number to retrieve other subject-specific data;
proc sql noprint;
    create table bootsamp as
    select b.boot, a.subj, a.treated, a.followup, a.time, a.status a.complete a.episode
    from raw as a, bootid as b
    where a.subj=b.subj
    order by boot, subj;
quit;

* obtain posterior draws of model parameters from bootstrap samples;
proc phreg data=bootsamp;
    by boot;
    class episode region treated(ref='1');
    model time*status(0)=episode region treated;
    bayes nmc=%eval(&nimps*&thin) piecewise=hazard seed=314;
    ods output Partition=partitio PosteriorSample=postsamp;
run;
ods output close;

* Bootsamp data for both treatments
data bootsamp1;
set bootsamp;
if treated in (1,2); * Placebo Vs 1.5mg;
run;

data bootsamp2;
set bootsamp;
if treated in (1,3); * Placebo Vs 3.0;
if treated=3 then treated=2;
run;

/*Delta-Adjusted Method*/
%macro delta(postsamp=, bootsamp=, trt=, dataout=);

data postsam2;
    set &postsamp.;
    temp = (Iteration - 2000 - 1)/&thin + 1;
    _imputa_ = floor(temp);
    if _imputa_ = temp;
    rename &trt.=beta;
    keep boot _imputa_ lambda1-lambda&ninterval &trt.;
run;
```

```
*merge with raw data;
proc sql noprint;
    create table raw2 as
    select a.*, b.subj, b.treated, b.followup, b.time, b.status, b.complete, b.episode
    from postsam2 as a, &bootsamp. as b
    where a.boot=b.boot
    order by boot, _imputa_, subj;
quit;

* obtain maximum follow-up;
proc univariate data=&bootsamp. noprint;
    by boot;
    var time;
    output out=maxtime max=maxtime; * maximum survival time;
run;

* organize partition information;
proc transpose data=partitio out=partitit(drop=_name_ _label_)
    prefix=a;
    by boot;
    var UpperTime;
run;

data partitit;
    merge partitit maxtime;
    by boot;
    a&ninterval = maxtime+1;  * a large number to represent infinity;
    drop maxtime;
run;

data raw2;
    merge raw2 partitit;
    by boot;
run;

* impute censored event times for early dropouts;
data raw4;
    set raw2 end=eof;
    if _n_=1 then seed=789;
    retain seed;

    array a{&ninterval};
    array lambda{&ninterval};

    call ranuni(seed, u);
    do delta=0 to 2 by 0.147;
    nlogu = -log(u)/exp(treated*(beta+delta)); * MNAR;

    * no imputation needed for subjects with events or for completers;
    if status=1 or (status=0 and time=followup) then do;
        time3 = time;
        status3 = status;
    end;
    else do; * impute censored event time;
        * locate the time interval that contains the censoring time;
        j1 = 1;
        do while (time >= a[j1]);
            j1 = j1 + 1;
        end;

        * locate the time interval containing the censored event time;
        * cumulative hazard in the first interval;
        v = lambda[j1]*(a[j1] - time);
        j2 = j1;
        do while (nlogu > v and j2 < &ninterval);
            j2 = j2 + 1;    * cumulative hazard in current interval;
            v = v + lambda[j2]*(a[j2] - a[j2-1]);
        end;

        * obtain the event time;
        if j2 = j1 then
            u3 = nlogu/lambda[j1] + time; * event in interval j1;
        else
            u3 = a[j2] - (v - nlogu)/lambda[j2]; * event in interval j2;
```

```
        time3 = min(u3, followup);
        status3 = (u3 <= followup);
    end;
    output;
    end;

    if eof then call symput("seed", strip(put(seed,12.)));
    keep boot _imputa_ subj episode treated delta time3 status3;
run;

proc sort data=raw4;
    by boot _imputa_ delta;
run;

* perform log-rank test for each imputed data set;
proc lifetest data=raw4;
    by  boot _imputa_ delta;
    time time3*status3(0);
    strata episode region /test=logrank group=treated;
    ods output HomStats=lrdiff2 LogrankHomCov=vlrdiff2;
run;
ods output close;

data vlrdiff2;
set vlrdiff2;
new=input(treated, 8.);
drop treated;
rename new=treated;
run;

* combine numberator and denominator of the log-rank test;
data lrtest2;
    merge lrdiff2(where=(treated=1)) vlrdiff2(where=(treated=1));
    by boot _imputa_ delta;
    stderr = sqrt(_1);  * standard error of log-rank test statistic;
run;

proc sort data=lrtest2;
    by boot delta _imputa_;
run;

* use Rubin rule to make multiple imputation inference based on log-rank test;
proc mianalyze data=lrtest2;
    by boot delta;
    modeleffects logrank ;
    stderr stderr;
    ods output ParameterEstimates=milrtes2;
run;
ods output close;

* fit Cox model to each imputed data set;
proc phreg data=raw4;
    class episode;
    by  boot _imputa_ delta;
    model time3*status3(0)=episode treated;
    ods output ParameterEstimates=phest2;
run;
ods output close;

proc sort data=phest2;
    by boot delta _imputa_;
run;

* use Rubin rule to make multiple imputation inference based on Cox model;
proc mianalyze data=phest2(where=(parameter="treated"));
    by boot delta;
    modeleffects estimate;
    stderr stderr;
    ods output ParameterEstimates=miphest2;
run;
ods output close;

data miout2a;
    merge milrtes2(keep=boot delta probt)
          miphest2(keep=boot delta estimate stderr lclmean uclmean);
```

```
    by boot delta;
    plogrank = probt;
    hazardra = exp(estimate);
    hrlowerc = exp(lclmean);
    hrupperc = exp(uclmean);
    *drop probt estimate lclmean uclmean;
run;

proc sort data=miout2a out=miout2b;
    by delta boot;
    where boot>0;
run;

proc univariate data=miout2b noprint;
    by delta;
    var estimate;
    output out=miout2c std=StdErrbo;
run;

data miout2;
    merge miout2a(where=(boot=0)) miout2c;
    by delta;
    bhrlower = exp(estimate - 1.96*stderrbo);
    bhrupper = exp(estimate + 1.96*stderrbo);
    label stderrbo=" ";
run;

data &dataout.;
    format Analysis $20.;
    set miout2(in=b);
    analysis="Sensitivity";
    drop boot probt lclmean uclmean;
    format estimate stderr stderrbo bhrlower bhrupper 8.3;
run;

%mend;

%delta(postsamp=postsamp, bootsamp=bootsamp1, trt=treated2, dataout=sensi3);
%delta(postsamp=postsamp, bootsamp=bootsamp2, trt=treated3, dataout=sensi4);

* /*placebo-based pattern mixture model*/
%macro pattern(postsamp=, bootsamp=, trt=, dataout=);*;

data postsam2;
    set &postsamp.;
    *set postsamp;
    temp = (iteration - 2000 - 1)/&thin + 1;
    _imputa_ = floor(temp);
    if _imputa_ = temp;
    rename &trt.=beta;
         *rename treated2=beta;
    keep boot _imputa_ lambda1-lambda&ninterval &trt.;
run;

* merge with raw data;
proc sql noprint;
    create table raw2 as
    select a.*, b.subj, b.treated, b.followup, b.time, b.status, b.episode
    from postsam2 as a, &bootsamp. as b
    where a.boot=b.boot
    order by boot, _imputa_, subj;
quit;

* obtain maximum follow-up;
proc univariate data=&bootsamp. noprint;
    by boot;
    var time;
    output out=maxtime max=maxtime; * maximum survival time;
run;

* organize partition information;
proc transpose data=partitio out=partitit(drop=_name_ _label_) prefix=a;
    by boot;
    var uppertime;
run;
```

```
data partitit;
    merge partitit maxtime;
    by boot;
    a&ninterval = maxtime+1;  * a large number to represent infinity;
    drop maxtime;
run;

data raw2;
    merge raw2 partitit;
    by boot;
run;

* impute censored event times for early dropouts;
data raw3;
    set raw2 end=eof;
    if _n_=1 then seed=789;
    retain seed;

    array a{&ninterval};
    array lambda{&ninterval};

    call ranuni(seed, u);
    do phi=0 to 1 by 0.2;
    nlogu = -log(u)/exp(treated*(1-phi)*beta ); * MNAR;

    * no imputation needed for subjects with events or for completers;
    if status=1 or (status=0 and time=followup) then do;
        time3 = time;
        status3 = status;
    end;
    else do; * impute censored event time;
        * locate the time interval that contains the censoring time;
        j1 = 1;
        do while (time >= a[j1]);
            j1 = j1 + 1;
        end;

        * locate the time interval containing the censored event time;
        * cumulative hazard in the first interval;
        v = lambda[j1]*(a[j1] - time);
        j2 = j1;
        do while (nlogu > v and j2 < &ninterval);
            j2 = j2 + 1;    * cumulative hazard in current interval;
            v = v + lambda[j2]*(a[j2] - a[j2-1]);
        end;

        * obtain the event time;
        if j2 = j1 then
            u3 = nlogu/lambda[j1] + time; * event in interval j1;
        else
            u3 = a[j2] - (v - nlogu)/lambda[j2]; * event in interval j2;

        time3 = min(u3, followup);
        status3 = (u3 <= followup);
    end;
    output;
    end;

    if eof then call symput("seed", strip(put(seed,12.)));
    keep boot _imputa_ subj treated phi time3 status3 episode;
run;

proc sort data=raw3;
    by boot _imputa_ phi;
run;

* perform log-rank test for each imputed data set;
proc lifetest data=raw3;
    by boot _imputa_ phi;
    time time3*status3(0);
    strata episode region /test=logrank group=treated;
    ods output HomStats=lrdiff LogrankHomCov=vlrdiff;
run;
```

```
data vlrdiff;
set vlrdiff;
new=input(treated, 8.);
drop treated;
rename new=treated;
run;

* combine numberator and denominator of the log-rank test;
data lrtest1;
    merge lrdiff(where=(treated=1)) vlrdiff(where=(treated=1));
    by boot _imputa_ phi;
    stderr = sqrt(_1);  * standard error of log-rank test statistic;
run;

proc sort data=lrtest1;
    by boot phi _imputa_;
run;

* use Rubin rule to make multiple imputation inference based on log-rank test;
proc mianalyze data=lrtest1;
    by boot phi;
    modeleffects logrank ;
    stderr stderr;
    ods output ParameterEstimates=milrtest;
run;

* fit Cox model to each imputed data set;
proc phreg data=raw3;
    class episode;
    by boot _imputa_ phi;
    model time3*status3(0)=episode treated;
    ods output ParameterEstimates=phest1;
run;

proc sort data=phest1;
    by boot phi _imputa_;
run;

* use Rubin rule to make multiple imputation inference based on Cox model;
proc mianalyze data=phest1(where=(Parameter="treated"));
    by boot phi;
    modeleffects estimate ;
    stderr stderr;
    ods output ParameterEstimates=miphest;
run;

data miout1a;
    merge milrtest(keep=boot phi probt)
          miphest(keep=boot phi estimate stderr lclmean uclmean);
    by boot phi;
    plogrank = probt;
    hazardra = exp(estimate);
    hrlowerc = exp(lclmean);
    hrupperc = exp(uclmean);
    *drop probt estimate lclmean uclmean;
run;

proc sort data=miout1a out=miout1b;
    by phi boot;
    where boot>0;
run;

proc univariate data=miout1b noprint;
    by phi;
    var estimate;
    output out=miout1c std=StdErrbo;
run;

data miout1;
    merge miout1a(where=(boot=0)) miout1c;
    by phi;
    bhrlower = exp(estimate - 1.96*stderrbo);
    bhrupper = exp(estimate + 1.96*stderrbo);
    label stderrbo=" ";
run;
```

```
data &dataout.;
    format Analysis $20.;
    set mioutl(in=b);
    Analysis="Sensitivity";
    drop boot probt lclmean uclmean;
    format estimate stderr stderrbo bhrlower bhrupper 8.3;
run;

%mend;

/*Placebo Vs 3.0mg/day*/
%pattern(postsamp=postsamp, bootsamp=bootsamp1, trt=treated2, dataout=sensi1);
/*Placebo Vs 1.5mg/day*/
%pattern(postsamp=postsamp, bootsamp=bootsamp2, trt=treated3, dataout=sensi2);

data placebo;
        set sensi1(in=a) sensi2(in=b);
        if a then compare="Placebo Vs Cariprazine 1.5mg/day";
        if b then compare="Placebo Vs Cariprazine 3.0mg/day";
run;

title 'Placebo-based pattern mixture model (Lu, 2014, 2015)';
proc print data=placebo label;
    var analysis phi plogrank hazardra hrlowerc hrupperc;
    format plogrank  6.4;
run;

data delta;
        set sensi3(in=a) sensi4(in=b);
        if a then compare="Placebo Vs Cariprazine 1.5mg/day";
        if b then compare="Placebo Vs Cariprazine 3.0mg/day";
run;

title 'Delta-adjusted Method (Zhao, 2014)';
proc print data=delta label;
    var analysis delta plogrank hazardra hrlowerc hrupperc;
    format plogrank  6.4;
run;
```

APPENDIX III. REPORTING SELECTED LABORATORY PARAMETERS IN CONVENTIONAL UNITS

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table 20-1 below.

Table 20-1. List of Selected Parameters to be Reported in Conventional Units

Number	Laboratory Parameter	Conventional Unit
1	Alanine Aminotransferase (SGPT)	U/L
2	Albumin	G/dL
3	Alkaline Phosphatase	U/L
4	Aspartate Aminotransferase (SGOT)	U/L
5	Bilirubin, Direct (Conjugated)	mg/dL
6	Bilirubin, Indirect (Unconjugated)	mg/dL
7	Bilirubin, Total	mg/dL
8	Blood Urea Nitrogen	mg/dL
9	Calcium	mg/dL
10	Cholesterol, HDL	mg/dL
11	Cholesterol, LDL	mg/dL
12	Cholesterol, LDL direct and calculated (combined) (This lab parameter could be the same as #11)	mg/dL
13	Cholesterol, Total	mg/dL
14	Creatine Kinase	U/L
15	Creatinine	mg/dL
16	Glucose	mg/dL
17	Insulin	uIU/mL
18	Triglycerides	mg/dL
19	Uric Acid	mg/dL
20	Hemoglobin	G/dL

Patients narratives will also include the values in conventional units for the selected lab parameters. That might be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units.

APPENDIX IV. SAP AMENDMENT SUMMARY

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

Study RGH-MD-25 SAP Amendment #1 (28 February 2019)

Study RGH-MD-25 SAP Amendment #2 (13 June 2022)

Study RGH-MD-25 SAP Amendment #3 (23 November 2022)

Amendment Summary

This summary includes changes made to SAP RGH-MD-25 (11 October 2017).

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

SAP Amendment	Section	Major Revision	Rationale
#1	Global	*Depressive with or without mixed feature as one more current Episode was added.*	To align with Protocol Amendment #3. Depressive episodes have been included as potential index episodes following proven efficacy in bipolar I depression (RGH-MD-56 and RGH-MD-54).
#1	Global	*Doses (Open-Label Period – Changed from 4.5 mg to 3.0 mg; DB Period: 2 Cariprazine Dose arms are now: 3.0 mg and 1.5 mg) were changed.*	To align with Protocol Amendment #3. Depressive episodes have been included as potential index episodes, so OL dose was adjusted to reflect efficacy dose range in both bipolar I manic and bipolar I depressed patients.
#1	Section 4.0, Table 4-2	*Visit schedule was changed. Day 4 and Day 10 study visits were deleted and a Day 22 visit was added. Study Visits have been renumbered throughout entire amendment 2. Study days have been renumbered to allow 1 full week of dosing before Visit 3 (Day 8).*	Day 22 Visit was added to improve the potential to capture remission/stability criteria during the first weeks of OL treatment.

SAP Amendment	Section	Major Revision	Rationale
#1	Table 4-2	*Symbol Digit Coding (SDC) – additional efficacy assessment was deleted.*	Operational concerns, and clinical decision to remove cognitive battery
#1	Table 4-2	*Visit windows of +3 days for Visit 2/Baseline and ± 3 days for Visits 3 through 33 to the table header were added.*	For clarity
#1	Table 4-2	*"Blood Alcohol Level" was changed to "Blood Alcohol Concentration by Breathalyzer".*	To expedite turnaround time for blood alcohol concentration results
#1	Table 4-2	*Serum pregnancy tests at Visits 7, 18, 24, and 33 were added.*	For clarity and for consistency with approved labeling
#1	Table 4-2	*Text to clarify the timing of visits was added.*	For clarity
#1	Section 4.0, Section 10.1	*MADRS total score was changed from MADRS total score ≥ 17 to ≥ 20.*	To align MADRS discontinuation score with moderate depression. MADRS ≥ 17 is considered mild depression and may not be suggestive of a true depressive episode
#1	Section 6.4	*OL SFU population was added.*	For analysis clarity
#1	Section 6.6	*One paragraph "patients will be included in the treatment group corresponding to the DB IP they actually received regardless of the treatment they were randomized to" was added.*	For clarity
#1	Section 6.7	*One paragraph "patients will be included in the randomized treatment group for the DB ITT population" was added.*	For clarity
#1	Section 8.0	*The rescue medication categories were added.*	For clarity

SAP Amendment	Section	Major Revision	Rationale
#1	Section 10.1	*1.The primary analysis was updated to use stratified log-rank test instead of unstratified log-rank test* *2. The first sensitivity analyses was updated.*	1. To ensure each analysis stratum has sufficient number of events, the log-rank test is stratified by modified index episode (manic and depressed) only. 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). 2. Previous proposed first sensitivity analyses was deleted because of the duplication (time to all-cause discontinuation is one of other efficacy analyses in Section 7.3.3). Newly added delta-adjusted method by Zhao et al. (2014) aligned with the discussion with FDA for schizophrenia maintenance sNDA filing (based on single study RGH-MD-06).
#1	Section 11.1	*All text to define how Aes and TEAEs will be coded and summarized was replaced.*	To reflect current sponsor standards
#1	Section 11.1	*All text about NEAE was deleted.*	To reflect current sponsor standards
#1	Section 11.1	*All text about TESAE definition and related analysis was added.*	To reflect current sponsor standards
#1	Section 11.1	*The period for reporting of pregnancies during the study from 30 days after last dose was changed to approximately 12 weeks following last dose.*	These are standard components of a slit-lamp examination.
#1	Section 11.1	[redacted]	[redacted] updated before data base lock.
#1	Section m11.2	*The text for analysis of central lab transition during the clinical trial was added.*	The central lab was changed from Q2 to Covance during the clinical trial.
#1	Section 11.2	*The analysis for some urinalysis parameters was deleted.*	These urinalyses deleted were not measured.

SAP Amendment	Section	Major Revision	Rationale
#1	Section 11.2	*The analysis on some lab parameters in conventional units was added.*	To reflect current sponsor standards
#1	Section 14.0	*Sample size was changed.*	Sample size was modified for the following reasons 1. As the study population changed due to inclusion criteria changes, related assumptions were modified. The assumed probability of relapse in the placebo arm at Week 39 was updated to 50%. 2. The assumed hazard ratio was updated to reflect modified relapse data based on feedbacks from FDA review of maintenance filing for study RGH-MD-06.
#1	Table 16.1-1, Table 16.1-2, Table 16.1-3	*Analysis windows were changed.*	To align with updated visit schedule.
#1	Section 17.0	*Paragraphs to describe the changes to analyses specified in protocol were added.*	To align with Protocol Amendment #3.
#2	Table 4-2	Updated table.	To align with COVID-19 Global Protocol Addendum and Protocol Amendment #5
#2	Section 7.1	Added summary of number and percentage of patients in each analysis population.	For completeness
#2	Section 8.0	Defined baseline efficacy variables for OLTP and DBTP	For clarity
#2	Section 10.1	Added subgroup analyses for primary efficacy parameter by age group, sex, race, region and modified index episode.	Evaluate the efficacy in different subgroups
#2	Section 10.3	Listed additional efficacy parameters for OLTP and DBTP	For clarity
#2	Section 11.1	Added summary of TEAEs during the OL SFU period and DB SFU period	Evaluate safety in safety follow-up periods
#2	Section 11.2	Added summary for potential Hy's Law cases during the OLTP and DBTP.	Evaluate liver function tests
#2	Section 11.2	Added Table 11.2-2	Define criteria for treatment-emergent significant changes in glucose

SAP Amendment	Section	Major Revision	Rationale
#2	Section 11.2	Added Table 11.2-3	Define criteria for treatment-emergent significant changes in lipids
#2	Section 14.0	Revised assumptions for sample size determination	To align with protocol Amendment #5
#2	Section 16.1	Added Table 16.1-2	Define analysis windows in OLTP for lab and waist circumference parameters
#2	Section 16.1	Added Table 16.1-3	Define analysis windows in OLTP for PSP
#2	Section 16.1	Added Table 16.1-4	Define analysis windows in OLTP for EPS
#2	Section 16.1	Added Table 16.1-6	Define analysis windows in DBTP for lab and waist circumference parameters
#2	Section 16.1	Added Table 16.1-7	Define analysis windows in DBTP for PSP
#2	Section 16.1	Added Table 16.1-8	Define analysis windows in DBTP for WPAI-BD
#2	Section 16.1	Added Table 16.1-9	Define analysis windows in DBTP for EPS
#2	Section 17.0	New section specifying analyses for evaluating the impact of COVID-19	Evaluate impact of COVID-19
#3	Section 6.7	Updated the DB ITT population definition by including patients with relapse event but no efficacy assessments.	To account for relapses during the double-blind treatment period for patients without any efficacy assessments.
#3	Sections 10.1 and 10.3 and SAS codes in Appendices	Added 'region' to the models.	The study was stratified by region as well.
#3	Section 10.1	Updated age cutoff from 55 to 45 years.	Due to imbalance of age categories for 55 cutoff based on blinded data review.
#3	Section 10.1	New sensitivity analysis of primary endpoint, censoring ongoing Russian and Ukrainian participants after 24Feb2022.	Due to Russian-Ukrainian conflict that began on 24Feb2022.
#3	Section 10.1	Added 2 Kaplan-Meier figures.	To explore data further.
#3	Section 12.0	Updated text in WPAI.	WPAI description was missing.

SAP Amendment	Section	Major Revision	Rationale
#3	Section 12.0	Removed "The medical resource utilization and health economics assessments will be specified in a separate prospective analysis plan. "	No longer the process. HEOR now is part of this SAP document.
#3	Section 16.3	[redacted]	[redacted]