1.0 TITLE PAGE

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RGH-MD-24

A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED WITHDRAWAL, MULTICENTER CLINICAL TRIAL EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF CARIPRAZINE IN A DOSE-REDUCTION PARADIGM IN THE PREVENTION OF RELAPSE IN PATIENTS WITH SCHIZOPHRENIA

STATISTICAL ANALYSIS PLAN

Final Date: **12 Feb 2019**

Amendment #1: **7 June 2021**

2.0 TABLE OF CONTENTS

2.1 LIST OF TABLES

3.0 LIST OF ABBREVIATIONS

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
BACS	Brief Assessment of Cognition in Schizophrenia scale
BARS	Barnes Akathisia Rating Scale
BCVA	Best corrected visual acuity
BMI	Body mass index
CGI-I	Clinical Global Impressions–Improvement
CGI-S	Clinical Global Impressions–Severity
CI	Confidence interval
C-SSRS	Columbia–Suicide Severity Rating Scale
DB	Double-blind
DBTP	Double-blind treatment period
ECG	Electrocardiogram, electrocardiographic
eCRF	Electronic case report form
EPS	Extrapyramidal symptom
ET	Early termination
IOP	Intraocular pressure
IP	Investigational product
ITT	Intent to treat
LOCF	Last observation carried forward
NEAE	Newly emergent adverse event
OC	Observed cases
OL	Open-label
OLTP	Open-label treatment period
PANSS	Positive and Negative Syndrome Scale

PCS	Potentially clinically significant
PID	Patient identification
PSP	Personal and Social Performance Scale
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SAP	Statistical analysis plan
SCI-PANSS	Structured Clinical Interview for the Positive and Negative Syndrome Scale
SD	Standard deviation
SFU	Safety follow-up
SI	*Le Système International d'Unités* (International System of Units)
sNDA	Supplemental New Drug Application
TEAE	Treatment-emergent adverse event

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 original protocol of Study RGH-MD-24 (version dated 28 June 2017) and its most recent amendment #4 dated 17 December 2019. On 14 DEC 2020, FDA provided Type C Written Response in which they agreed to release Allergan of the postmarketing requirement (PMR 2947-9) to conduct Study RGH-MD-24, based on new information obtained since initial Vraylar approval in SEP 2015. Study RGH-MD-24 was thus early terminated. The analyses for abbreviated CSR are specified in Appendix IV.

Study RGH-MD-24 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 patients with schizophrenia. The key inclusion criteria are listed below: male or female 18 to 64 years of age, inclusive; meeting DSM-5 criteria for schizophrenia, whose current psychotic episode is < 4 weeks in duration at Visit 1; and having a Positive and Negative Syndrome Sale (PANSS) total score ≥ 70 and ≤ 120 at Visits 1 and 2, and a rating of at least 4 (moderate) on at least 2 of the following 4 PANSS positive symptoms; P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior, and P6: suspiciousness/persecution at Visits 1 and 2.

The length of this study will be up to 49 weeks, including a screening period of up to 7 days, followed by an up-to-18-week open-label treatment period (OLTP), and a 26-week double-blind treatment period (DBTP) and a 4-week safety follow-up (SFU) period. The details could be found in the protocol Section 3.

Screening/Washout Period: Patients meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for schizophrenia will undergo a screening/washout period up to 7 days, during which consent, assessment of eligibility, and withdrawal of prior psychiatric and prohibited medications will occur. Patients may be hospitalized during initiation of the study. This hospitalization can be for up to 14 days during the screening and OLTP (with the end of hospitalization no later than Day 8 of the OLTP).

Open-label Treatment Period: Patients who continue to meet eligibility criteria at Visit 2/Baseline will enter an OLTP for up to 18 weeks. Patients need to respond to initial treatment (attain response threshold) and subsequently meet stability (confirmation of response threshold criteria at the subsequent visit) and then maintain it for an additional 8 weeks before being randomized.

Patients will receive OL cariprazine dosed as 1.5 mg/d beginning at Visit 2; titrated to 3.0 mg/d at Visit 3 (Day 8) and then titrated to 4.5 mg/d at Visit 4 (Week 2). Patients will continue on the 4.5 mg/d dose for the remainder of the OLTP. Following the dose increase to 4.5 mg/d, if there are significant tolerability issues, the investigator should utilize rescue medications as clinically appropriate. If further tolerability issues arise, a temporary drug holiday up to 3 days, patients who are unable to tolerate the 4.5 mg/d must be discontinued. Beginning at Visit 6 (Week 4), patients will be assessed for attainment of response threshold.

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

Safety Follow-up 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 Visits 27 (Week 46) and 28 (Week 48) during the SFU period. During the SFU period, patients will continue as outpatients and will receive treatment as usual at the discretion of the investigator or designee. Patients will not receive investigational product (IP) during the SFU period.

Treatment regimen and dosing is provided in protocol Section 5.5. The schedule of evaluations is presented in Table 4-1 and Table 4-2.

Approximately 345 patients are planned to be randomized (115 patients per arm) in a 1:1:1 ratio to Cariprazine 4.5 mg/d, Cariprazine 3 mg/d, and Placebo groups. Stratified randomization by site with a block size 3 will be used which is a process upon randomization of the first subject at a given site, an entire block of randomization will be assigned to that site. The system will assign the lowest available randomization number within that block to each subject randomized at that site. Additional blocks will be assigned to the site only when necessary. The stratified randomization by site will ensure that the treatment allocation is maintained across the study, and within each site.

Specifications of tables, figures, and data listings are contained in a separate document.

Table 4-1. Schedule of Visits and Procedures—Screening/Washout and Open-label Treatment Periods

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

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

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

[a] Verified Clinical Trials database check to be performed where applicable.
[b] For women of childbearing potential only.
[c] Blood pressure and pulse rate will be measured both standing and supine.
[d] The Screening ophthalmological examination must be completed prior to Visit 2/Baseline and the start of OL IP.
[e] For patients eligible for randomization, every attempt should be made to complete the Visit 13/End of OL ophthalmological examination on the same day as all other Visit 13/End of OL procedures. If the examination cannot be accommodated, it must occur within 7 days after randomization.
[f] Assess response threshold criteria beginning at Visit 6/Week 4. Patients who do not meet response threshold criteria by Visit 8/Week 8 must be discontinued and will undergo procedures for Visit 26/early termination (ET) and subsequently complete the Safety follow-up (SFU) period.
[g] Assess patient for attainment of stability criteria. If response threshold criteria are met but are not confirmed at the subsequent visit (ie, stability is not attained), reassess patient for attainment of stability (reconfirmation of response threshold criteria) at the next visit. Patients not meeting the response threshold criteria following the excursion must be discontinued. Patients who do not otherwise meet stability of response threshold criteria by Visit 9/Week 10 must be discontinued and will undergo procedures for Visit 26/ET and subsequently complete the SFU period.
[h] Assess PANSS and CGI-S during the 8-week period following achievement of stability to ensure that response threshold criteria continue to be met. During the 8 weeks, 1 excursion is allowed.
[i] Patients who have met stability of maintenance criteria should be assessed for fulfillment of randomization criteria. Patients who meet randomization criteria should undergo Visit 13/End of OL procedures and be randomized to DB treatment. Patients eligible for early randomization will skip any remaining visits in the OL treatment period.
[j] Pharmacogenetic consent may be obtained at any time between Visit 1/Screening and Visit 8/Week 8.
[k] Pharmacogenetic sampling (one sample) may be obtained at any time between Visit 2/Baseline and Visit 8/Week 8.

Table 4-2. Schedule of Visits and Procedures—Double-blind Treatment Period

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

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

Note: If necessary, Visits 14 to 28 may be conducted up to 3 days before or after the scheduled visits. The visit windows for each scheduled visit are relative to Visit 13 for Visits 14 through 26/ET, and relative to Visit 26/ET for Visits 27 and 28.
AE = adverse event; AIMS = Abnormal Involuntary Movement Scale; BACS = Brief Assessment of Cognition in Schizophrenia scale; BARS = Barnes Akathisia Rating Scale; CGI-I = Clinical Global Impression-Improvement scale; CGI-S = Clinical Global Impression-Severity scale; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; EPS = extrapyramidal symptoms; ET = early termination; IP = investigational product; SCI-PANSS = Structured Clinical Interview for the Positive and Negative Syndrome Scale; PSP = Personal and Social Performance scale; SAE = serious adverse event; SAS = Simpson-Angus Scale.

[a] For women of childbearing potential only.

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

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

5.0 OBJECTIVES

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

2) To evaluate the efficacy and safety of cariprazine at a target dose of 3.0 mg/d compared with placebo in prevention of relapse in patients with schizophrenia who were initially stabilized on a target dose of 4.5 mg/d.

6.0 ANALYSIS 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 PANSS or Clinical Global Impressions–Severity (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 and completed at least one visit in the SFU period.

6.5 RANDOMIZED POPULATION

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

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 patients who took at least 1 dose of DB IP and had at least 1 post-randomization assessment of the PANSS or CGI-S scores during the DBTP of the study.

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 the Visit 13/end of OLTP (Week 18) or early termination (ET) before Visit 13 (Week 18) for patients who do not enter the DBTP; or 1 day before 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 26 (Week 44) 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 27 (Week 46) or Visit 28 (Week 48) 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 respective disposition pages of the electronic case report form (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 DB treatment group and by reasons for premature discontinuation as recorded on the respective disposition pages 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 (age; age group; region; race; ethnicity; sex; weight; height; and body mass index [BMI], calculated as weight [kg]/(height [m])^2) and other baseline characteristics (medical and surgical history, psychiatric disorders, , and nondrug psychiatric treatment) 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.

Continuous variables will be summarized by number of patients and mean, standard deviation (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 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 OLTP 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, SD, 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, SD, 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, SD, 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 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, Q1, Q3, 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, Q1, Q3, 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 non-missing 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 during the DBTP, defined as the number of days from the randomization date to the first relapse date. Relapse during the DBTP will be defined as the occurrence of any of the following:

- Increase in PANSS total score by ≥ 30% for patients who had a PANSS total score of ≥ 50 at Randomization/Visit 13 (Week 18) or a ≥ 10-point increase in PANSS total score for patients who had a PANSS total score < 50 at Randomization/Visit 13 (Week 18)

- Increase in CGI-S score by 2 or more points relative to Randomization/Visit 13 (Week 18)

- Score of > 4 on 1 or more of the following 7 PANSS items: P1: delusions; P2: conceptual disorganization; P3: hallucinatory behavior; P6: suspiciousness/persecution; P7: hostility; G8: uncooperativeness; G14: poor impulse control

- Deliberate self-injury or aggressive/violent behavior

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

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

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

Patients who did not meet the above relapse criteria will be censored at the time of completion or discontinuation from the study.

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

The fixed-sequence testing procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. The comparison of cariprazine 4.5 mg/d versus placebo for the primary endpoint will be tested first at a 0.05 significance level using the log rank test; the comparison of cariprazine 3.0 mg/d versus placebo will be tested only when the test for cariprazine 4.5 mg/d versus placebo is significant at 0.05 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 is delta-adjusted imputation method (Zhao 2014). The delta-adjusted sensitivity analysis specifies that the hazard of having an event for subjects who discontinued before the timepoint is multiplicatively increased relative to the hazard for subjects who continued beyond the timepoint for the cariprazine treatment group. The second sensitivity analysis is based on the reference-based imputation method (Lu 2015). The reference-based sensitivity analyses use a sensitivity parameter to characterize the gradual deviation from the noninformative censoring underlying the primary analyses toward the informative censoring, which assumes that the hazard of relapse for cariprazine-treated patients who discontinued is the same as the hazard for relapse for placebo-treated patients. A multiple imputation approach will be used to implement the sensitivity analyses. Details for two sensitivity analyses including SAS codes were provided in Appendix II.

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

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

SAS codes for planned analyses of the primary efficacy variable were provided in Appendix I and Appendix II.

10.2 SECONDARY EFFICACY PARAMETER

Not applicable.

10.3 ADDITIONAL EFFICACY PARAMETERS

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

- Change from baseline in the PANSS total score
- Change from baseline in PANSS positive subscale score
- Change from baseline in PANSS negative subscale score
- Change from baseline in PANSS factor score for positive symptoms
- Change from baseline in PANSS factor score for negative symptoms
- Percentage response (PANSS improvement ≥ 30%)
- Change from baseline in the CGI-S score
- Clinical Global Impressions–Improvement (CGI-I) score

- Change from baseline in the Brief Assessment of Cognition in Schizophrenia scale (BACS) individual subtest scores
- Change from baseline in BACS composite score Z score
- Change from baseline in the BACS composite T score
- Change from baseline in personal and social performance (PSP) score and sub-domain scores

For the continuous endpoints, 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 CGI-I, the OL baseline CGI-S value will be used as the baseline variable.

Descriptive statistics for additional quantitative 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 cases (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 continuous variables (change from DB baseline) will be analyzed by using a mixed-effects model for repeated measures (MMRM) with treatment group, country, visit, and treatment group-by-visit interaction as fixed effects and the baseline value and baseline-by-visit interaction as the covariates. An unstructured covariance matrix will be used. The Kenward-Roger approximation (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.

Within regions, countries will be ranked on number of patients that are part of the ITT population and lowest ranked countries will be pooled (sequentially, ie, a new ranking is made after each step) until the smallest pooled country has reached at least 2 patients in each arm.

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

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

11.0 SAFETY ANALYSES

The safety analyses will be performed for the OL safety, OL SFU and DB safety populations. The summarization will be overall for the 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 population or the DB safety population as the denominator respectively.

Safety parameters will include adverse events (AEs), clinical laboratory parameters, vital signs, Electrocardiographic (ECG) parameters, ophthalmological parameters, Columbia–Suicide Severity Rating Scale (C-SSRS), and EPS scales, including Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Scale (SAS).

For each safety parameter, the last assessment made before the first dose of OL IP will be used as the baseline for all analyses of that safety parameter, unless stated otherwise. 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 21.1 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 TESAE if it is a TEAE that additionally meets any 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 any 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 changes 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)
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 11-1. 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 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 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 and Table 11-3. 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.

Table 11-1 Criteria for Potentially Clinically Significant Laboratory Tests

Laboratory Parameter	*SI Units*	*Conversion Factor*[a]	*Traditional Units*	*PCS Criteria*[b] *Low Values*	*PCS Criteria*[b] *High Values*
Hematology					
Hemoglobin	g/L	0.1	g/dL	< 0.9 × LLN	—
Hematocrit	volume fraction	100	%	< 0.9 × LLN	—
Eosinophils	%	1	%	—	> 10
Neutrophils	%	1	%	< 30	> 90
Basophils	%	1	%	—	> 6
Monocytes	%	1	%	—	> 20
Lymphocytes	%	1	%	< 10	> 60
Abs Neutrophils (ANC)	10^9/L	1	1000/µL	< 1.0	—
Platelet count	10^9/L	1	1000/µL	≤ 75	≥ 700
White blood cell count	10^9/L	1	1000/µL	≤ 2.5	≥ 15
Chemistry					
Albumin	g/L	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN
Alkaline phosphatase	U/L	1	U/L	—	≥ 3 × ULN
ALT	U/L	1	U/L	—	≥ 3 × ULN
AST	U/L	1	U/L	—	≥ 3 × ULN
GGT	U/L	1	U/L	—	≥ 3 × ULN
LDH	U/L	1	U/L	—	≥ 3 × ULN
Blood urea nitrogen	mmol/L	2.8011	mg/dL	—	> 1.2 × ULN
Calcium	mmol/L	4.008	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	1	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Cholesterol	mmol/L	38.6698	mg/dL	—	> 1.3 × ULN
HDL	mmol/L	39	mg/dL	< 0.8 × LLN	—
LDL	mmol/L	39	mg/dL	—	> 1.2 × ULN
CPK	U/L	1	U/L	—	> 1.5 × ULN
Creatinine	µmol/L	0.0113	mg/dL	—	> 1.3 × ULN
Glucose, fasting	mmol/L	18.018	mg/dL	< 0.8 × LLN	> 1.2 × ULN
Magnesium	mmol/L	2	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Total bilirubin	µmol/L	0.0585	mg/dL	—	> 1.5 × ULN
Total protein	g/L	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN
Triglycerides, fasting	mmol/L	88.4956	mg/dL	—	> 1.2 × ULN
Uric acid	µmol /L	0.0168	mg/dL	—	> 1.1 × ULN
Urinalysis					
Protein	—	—	—	—	At least 2 +
Glucose	—	—	—	—	At least 2 +
Blood	—	—	—	—	At least 2 +

a Conversion factor from SI units to traditional units.

b Criteria refer to SI units.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LLN = lower limit of normal laboratory reference range; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal laboratory reference range.

Table 11-2 Criteria for Treatment-emergent Significant Changes in Glucose

Criteria	*Baseline*	*Postbaseline*
Fasting Serum Glucose		
Normal to High	< 100 mg/dL	≥ 126 mg/dL
Impaired Fasting Glucose to High	100-125 mg/dL	≥ 126 mg/dL
Normal/Impaired Fasting Glucose to High	< 126 mg/dL	≥ 126 mg/dL
Change in fasting serum glucose ≥ 10 mg/dL at any time postbaseline	Any value	increase from baseline ≥ 10 mg/dL
Non-Fasting Serum Glucose		
Normal to High	< 140 mg/dL	≥ 200 mg/dL
Borderline to High	140-199 mg/dL	≥ 200 mg/dL
Normal to Borderline/High	< 140 mg/dL	≥ 140 mg/dL
Normal/Borderline to High	< 200 mg/dL	≥ 200 mg/dL
Change in non-fasting serum glucose ≥ 20 mg/dL at any time postbaseline	Any value	increase from baseline ≥ 20 mg/dL

Table 11-3 Criteria for Treatment-emergent Significant Changes in Lipids

Criteria	*Baseline*	*Postbaseline*
Total Cholesterol (Fasting and Non-Fasting)		
Normal to High	< 200 mg/dL	≥ 240 mg/dL
Borderline to High	≥ 200 and < 240 mg/dL	≥ 240 mg/dL
Normal/Borderline to High	< 240 mg/dL	≥ 240 mg/dL
Normal to Borderline/High	< 200 mg/dL	≥ 200 mg/dL
LDL Cholesterol (Fasting)		
Normal to High	< 100 mg/dL	≥ 160 mg/dL
Borderline to High	≥ 100 and < 160 mg/dL	≥ 160 mg/dL
Normal/Borderline to High	< 160 mg/dL	≥ 160 mg/dL
Normal to Borderline/High	< 100 mg/dL	≥ 100 mg/dL
HDL Cholesterol (Fasting and Non-Fasting)		
Normal to Low	≥ 40 mg/dL	< 40 mg/dL
Triglycerides (Fasting)		
Normal to High	< 150 mg/dL	≥ 200 mg/dL
Normal to Very High	< 150 mg/dL	≥ 500 mg/dL
Borderline to High	≥ 150 and < 200 mg/dL	≥ 200 mg/dL
Borderline to Very High	≥ 150 and < 200 mg/dL	≥ 500 mg/dL
Normal/Borderline to High	< 200 mg/dL	≥ 200 mg/dL
Normal/Borderline to Very High	< 200 mg/dL	≥ 500 mg/dL
Normal to Borderline/High/Very High	< 150 mg/dL	≥ 150 mg/dL
Treatment-emergent very high triglycerides (fasting)	Fasting triglycerides < 500 mg/dL	Fasting triglycerides ≥ 500 mg/dL

Table 11-3 Criteria for Treatment-emergent Significant Changes in Lipids

Criteria	*Baseline*	*Postbaseline*
Total Cholesterol (Fasting and Non-Fasting)		
Treatment-emergent very high triglycerides (non-fasting and random)	< 500 mg/dL	≥ 500 mg/dL
Treatment-emergent triglycerides > 1000 mg/dL (All cases—fasting, non-fasting, and random)	Triglycerides < 1000 mg/dL	Triglycerides ≥ 1000 mg/dL
Change in fasting or non-fasting total cholesterol ≥ 40 mg/dL at any time postbaseline	Any value	Increased ≥ 40 mg/dL
Change in fasting LDL cholesterol ≥ 30 mg/dL at any time postbaseline	Any value	Increased ≥ 30 mg/dL
Change in fasting or non-fasting HDL cholesterol ≥ 20 mg/dL at any time postbaseline	Any value	Decreased ≥ 20 mg/dL
Change in fasting triglycerides ≥ 50 mg/dL at any time postbaseline	Any value	Increased ≥ 50 mg/dL

11.3 VITAL SIGNS

Descriptive statistics (n, mean, SD, minimum, median, 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 11-4. 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 11-4 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, SD, 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 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 11-5. The number and percentage of patients with PCS postbaseline ECG values will be tabulated 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, 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 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 11-5 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/ $(RR)^{½}$); QTcF = QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/ $(RR)^{⅓}$).

11.5 OTHER SAFETY PARAMETERS

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

11.6 OPHTHALMOLOGIC PARAMETERS

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

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for each numeric ophthalmologic parameter and changes from baseline at each assessment time point will be presented overall for the OLTP and by treatment group for the DBTP.

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

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

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

supportive listing will be provided, including PID number, baseline and postbaseline assessment values.

In addition, a shift table from normal baseline to abnormal postbaseline in color discrimination, slit-lamp biomicroscopy examination results will be provided overall for the OLTP and by treatment group for the DBTP.

11.7 COLUMBIA-SUICIDE SEVERITY RATING SCALE

For the C-SSRS, the number and percentage of patients with suicidal ideation or suicidal behavior, as recorded on the C-SSRS scale, will be presented. The distribution of response for most severe suicidal ideation and suicidal behavior during the lifetime history, the OLTP, and the DBTP will be presented. 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 during DBTP will also be provided.

11.7.1 Extrapyramidal Symptom Scales

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

Descriptive statistics (n, mean, SD, minimum, median, and maximum) for EPS scale parameters (AIMS, BARS, and SAS) and changes from baseline values at each assessment timepoint in this study will be presented overall for the OLTP and by treatment group for the DBTP.

12.0 HEALTH OUTCOMES ANALYSES

Not applicable.

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 in the DBTP to compare each cariprazine dose group versus placebo using a log-rank test. The trial will be a fixed follow-up design. Patients are followed from randomization until dropout, relapse or a fixed duration of 26 weeks.

Based on the results from RGH-MD-06, the relapse hazard ratio is assumed to be 0.50, and cumulative relapse rate at Week 26 for the placebo group is 46% (Study RGH-MD-06, 2015). In addition, the cumulative dropout rate due to reasons other than relapse at 26 weeks is assumed to be 20%.

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

A fixed-sequence procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. First, the cariprazine 4.5 mg/d group will be compared with the placebo group in the primary endpoint; if the test for cariprazine 4.5 mg/d versus placebo is significant at the 0.05 level, then cariprazine 3.0 mg/d arm will be tested versus placebo at 0.05 level.

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

15.0 STATISTICAL SOFTWARE

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

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

Table 16-1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 16-1 Visit Time Windows

Derived Visit	**Open-label Period**	
	Scheduled Visit Day Relative to the first dose of OL IP	**Window**
OL Baseline	Day 1	Days ≤ 1
OL Week 1	Day 8	Days [2, *11*]
OL Week 2	Day 15	Days [*12*, *18*]
OL Week 3	Day 22	Days [*19*, *25*]
OL Week 4	Day 29	Days [*26*, *35*]
OL Week 6	Day 43	Days [*36*, *49*]
OL Week 8	Day 57	Days [*50*, *63*]
OL Week 10	Day 71	Days [*64*, *77*]
OL Week 12	Day 85	Days [*78*, *91*]
OL Week 14	Day 99	Days [*92*, *105*]
OL Week 16	Day 113	Days [*106*, *119*]
OL Week 18	Day 127	120 ≤ days ≤ the day of the last visit during the OL period*
End of the OL Period [a]	Last Assessment during the OL	
	Double-blind Period	
	Scheduled Visit Day Relative to the first dose of DB IP	**Window**
DB Baseline (for efficacy endpoints only)	Day 1	Days ≤ 1
DB Week 2	Day 15	Days [2, *21*]
DB Week 4	Day 29	Days [*22*, *35*]
DB Week 6	Day 43	Days [*36*, *49*]
DB Week 8	Day 57	Days [*50*, *63*]
DB Week 10	Day 71	Days [*64*, *77*]
DB Week 12	Day 85	Days [*78*, *91*]
DB Week 14	Day 99	Days [*92*, *105*]
DB Week 16	Day 113	Days [*106*, *119*]

Derived Visit	**Open-label Period**	
	Scheduled Visit Day Relative to the first dose of OL IP	**Window**
DB Week 18	Day 127	Days [*120*, *133*]
DB Week 20	Day 141	Days [*134*, *147*]
DB Week 22	Day 155	Days [*148*, *161*]
DB Week 24	Day 169	Days [162, *175*]
DB Week 26	Day 183	176 ≤ days ≤ the day of the last visit during the DB period
End of the DB period [a]	Final or Termination Visit during the double-blind treatment period	
	Safety-follow-up (SFU) Period[b]	
	Scheduled Visit Day Relative to the start of SFU	**Window**
SFU Week 2[b]	Day 15	+1 ≤ days ≤ 21
SFU Week 4[b]	Final or Termination Visit of the study *after day 21*.	

OL Day 1 = the date of the first dose of open-label investigational product;

DB Day 1 = the date of the first dose of double-blind investigational product. There is no Day 0.

a Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.

b Presented in analysis tables for vital signs.

OL = Open Label; DB = Double-blind; SFU= Safety Follow-up; ET = Early Termination; IP = Investigational Products.

* All the available OL week 18/visit 13 Ophthalmological examination will be mapped to the OL safety period.

If a patient has 2 or more visits within the same window, the last visit with a non-missing value will be used for analysis.

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 non-missing items / number of items with non-missing values). The maximum number of missing items allowed for the total scores imputation is specified below.

Structured Clinical Interview for the Positive and Negative Syndrome Scale Total Score

The total score is derived as the sum of the 30 items (P1-P7, N1-N7, and G1-G16) of the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS). If more than 3 items for the SCI-PANSS total score are missing, then the total score will be set to missing.

Structured Clinical Interview for the Positive and Negative Syndrome Scale Positive Score
The score is the sum of the 7 items (P1-P7) of the SCI-PANSS. If any item for the SCI-PANSS positive score is missing, the respective score will be set to missing.

Structured Clinical Interview for the Positive and Negative Syndrome Scale Negative Score
The score is the sum of the 7 items (N1-N7) of the SCI-PANSS. If any item for the SCI-PANSS negative score is missing, the respective score will be set to missing.

PANSS factor score for negative symptoms
The score is the sum of questions N1, N2, N3, N4, N6, G7, and G16. If any sub item is missing, the PANSS factor score for negative symptoms will be missing.

PANSS factor score for positive symptoms
The score is the sum of questions P1, P3, P5, P6, and G9. If any sub item is missing, the PANSS factor score for positive symptoms will be missing.

PANSS Responder
PANSS responder is defined as patients with 30% or more improvement in PANSS total score relative to baseline.

Abnormal Involuntary Movement Scale Total Score
The total score is the sum of the first 7 items of the AIMS. If more than 1 item for the AIMS (items 1-7) is missing, then the total score will be set to missing. Items 8 through 12 will be summarized separately

Simpson-Angus Scale Total Score
The total score is the sum of the 10 items of the SAS. If more than 1 item for the SAS is missing, the total score will be set to missing.

Barnes Akathisia Rating Scale Total Score
The total score is the sum of the first 3 items of the BARS. If any item for the BARS (items 1-3) is missing, the total score will be set to missing.

Brief Assessment of Cognition in Schizophrenia Composite Score
BACS includes 6 subtests: verbal memory (0-75), digit sequencing task (0-28), token motor task (0-100), verbal fluency (≥ 0), symbol coding (0-110), and tower of London (0-22). The BACS composite score is an average of the standardized scaled score from each of 6 subtests with sex (male and female) and age group (18-29, 30-39, 40-49, 50-59, and 60-64) adjusted.

Let X_{ij} be the raw score on the test j (j=1 to 6) for subject i. Assume that subject i has sex m (1= male and 2 = female) and is in age category n (1= 18-39, 2=40-40, 3=50-59, and 4=60-64 years). The scaled score for subject i on test j is computed as follows:

$$C_{ij}=(X_{ij}-M_{mnj})/\mathrm{SD}_{mnj},$$

where M_{mnj} and SD_{mnj} are the mean and SD for test j, respectively, of the index population for sex m and age category n.

The composite Z score for subject i is calculated as following:

$$Z_i = \sum_{j=1}^{6} Cij \Big/ SD_{mn},$$

where SD_{mn} is the SD for all tests of the index population for sex m and age category n.

The composite T score for subject i is calculates as $T_i = 10 * Z_i + 50$.

If more than 1 subtest for the BACS is missing, then the composite Z score and T score will be set to missing. 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 LOCF approach, only the postbaseline total score of a parameter will be imputed; individual item score will not be carried forward. Baseline total score will be carried forward only for the intermittent missing scores immediately after baseline. If all the postbaseline values are missing, baseline value will not be carried forward.

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 non-missing assessment made before the start of the OL IP will be used as OL baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing 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 Phase Safety Population, all efforts should be made to obtain the date from the Investigator. 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 ***available dosing record date*** during the corresponding period will be used as the last dose date for the corresponding period.

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 open-label 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 open-label 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 open-label 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 open-label IP, the day of the first dose of open-label 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 and then the stop date will be imputed. If the imputed start date is after the imputed stop date, the imputed stop date will be equal to the imputed start date.

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 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 open-label 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 non-imputed 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.

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

In Section 11.1 (Adverse Events), AE summary timeframe was modified to align with AE reporting period specified in the protocol amendment 4 (dated in December 17th, 2019). The new time frame is defined below.

> 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 summary of SAEs was modified in Section 11.1. The definition of on-therapy SAE was updated to TESAE, and summary timeframe will align with general AE summary timeframe as specified above.

18.0 COVID-19 RELATED LISTING

A listing of patients with visits impacted by COVID-19 will be provided.

19.0 REFERENCES

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997; 53:983-97.

Lu K, Li D, Koch GG. Comparison between two controlled multiple imputation methods for sensitivity analyses of time-to-event data with possibly informative censoring. Statistics in Biopharmaceutical Research 2015. DOI: 10.1080/19466315.2015.1053572

National Institutes of Health, National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 04-5230, 2014

Zhao Y, Herring AH, Zhou H, Ali MW, Koch GG. A multiple imputation method for sensitivity analyses of time-to-event data with possibly informative censoring. *Journal of Biopharmaceutical Statistics* 2014; 24:229-253.

20.0 APPENDICES

APPENDIX I SAS CODE FOR PLANNED ANALYSES OF THE PRIMARY EFFICACY VARIABLE

The primary efficacy analysis for time to relapse include (1) the log-rank test, (2) the Cox proportional hazards model with treatment group as covariate, (3) subgroup analysis. The sample SAS code for these analyses are provided below. Note in the data set `adtte` (DB ITT population), variables `trt02pn` and `trt02p` are for the double-blind treatment group, subgroup is for subgroups of age, gender, race, or region, `aval` is for the time (days) to censor/relapse, and `cnsr` is for the status of censored (=0) or relapse (=1).

- SAS codes for testing the primary null hypotheses that the distribution of the time to first relapse for each of the cariprazine 4.5 mg/d and 3.0 mg/d treatment groups are not different from that for the placebo treatment group using log-rank test

```
proc lifetest data=adtte atrisk plots=survival(f atrisk=0 to 200 by
10 );
    time aval*cnsr(0);
    strata trt02p/test=logrank diff=control('Placebo');
   ods output ProductLimitEstimates=outests1 HomTests=test;
   run;
```

- SAS codes for estimating the hazard ratio and 95% CIs based on the Cox proportional hazards model

```
proc phreg data=adtte;
    class trt02p(ref="Placebo");
    model aval*cnsr(0)=trt02p/rl=wald;
   run;
```

- SAS codes for subgroup analyses

```
proc lifetest data=adtte atrisk plots=survival(f atrisk=0 to 200 by
10 );
   by subgroup;
    time aval*cnsr(0);
    strata trt02p/test=logrank diff=control('Placebo');
run;


proc phreg data=adtte;
   by subgroup;
    class trt02p(ref="Placebo");
    model aval*cnsr(0)=trt02p/rl=wald;
run;
```

APPENDIX II DETAILS ON TWO SENSITIVITY ANALYSES MODELS AND SAS CODES TO EVALUATE THE POSSIBLE VIOLATION OF THE NONINFORMATIVE CENSORING ASSUMPTIONS

Two sensitivity analyses will be performed to assess the robustness of the primary analysis results to the possible violation of the noninformative censoring assumption. Both methods were used in maintenance supplemental New Drug Application (sNDA) filing based on single study RGH-MD-06 according to the discussion with the agency. One is delta-adjusted imputation method, 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 based on the reference-based imputation method which specifies that the hazard for subjects in cariprazine arm who discontinued lies between the hazard for cariprazine subjects who continued and the hazard for the subjects in the placebo arm.

Two sets of sensitivity analyses were expressed below in the form of hazard rate function to illustrate the difference (Lu 2015). Suppose $h_0(t) and\ h_1(t)$ are the hazard rate functions for placebo arm and treatment arm respectively. Under the non-informative censoring, one has $h_1(t) = h_0(t)e^{\beta}, where\ \beta$ is the log hazard ratio characterizing the treatment effect. Under the informative censoring, hazard ratio function for two models are expressed as following,

- Before loss to follow up: $h_1(t) = h_0(t)e^{\beta}$
- After loss to follow up:
  - Reference-based method: $h_1(t) = h_0(t)e^{(1-\varphi)\beta}$, where $\varphi \in [0,1]$ is the sensitivity parameter
  - Delta-adjusted method: $h_1(t) = h_0(t)e^{\delta+\beta}$

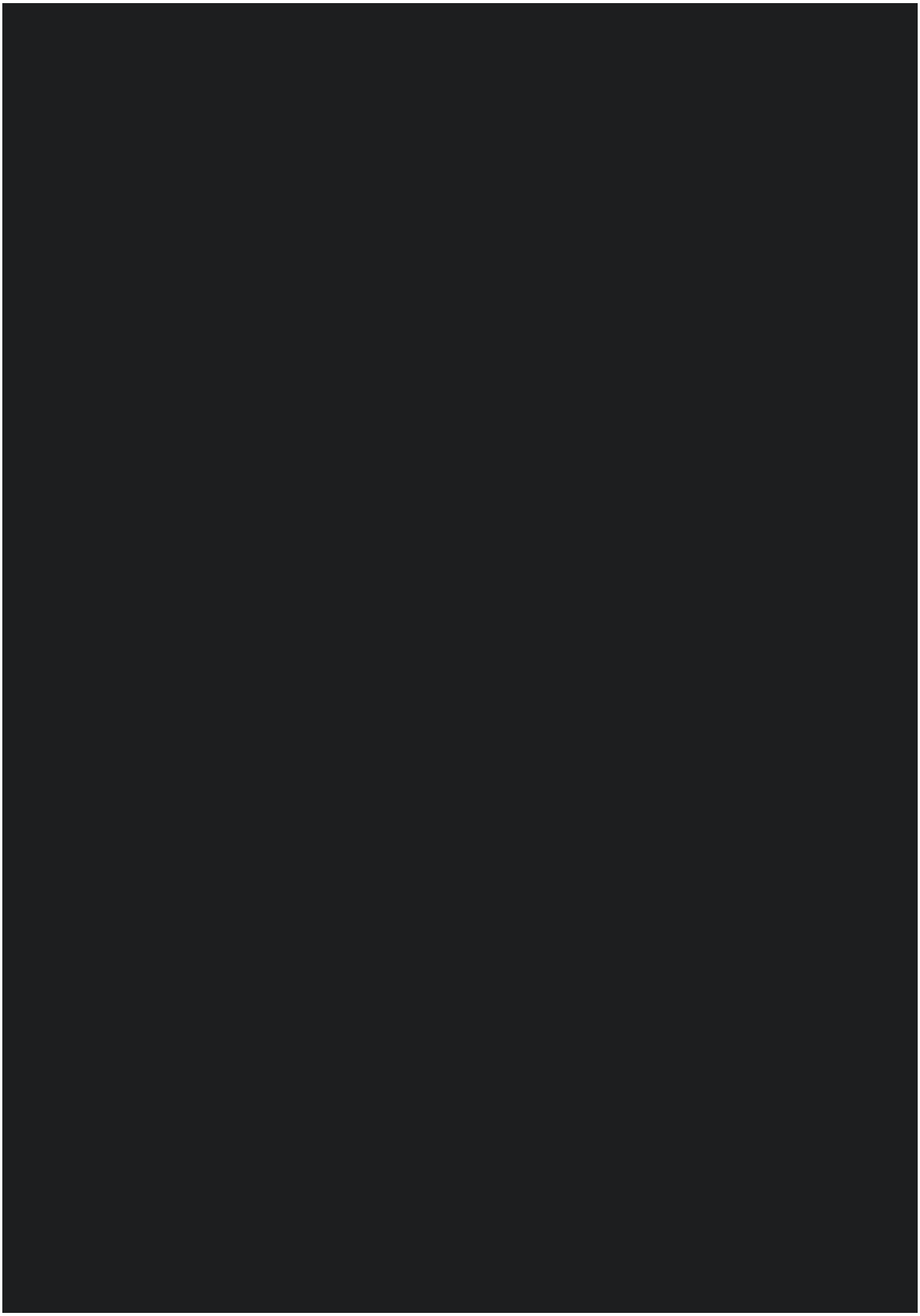
Here, $\delta = -\varphi\beta$ implies the same underlying treatment effect. However, β will be estimated from the data, φ and δ should be prespecified. For reference based method, φ can take 1 as the maximum, which implies the extreme of change of $h_1(t)$ after the loss to follow up will be the same as the hazard for relapse for placebo-treated patients, ie the change will be in a clinical meaningful range. The selected sensitivity parameter φ will be 0, 0.2, 0.4, 0.6,0.8 and 1 for this study for reference -based method. The selected δ in the delta-adjusted method will vary in steps of 0.1 or 0.2 till reaching tipping point when the statistical significance of the primary efficacy endpoint is overturned.

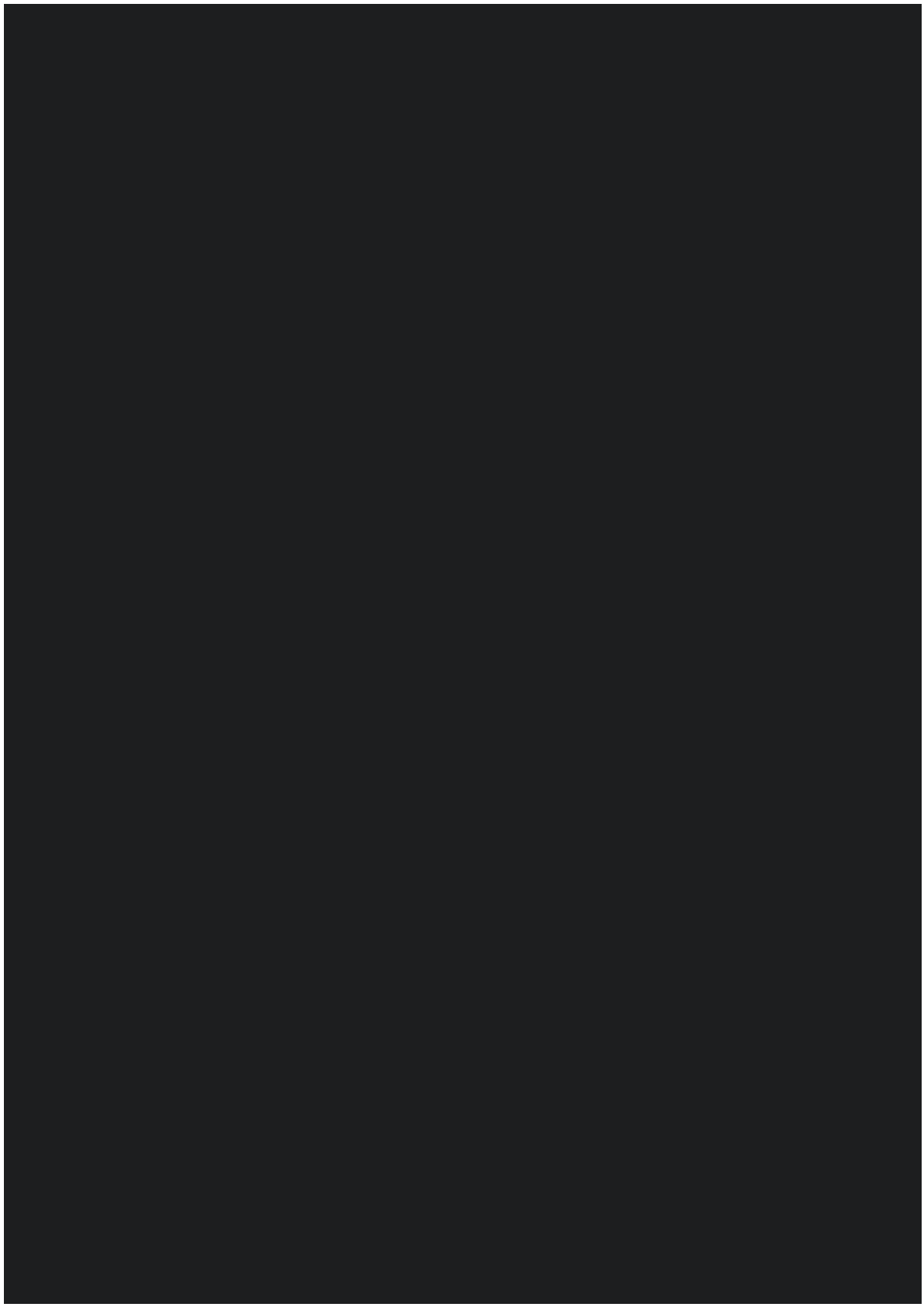
A multiple imputation approach will be used to implement the sensitivity analyses, which involves three periods.

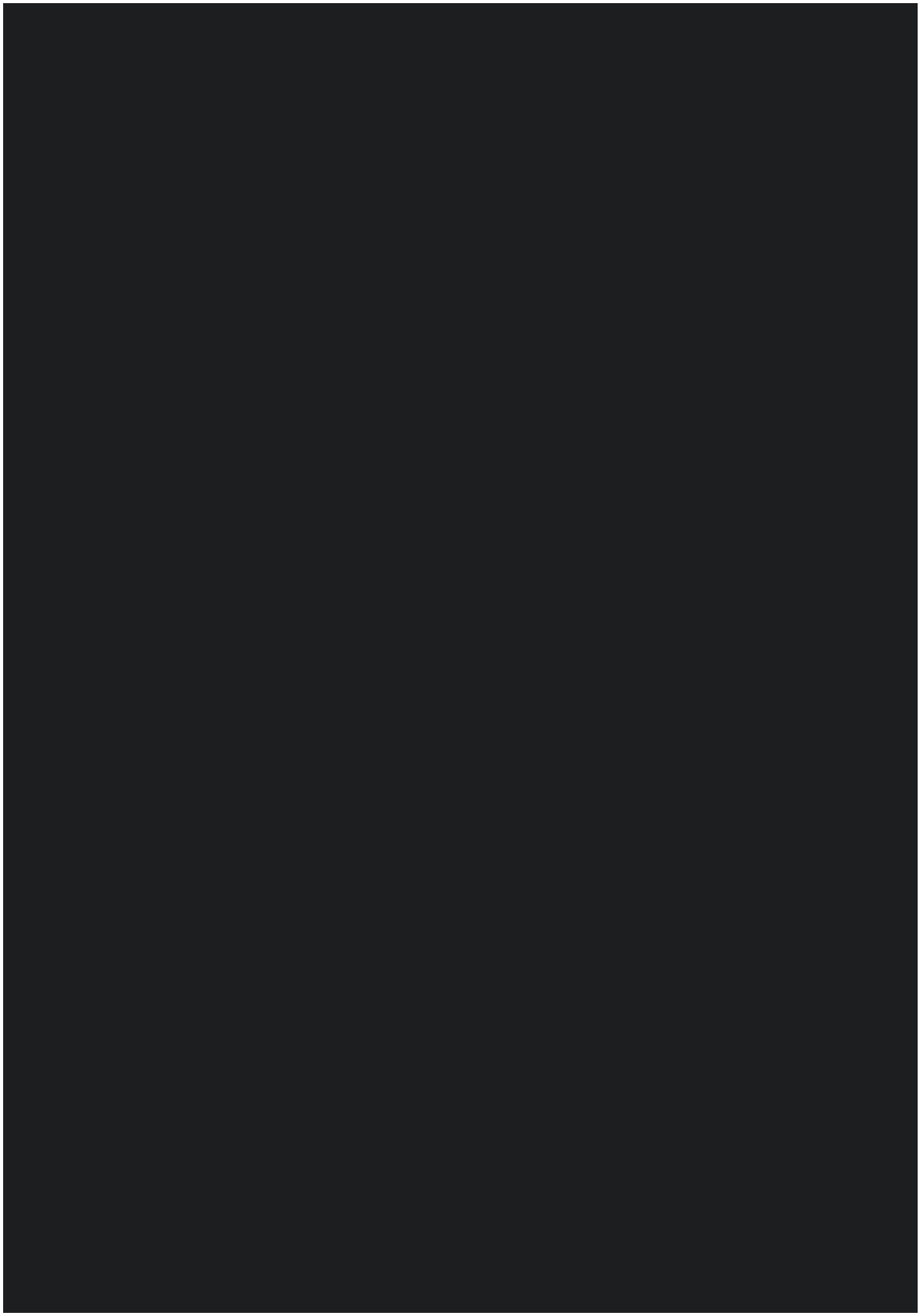
1. The missing time to event are imputed m times to generate 50 complete datasets
2. The 50 complete datasets are analyzed using log rank test and cox model
3. The results from the 50 completer datasets are combined using Rubin's rule.

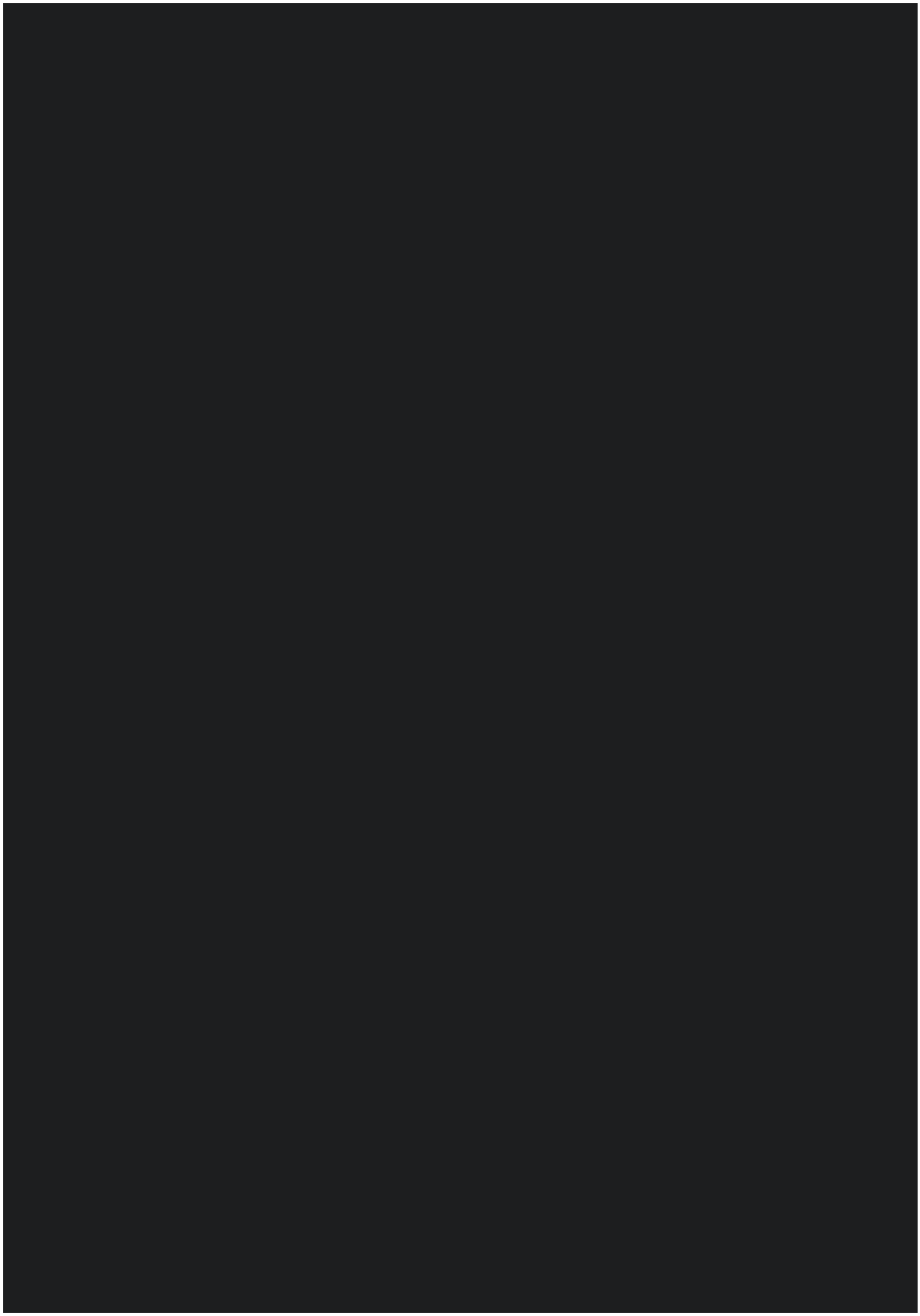
For the imputing stage, the latent event time will be imputed between censoring and planned follow up for subjects who prematurely discontinued. The baseline hazard function will be estimated using piecewise exponential approximation, and parameter $\boldsymbol{\beta}$ will be estimated from the data, which can be obtained using Gibbs sampling using the Bayes statement of the SAS PHREG procedure. Censored event times will be imputed for early withdrawals by inverting the conditional survivor function.

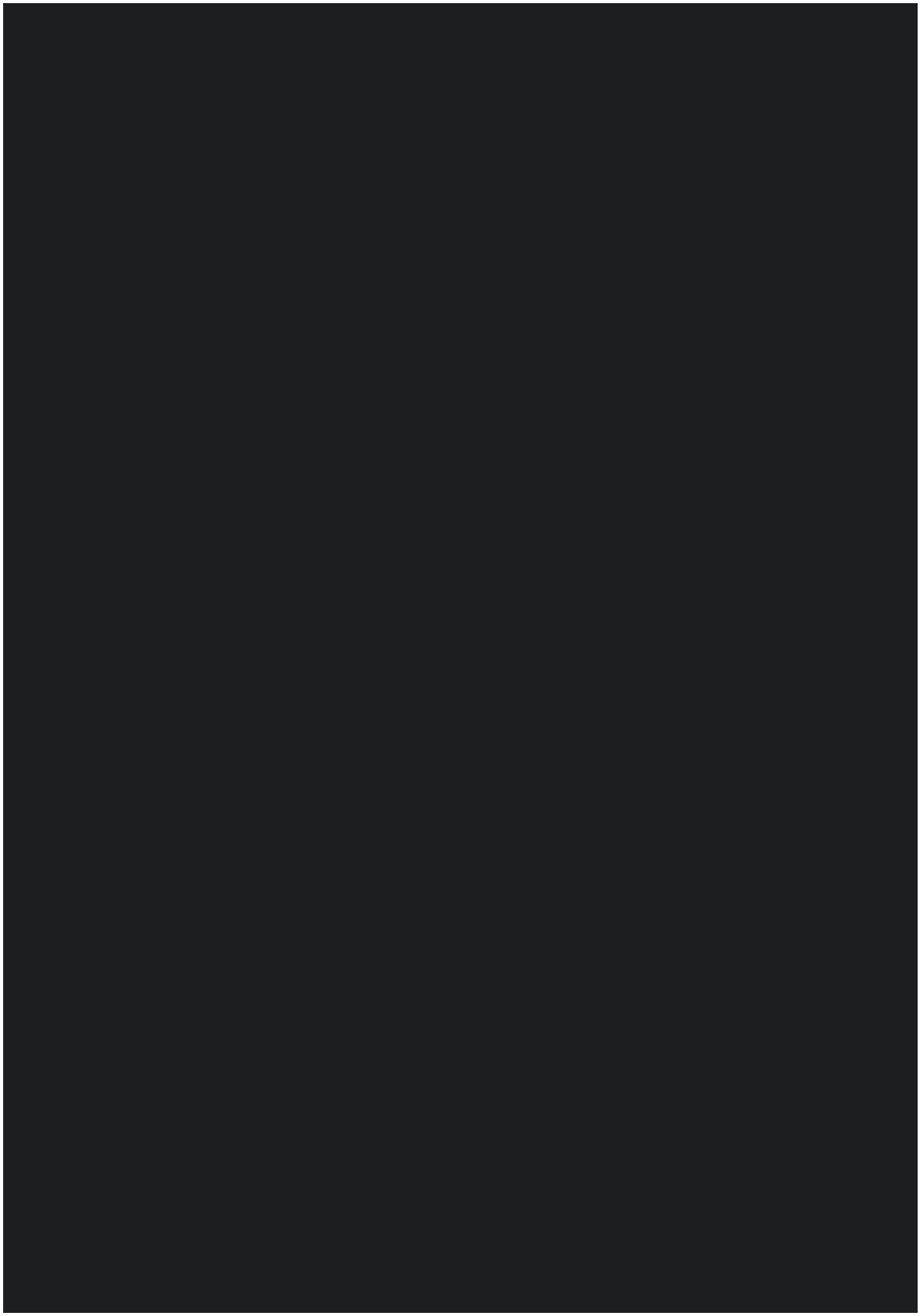
Texts below provide SAS codes to implement the multiple imputation, mainly based on the SAS codes for implementing the reference-based imputation method (Lu 2015).

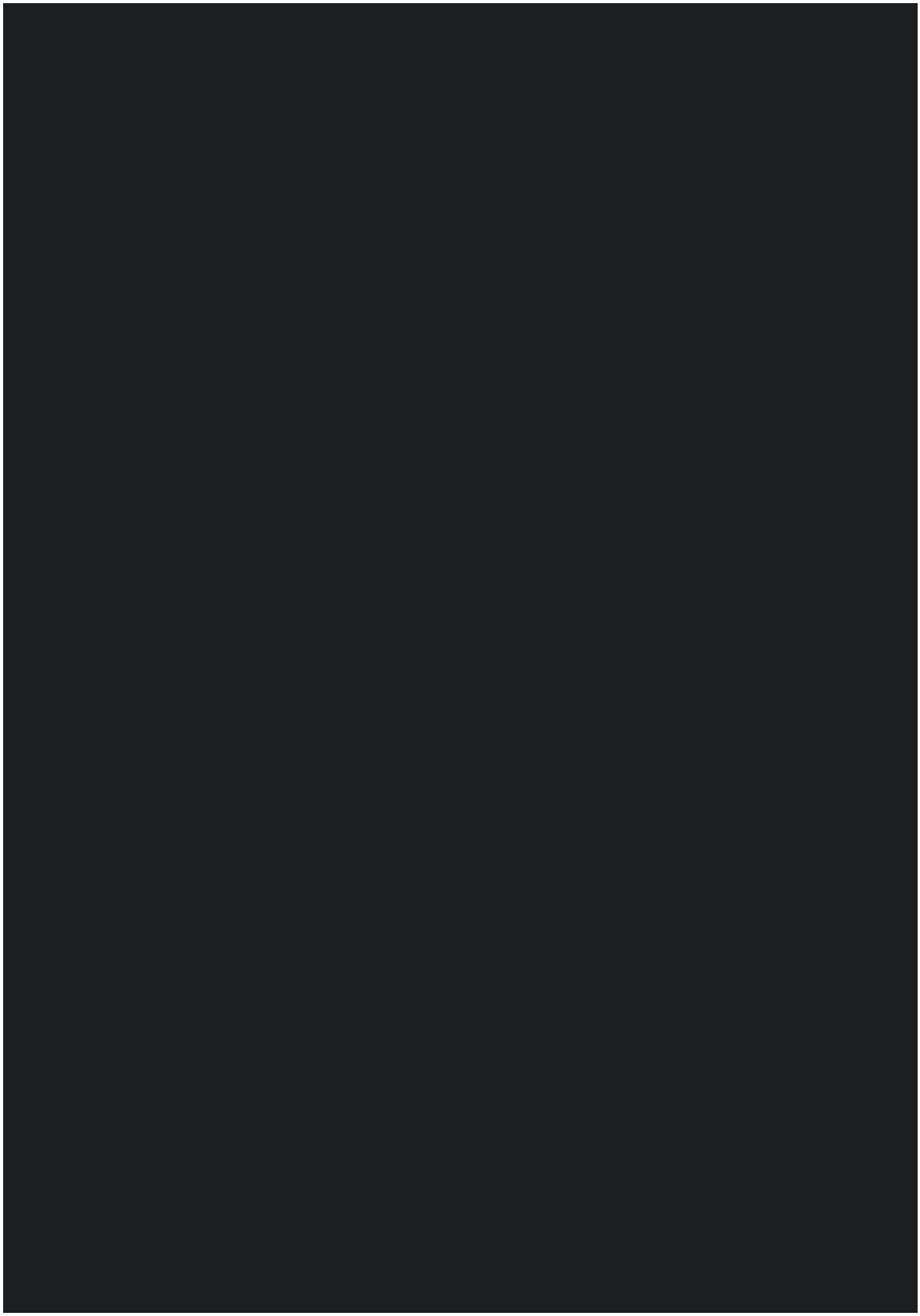


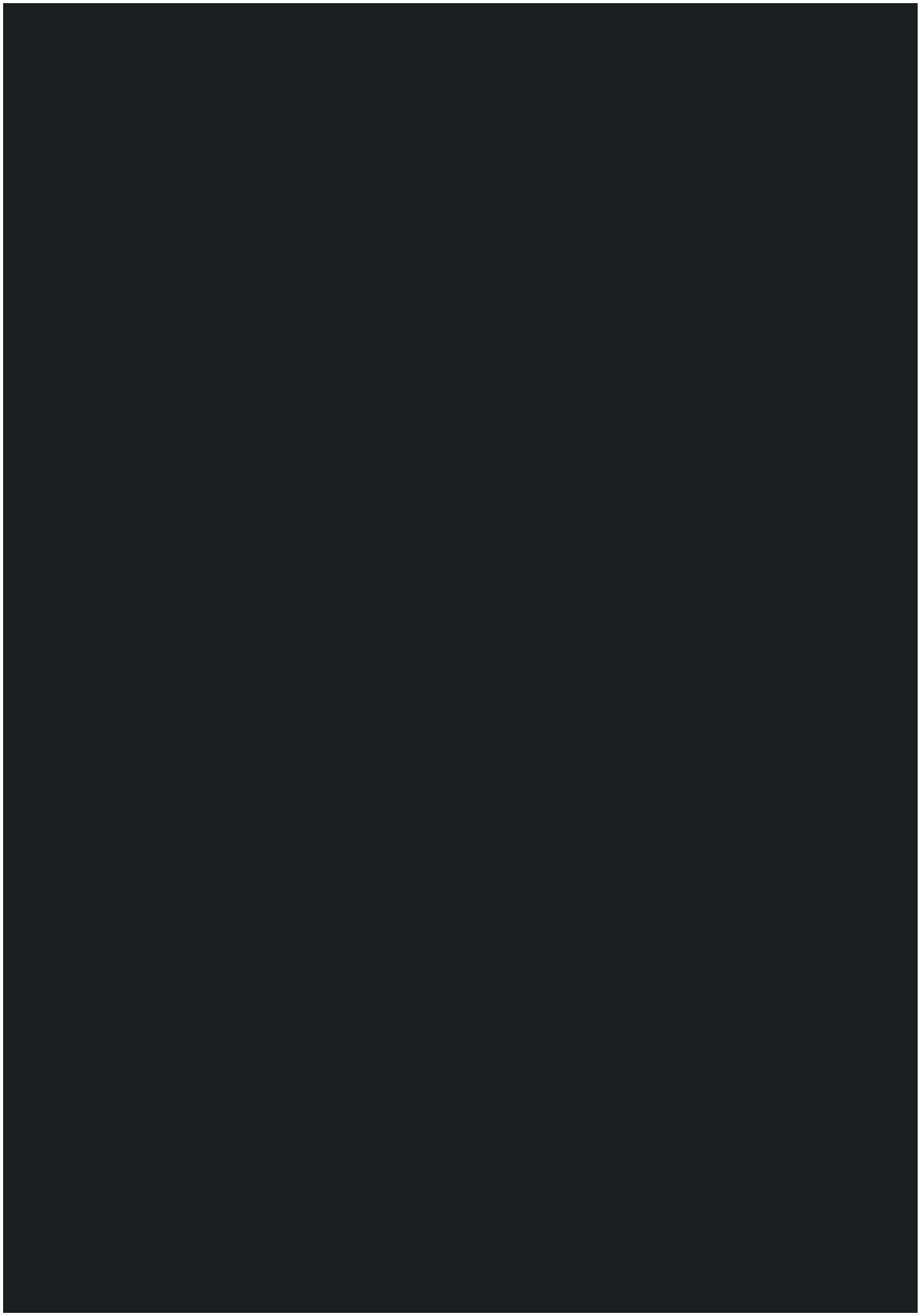


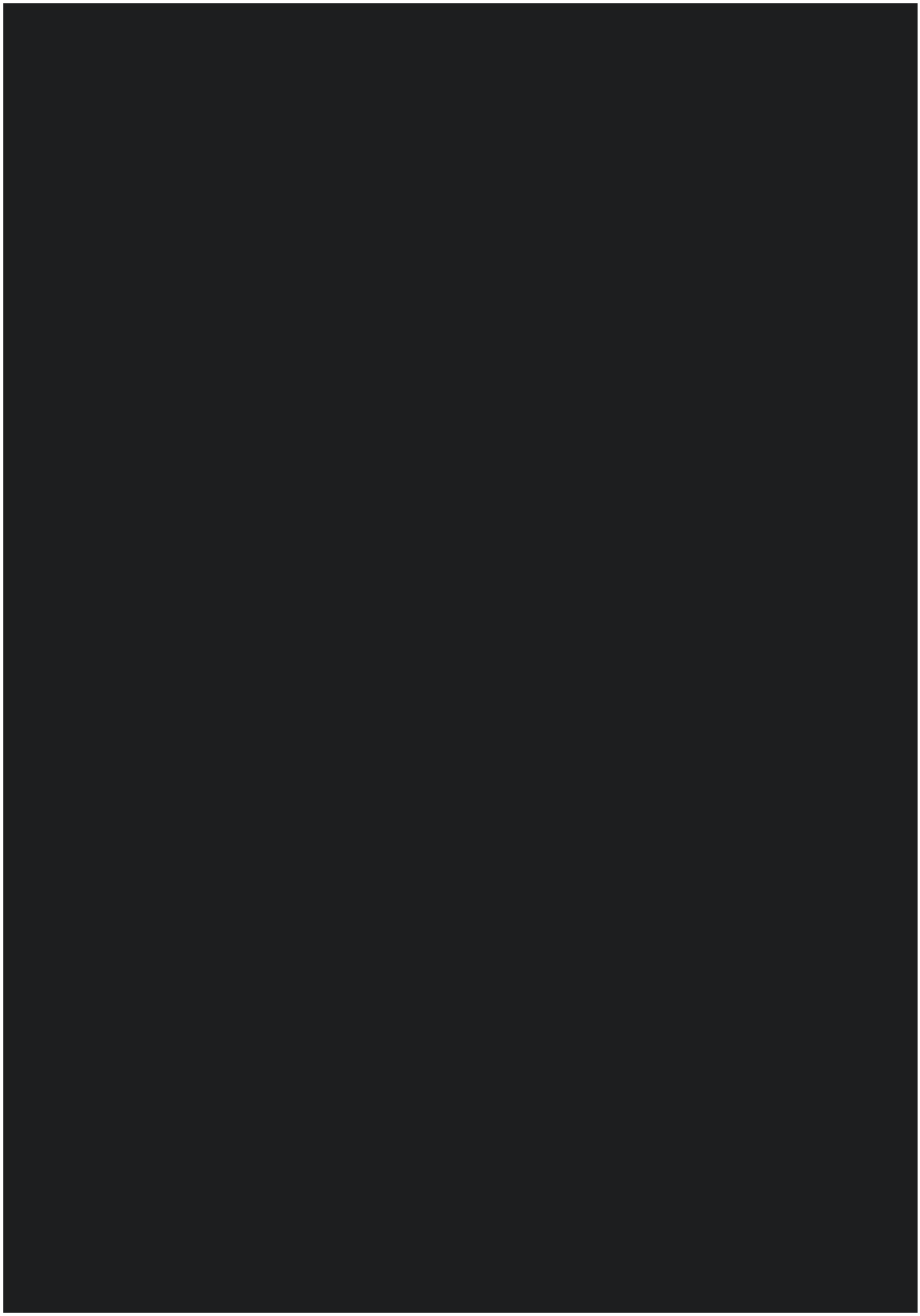


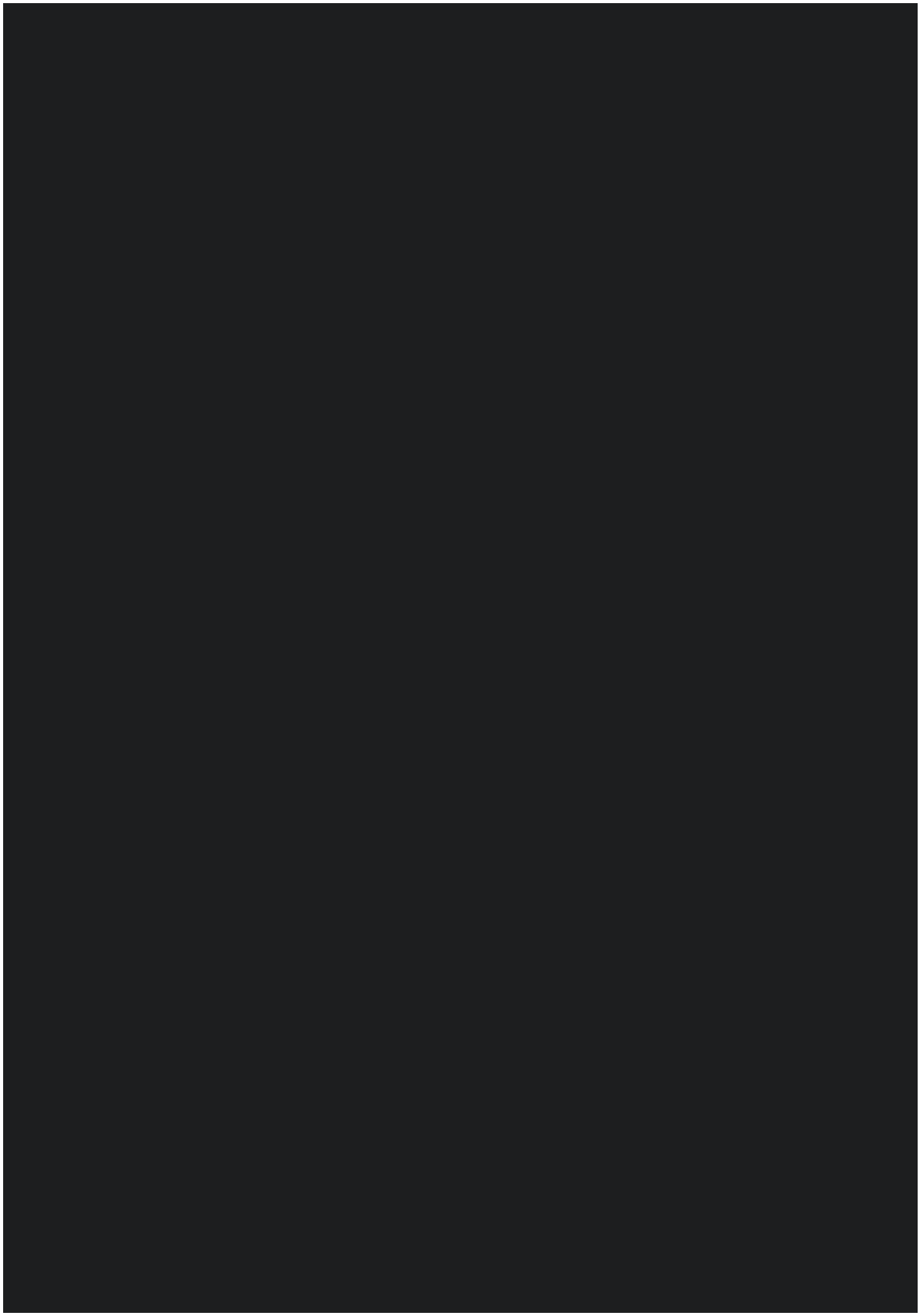












APPENDIX III REPORTING SELECTED LABORATORY PARAMETERS IN CONVENTIONAL UNITS

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

Patient 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 ANALYSES SPECIFIED FOR ABBREVIATED CSR

On 14 DEC 2020, FDA provided Type C Written Response in which they agreed to release Allergan of the postmarketing requirement (PMR 2947-9) to conduct Study RGH-MD-24, based on new information obtained since initial Vraylar approval in SEP 2015. Study RGH-MD-24 was thus early terminated. The analyses for the abbreviated CSR are the subset of analyses specified in the SAP and listed below. The details are provided in the corresponding SAP sections.

Patient disposition and analysis populations

- Summary of screen failure patients and the associated reasons for failure
- Summary of patient disposition during OLTP and DBTP respectively
- Summary of analysis populations

Demographics and other baseline characteristics

- Summary of demographic and other baseline characteristics, and baseline efficacy variables
- Summary of prior and concomitant medications

Efficacy analyses

- Primary efficacy analysis
- Analyses of change from baseline in the PANSS total score during OLTP and DBTP
- Analyses of change from baseline in BACS composite score

Extent of exposure

- Summary of exposure during OLTP, DBTP and entire study

Safety analyses

- Overall summary of AEs during OLTP, OL Safety Follow-up, DBTP, and DB Safety Follow-up
- Summary of TEAEs during OLTP, OL Safety Follow-up, DBTP, and DB Safety Follow-up

- Summary of treatment-related TEAEs during OLTP and DBTP
- Summary of TEAEs leading to premature discontinuation of IP during OLTP and DBTP
- Summary of ocular events during OLTP, OL Safety Follow-up, DBTP, and DB Safety Follow-up
- Summary of TESAEs during OLTP, OL Safety Follow-up, DBTP, and DB Safety Follow-up
- Summary of TESAEs of ocular events during OLTP and DBTP
- Summary of laboratory PCS during OLTP and DBTP
- Summary of CSSRS during OLTP and DBTP

The following listings will be provided for the abbreviated CSR

- Patients with TEAEs leading to premature discontinuation of IP
- AEs for patients with TEAEs leading to premature discontinuation of IP
- Patients with ocular events
- AEs for patients with ocular events
- Patients who died
- AEs for patients who died
- Patients with SAEs
- Patients with laboratory PCS during OLTP and DBTP
- Patients who meet potential Hy's law criteria during OLTP and DBTP
- Patients with suicidal ideation or behavior
- Patient disposition
- Patients who discontinued OLTP or DBTP
- Patients with protocol deviations

- Demographics and other characteristics at baseline/randomization
- Medical and surgical history
- Prior and concomitant medications
- Psychiatric history
- OL/DB dosing data
- IP compliance during OLTP and DBTP
- Plasma concentration
- Relapse status
- Efficacy data analyzed for the abbreviated CSR
- BACS
- Adverse events
- Clinical laboratory results and comments
- Vital signs
- ECG results and overall interpretation
- Ophthalmologic examination and lens status
- CSSRS
- Patients with study visits impacted by COVID-19

APPENDIX V SUMMARY OF CHANGES FOR AMENDMENT 1

Amendment #1 specifies the following changes to the Statistical Analysis Plan for Study RGH-MD-24 dated 12 Feb 2019. The major changes are summarized below:

1. Specified the subset of analyses for abbreviated CSR in Appendix IV
2. Planned a listing of patients with visits impacted by COVID-19 in Section 18.0
3. Provided the rationale of performing a subset of planned analyses in the abbreviated CSR at the beginning of Section 4.0
4. Modified the definition of OL SFU population in Section 6.4
5. Modified the definition of DB ITT population in Section 6.5
6. Modified the definitions of OLTP and DBTP at the beginning of Section 7.1
7. Specified that the percentage of patients in each analysis population would be provided in Section 7.1
8. Specified the definitions of baseline efficacy variables for OLTP and DBTP respectively and planned summary for them respectively in Section 8.0
9. Removed the analysis of BACS composite Z score due to the reason that this value would not be derived by vendor that performs the BACS data analysis in Section 10.3
10. Specified that the OL baseline CGI-S value would be served as the baseline value for CGI-I in Section 10.3
11. Specified the descriptive statistics for safety continuous and categorical variables respectively in Section 11.0
12. Specified the summary of TEAEs during SFU would be separated as OL SFU and DB SFU respectively in Section 11.1
13. Specified the summary of common TEAEs would be separated as OLTP and DBTP respectively in Section 11.1
14. Removed the summary for patients with TEAEs leading to discontinuation if these occurred in 5 or more patients in Section 11.1
15. Specified the summary of patients with any EPS SAEs, and EPS SAEs, and EPS AEs leading to premature discontinuation of IP would be overall during OLTP and by treatment during DBTP in Section 11.1

16. Specified that for the summary of selected clinical laboratory parameters in conventional units, only patients with selected clinical laboratory data at baseline and at least one postbaseline visit during OLTP and DBTP will be included in the summary in Section 11.2

17. Specified that the summary of patients with orthostatic hypotension would be provided for OLTP and DBTP in Section 11.3