Statistical Analysis Plan for Study M22-509

A 6-Week, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Cariprazine in the Acute Exacerbation of Schizophrenia, with an Additional 18-Week Blinded Extension Period

Date: 01 August 2024

Version 3.0

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1.0 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 cariprazine Study M22-509's original protocol (version 1.0, 27Jan2022) and its most recent amendment (version 3.0, 25Jul2023).

The analyses pharmacokinetics (PK) endpoints will be analyzed separately and will not be covered in this SAP.

The Study M22-509 was early terminated as result of discussion due to an unexpected delay in enrollment. The main reasons for slow enrollment may include changes in the treatment environment with fewer relapses and exacerbations, difficulty obtaining informed consent due to washout of current antipsychotics during hospitalization, and the COVID-19 pandemic. Despite several protocol amendments to improve progress, approximately 30 subjects were enrolled (target: 250 subjects). 34 subjects were finally randomized at the time of early termination. The SAP will be part of the abbreviated CSR.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later.

2.0 Study Objectives and Design

2.1 Study Objectives

Primary Objective

The primary objective is to assess the efficacy, safety, and tolerability of cariprazine in comparison to placebo in subjects from Japan and Taiwan with acute exacerbation of schizophrenia.

Primary Efficacy Objective

The primary efficacy objective is to determine if cariprazine (6 mg/day) improves the Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS) total score compared to placebo in subjects from Japan and Taiwan with acute exacerbation of schizophrenia.

The hypothesis corresponding to the primary efficacy objective is that decrease in SCI-PANSS total score with cariprazine (6 mg/day) is greater than that with placebo.

The attributes of the primary estimand corresponding to the primary efficacy objective are as follows:

- Population: The modified intent-to-treat (mITT) population, which consists of all randomized subjects who receive at least 1 dose of study drug and have both baseline and at least 1 postbaseline value of SCI-PANSS total score during the double-blind period (DBP).
- Variable: The primary efficacy endpoint, change from baseline to Week 6 of the DBP in SCI-PANSS total score.
- Accounting for intercurrent events: regardless of whether rescue medications are used, data are included in the analysis. Data after discontinuation of study drug will not be included in the primary analysis and will be assumed missing at random.
- Population-level summary: The difference in means between cariprazine 6 mg/day and placebo.

Secondary Objectives

The secondary objective is to assess the maintenance of efficacy, safety, and tolerability of cariprazine in an 18-week blinded extension period (BEP) in subjects who completed the DBP of this study.

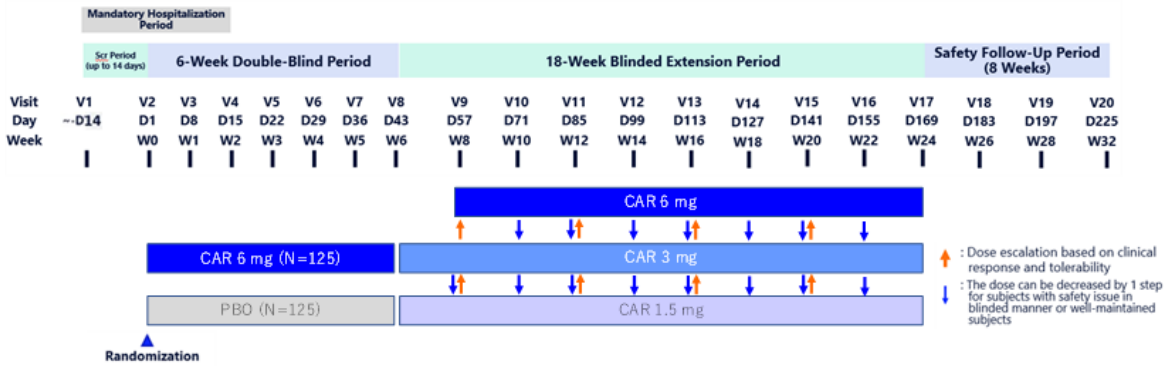
2.2 Study Design Overview

This is a randomized, double-blind, placebo-controlled Phase 3 study consisting of a 6-week DBP to assess the safety, tolerability, PK, and efficacy of cariprazine in subjects from Japan and Taiwan with acute exacerbation of schizophrenia, followed by an 18-week BEP.

This study consists of a screening period, a 6-week DBP, an 18-week BEP, and an 8-week follow-up period. The study has a planned enrollment of approximately 250 subjects (125 subjects per arm), randomized on Day 1 (Visit 2) in a 1:1 ratio to placebo or cariprazine 6 mg/day. Subjects who complete the DBP will have the option to enter the 18-week BEP, during which subjects who received placebo during the DBP will be switched to cariprazine 1.5 mg/day and subjects who received cariprazine 6 mg/day during the DBP will receive cariprazine 3 mg/day in a blinded manner in the BEP. Study sites and subjects will remain blinded to treatment assignment for the duration of the study.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



Handling of data from subjects who were randomized to cariprazine 3 mg/day prior to removal of this dose arm from the DBP

The data from subjects who were randomized to cariprazine 3 mg/day prior to removal of this dose arm from the DBP will be included in analyses of the DBP.

2.3 Treatment Assignment and Blinding

All subjects will be assigned a unique identification number by the interactive response technology (IRT) at screening (Visit 1). Approximately 250 subjects (125 subjects per arm) will be randomized to either the placebo arm or the cariprazine 6 mg/day arm in a 1:1 ratio on Day 1 (Visit 2). The randomization will be stratified by study site. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's treatment until database lock after DBP. The investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the cariprazine capsules and placebo capsules provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

2.4 Sample Size Determination

In terms of the change from baseline in the SCI-PANSS total score at Week 6, the sample size of 125 subjects per arm (N = 250) can achieve at least 90% power at overall 0.05 two-sided significant level to detect the statistically significant difference between placebo and cariprazine 6 mg/day based on these assumptions using a Mixed-Effect Model for Repeated Measurement (MMRM); treatment difference of -8.3 between 6 mg/day and placebo based on the full analysis set (FAS) 2 in Studies A002-A4 and RGH-MD-04, and common standard deviation of 20 at Week 6 taking into account dropout rates and correlation matrix based on FAS in Study A002-A4.

3.0 Endpoints

The following endpoint definitions apply to the efficacy variables described below:

3.1 Primary Endpoint

- Change in SCI-PANSS total score from baseline to DBP Week 6.

3.2 Secondary Endpoint

3.2.1 Key Secondary Endpoint for DBP

- Change in Clinical Global Impression-Severity (CGI-S) score from baseline to Week 6

3.2.2 Additional Secondary Endpoints for DBP

- Change in SCI-PANSS positive symptom score from baseline to Week 6
- Change in 16-Item Negative Symptom Assessment (NSA-16) total score to baseline to Week 6
- Change in SCI-PANSS negative symptom score from baseline to Week 6
- Change in SCI-PANSS negative factor score from baseline to Week 6

3.2.3 Efficacy Endpoints for BEP

- Change in SCI-PANSS total score from baseline and Week 6 to Week 24
- Change in CGI-S score from baseline and Week 6 to Week 24
- Change in SCI-PANSS positive score from baseline and Week 6 to Week 24
- Change in NSA-16 total score from baseline and Week 6 to Week 24
- Change in SCI-PANSS negative symptom score from baseline and Week 6 to Week 24
- Change in SCI-PANSS negative factor score from baseline and Week 6 to Week 24

3.3 Safety Endpoints

The safety endpoints are as follows:

- Adverse Events (AEs)
- Clinical laboratory tests
- Vital signs
- Electrocardiogram (ECG)
- Suicide severity rating (Columbia-Suicide Severity Rating Scale [C-SSRS])
- Extrapyramidal symptom (EPS) assessment:
  - Simpson-Angus Scale (SAS)
  - Abnormal Involuntary Movement Scale (AIMS)
  - Barnes Akathisia Rating Scale (BARS)

4.0 Analysis Populations

The following population sets will be used for the analyses.

Modified Intent-To-Treat (mITT) Population

The Modified Intent-To-Treat (mITT) population includes all randomized subjects who receive at least 1 dose of study drug and have both baseline and at least 1 postbaseline value of SCI-PANSS total score during the DBP. The mITT population will be used for all efficacy analyses for the DBP. Subjects will be included in the analysis according to the treatment group to which they were randomized (as randomized).

Safety Population

The safety population includes all randomized subjects who receive at least 1 dose of study drug. Subjects will be included in the treatment group corresponding to the double-blind treatment they actually receive in the safety population. The safety population will be used for demographic and safety analyses for the DBP. A subject's actual treatment

group will be determined by the kit type dosed most frequently during the DBP as follows:

- Placebo dose card: Placebo
- 3.0 mg dose card or 3.0 mg titration card: 3.0 mg/day (only for summaries described in Section 2.2)
- 6.0 mg dose card or 6.0 mg titration card: 6.0 mg/day

Kit types in the RN_KIT dataset will be described in the Statistical Programming Plan (SPP).

BEP Population

The BEP population will consist of all subjects who complete the 6-week DBP and take at least 1 dose of study drug during the BEP regardless of which treatment group they were randomized to during the DBP. Subjects will be grouped according to their modal (most frequent) daily dose during the BEP. The BEP population will be used for efficacy and safety analyses for the BEP.

5.0 Subject Disposition

A summary of subject accountability during the DBP will be provided where the number of subjects in each of the following categories will be tabulated for each treatment group and overall for all randomized subjects:

- Subjects randomized in the study;
- Subjects who took at least one dose of study treatment;
- Subjects who took at least one dose of study treatment (mITT population and safety population);
- Subjects who completed study treatment (mITT population and safety population);
- Subjects who prematurely discontinued study treatment (mITT population and safety population);

A summary of subject accountability during the BEP will be provided where the number of subjects in each of the following categories will be tabulated for each modal daily dose in the BEP population:

- Subjects who took at least one dose of study treatment;
- Subjects who completed study treatment;
- Subjects who prematurely discontinued study treatment;

The number and percentage of subjects who discontinued study drug during the DBP will be summarized by reason for each treatment group and overall for the all randomized subjects.

The number and percentage of subjects who discontinued study during the DBP will be summarized by reason for each treatment group and overall for the all randomized subjects.

The number and percentage of subjects who completed the DBP but did not enter the BEP will be summarized by reason for each treatment group and overall for all randomized subjects. In addition, the number and percentage of subjects in each treatment group according to modal daily dose for the BEP will be summarized by treatment group and overall according to randomization for the DBP for all randomized subjects.

The number and percentage of subjects who discontinued study drug during the BEP will be summarized by reason for each modal daily dose and overall for the BEP population.

The number and percentage of subjects who discontinued study during the BEP will be summarized by reason for each modal daily dose and overall for the BEP population.

6.0 Study Treatment Duration and Compliance

Unless otherwise stated, parameters in this section will be summarized for the DBP and BEP, respectively. The safety population and BEP population will be used for the DBP

and BEP, respectively. For parameters during the BEP, first and last dose dates are the ones during the BEP.

Duration of treatment (days) is defined for each subject as follows:

$$\text{Duration of treatment (days)} = \text{last dose date} - \text{first dose date} + 1$$

Duration of treatment will be summarized for each treatment group (modal daily dose for BEP) and each period using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval (1, 2 to 7, 8 to 14, 15 to 21, 22 to 28, 29 to 35, 36 to 42 and > 42 days for the DBP, 1, 2 to 14, 15 to 28, 29 to 42, 43 to 56, 57 to 70, 71 to 84, 85 to 98, 99 to 112, 113 to 126 and > 126 days for the BEP) will be summarized.

Patient-years, defined as exposure to study drug in years, will be summarized by treatment group (modal daily dose for BEP).

$$\text{Patient} - \text{years} = \frac{\text{Sum of treatment duration of all subjects (days)}}{365.25}$$

Overall mean daily dose of study drug will be summarized by treatment group (modal daily dose for BEP) and period. For DBP, placebo will not be summarized. In addition, final daily dose of study drug will be summarized by modal daily dose for the BEP.

Treatment compliance (TC) (%) will be summarized by treatment group (modal daily dose for BEP) using descriptive statistics. Treatment compliance for a specified period is defined as the number of capsules actually taken divided by the number of capsules that should have been taken multiplied by 100 as follows:

$$\text{TC (\%)} = \frac{\text{Total number of capsules taken}}{(\text{last dose date} - \text{first dose date} + 1) \times \text{number of capsules per day}} \times 100$$

Percent compliance and its categories (< 80, 80 to 100) will be summarized.

7.0 Subject Characteristics

Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

7.1 Definitions of Baseline and Baseline Derived Variables

Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of study drug for the DBP. For efficacy variables, baseline is defined as the non-missing value recorded at Visit 2.

7.1.1 Disease Duration

Disease duration (years) is defined for each subject as follows:

$$\begin{aligned}&\text{Disease duration (years)}\\&\quad = (\text{date of informed consent}\\&\quad - \text{date of initial diagnosis of schizophrenia} + 1)/365.25\end{aligned}$$

7.1.2 Time Since Exacerbation

Time since exacerbation (days) is defined for each subject as follows:

$$\begin{aligned}&\text{Time since exacerbation (days)}\\&= \text{date of informed consent}\\&- \text{Onset date of current psychotic episode of schizophrenia exacerbation} + 1\end{aligned}$$

7.2 Demographics and Baseline Characteristics

Demographics and baseline will be summarized descriptively, overall and by treatment group for the Safety and mITT populations, respectively. Medical history, procedure history, psychiatric history (disease duration and time since exacerbation), antipsychotic drug history, and nondrug psychiatric treatment history will also be summarized by treatment group.

Continuous demographic variables include age, weight, height and body mass index (BMI).

Continuous baseline variables include SCI-PANSS total score, SCI-PANSS positive symptom score, 16-Item Negative Symptom Assessment (NSA-16) total score, SCI-PANSS negative symptom score, SCI-PANSS negative factor score, disease duration and time since exacerbation.

Categorical demographic variables include:

- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (Asian (Japanese, Non- Japanese), Other (specify))
- Region (Japan or Taiwan)
- Age (< 40 or ≥ 40 years)
- Weight (< 60 or ≥ 60 kg)
- BMI (< 25 or ≥ 25 kg/m2)
- Smoking history (current, former, never, unknown)

Categorical baseline variables include:

- Medical history (Yes, No)
- Procedure history (Yes, No)
- Number of antipsychotic drug (0, 1, 2)

7.3 Medical History and Prior and Concomitant Medications

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class (SOC) and preferred term) will be summarized overall and by treatment group for the safety population. The SOC will be

presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

Prior and concomitant medications will be summarized separately. The number and percentage of subjects taking prior medications for the DBP will be summarized by treatment group and generic name for the safety population. The number and percentage of subjects taking concomitant medications for the DBP and BEP will be summarized by treatment group (modal daily dose for BEP), Anatomical Therapeutic Chemical (ATC) code level 2 and generic drug name for the safety population and BEP population, respectively. Generic name will be based on the World Health Organization (WHO) Drug Dictionary. The actual version of the WHO Drug Dictionary will be noted in the statistical tables and clinical study report.

A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication during the DBP and BEP is defined as any medication taken on or after the start of study drug for the DBP and BEP, respectively.

Prior antipsychotic drug will be summarized by treatment group and generic drug name for the safety population.

The use of rescue medications during the DBP and BEP will be summarized by treatment group (modal daily dose for BEP) and generic drug name for the safety population and BEP population, respectively.

If a subject took a specific medication multiple times or took multiple medications within a specific generic drug name, that subject would be counted only once for the coded drug name. Any medications started after the last dose of study drug will not be summarized but will be included in listings.

7.4 Protocol Deviations

For each of the following protocol deviation categories and across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by treatment group:

- Subject entered into the study even though did not satisfy entry criteria;
- Subject developed withdrawal criteria during the study but was not withdrawn;
- Subject received wrong treatment or incorrect dose of study treatment;
- Subject took prohibited concomitant medication.

8.0 Handling of Potential Intercurrent Events for Efficacy Endpoints

The potential intercurrent events are use of rescue medications and discontinuation of study drug in the analyses for efficacy endpoints.

Regardless of whether rescue medications are used, data are included in the analyses. Data after discontinuation of study drug will not be included in the analyses and will be assumed missing at random. Data on the same day of discontinuation from treatment as the last dose will be included in the analyses.

9.0 Efficacy Analyses

9.1 General Considerations

Due to the low number of randomized patients, for all efficacy endpoints, the descriptive statistics including mean difference between cariprazine group and placebo group will be provided by treatment group using the last observation carried forward (LOCF) approach or the observed case (OC) approach, respectively unless otherwise stated. Detailed definition on the approach is specified in Section 9.2.1. The statistics include number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables, and number and percent for discrete variables. The 2-sided 95% confidence

interval (CI) will be provided for the difference between cariprazine group and placebo group. In addition, figures for mean/standard deviation of primary and secondary continuous endpoints will be presented by treatment group using the LOCF approach or the OC approach. No statistical tests will be performed for comparison with placebo group.

The descriptive statistics and figures for all efficacy endpoints in BEP will be also provided by modal daily dose using the LOCF approach or the OC approach.

The efficacy analyses during the DBP and BEP will be based on the mITT population and BEP population, respectively. "Baseline" for efficacy is defined as the non-missing value recorded at Visit 2, before the first dose of study drug for the DBP as described in Section 7.1.

In principle, for all efficacy endpoints, the analysis during DBP for comparison with placebo group will be additionally performed based on the pooled cariprazine group.

9.1.1 Derived Efficacy 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 divided by number of items with non-missing values). The maximum number of missing items allowed for the total scores imputation and the details of the derivation is specified below Section 9.3.1 and Section 9.4.3.

9.2 Handling of Missing Data

Missing data could occur due to various reasons, including missing visits/assessments or early withdrawal from the clinical trials. Assessments on or after any intercurrent event will be handled as specified in Section 8.0.

Missing data for the efficacy analyses will be handled using the methods described below.

9.2.1 Continuous Endpoints

For missing data of continuous efficacy endpoints for the DBP and BEP, descriptive statistics and figures is provided using the following approach:

- LOCF: Only the post-baseline 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 post-baseline values are missing, baseline value will not be carried forward.

- OC: The OC analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit. OC will exclude values after a subject prematurely discontinues from study treatment.

9.2.2 Categorical Endpoints

For binary efficacy endpoints where logistic regression model is performed, missing data will be handled using the LOCF approach, the OC approach and the following approaches:

- Non-Responder Imputation (NRI): the NRI method will categorize any subject who does not have evaluation during a specific visit window as a non-responder for that visit.

The LOCF and OC approaches used for categorical efficacy endpoints are defined as the same method as for continuous efficacy endpoints.

Response for each subject will be derived based on the imputed score.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary endpoint for the primary analysis of efficacy is:

- Change in SCI-PANSS total score from baseline to DBP Week 6.

The SCI-PANSS total score will be derived as the sum of the 30 items (P1-P7, N1-N7, and G1-G16) of SCI-PANSS, using this formula: (total number of items in the scale) × (sum of non-missing items divided by number of items with non-missing values). If more than 3 items for the SCI-PANSS total score are missing, the total score will be set to missing.

9.3.2 Main Analysis of Primary Efficacy Endpoint

Analysis of the primary endpoint will be conducted on the mITT based on treatment as randomized. Descriptive statistics and figures including mean difference between cariprazine group and placebo group from baseline to Week 6 will be provided using the LOCF approach or the OC approach by treatment group and by time point, respectively. Details on the analysis, output are specified in Section 9.1 and Section 9.2.1.

The attributes of the estimand corresponding to the primary efficacy objective are summarized in Table 1.

Table 1. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Objective

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary	Cariprazine 6 mg/day vs. placebo	Change from baseline to Week 6 of the DBP in SCI-PANSS total score.	mITT (all randomized subjects who receive at least 1 dose of study drug and have both baseline and at least 1 postbaseline value of SCI-PANSS total score during the DBP)	Regardless of whether rescue medications are used, data are included in the analysis. Data after discontinuation of study drug will not be included in the primary analysis and will be assumed missing at random.	Difference in means between cariprazine 6 mg/day group and placebo

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoint for DBP

The key secondary endpoint of efficacy is:

- Change in Clinical Global Impression-Severity (CGI-S) score from baseline to Week 6

9.4.2 Main Analyses of Key Secondary Efficacy Endpoint for DBP

Analysis of key secondary endpoint will be conducted on the mITT based on treatment as randomized. Similar to the primary endpoint, descriptive statistics and figures including mean difference between cariprazine group and placebo group from baseline to Week 6 will be provided using the LOCF approach or the OC approach by treatment group and by time point, respectively.

The attributes of the estimand corresponding to the key secondary efficacy objective are summarized in Table 2.

Table 2. Summary of the Estimand Attributes Corresponding to the Key Secondary Efficacy Objective

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Key secondary	Cariprazine 6 mg/day vs. placebo	Change from baseline to Week 6 of the DBP in CGI-S score.	mITT (all randomized subjects who receive at least 1 dose of study drug and have both baseline and at least 1 postbaseline value of SCI-PANSS total score during the DBP)	Regardless of whether rescue medications are used, data are included in the analysis. Data after discontinuation of study drug will not be included in the primary analysis and will be assumed missing at random.	Difference in means between cariprazine 6 mg/day group and placebo

9.4.3 Additional Secondary Efficacy Endpoints for DBP and Analyses

The additional secondary efficacy endpoints for DBP are:

- Change in SCI-PANSS positive symptom score from baseline to Week 6
- Change in 16-Item Negative Symptom Assessment (NSA-16) total score to baseline to Week 6
- Change in SCI-PANSS negative symptom score from baseline to Week 6
- Change in SCI-PANSS negative factor score from baseline to Week 6

The below scores are derived using this formula: (total number of items in the scale) × (sum of non-missing items divided by number of items with non-missing values).

- The PANSS positive symptom score is the sum of the 7 positive items (P1-P7) of PANSS. If any item for the PANSS positive score is missing, the positive score will be set to missing.

- The NSA-16 total score is the sum of the 16 items of the NSA. If more than 2 items for the NSA-16 total score are missing, the total score will be set to missing.
- The PANSS negative symptom score is the sum of the 7 negative items (N1-N7) of PANSS. If any item for the PANSS negative score is missing, the negative score will be set to missing.
- The PANSS negative factor score was developed by Marder, et al (Marder et al, 1997) and is the sum of the 7 items (N1, N2, N3, N4, N6, G7 and G16) of PANSS. If any item for the PANSS negative factor score is missing, the negative factor score will be set to missing. Negative factor score ranges from 7-49.

For the above mentioned continuous endpoints, descriptive statistics including mean difference between cariprazine group and placebo group from baseline to Week 6 will be provided using the LOCF approach or the OC approach by treatment group and by time point, respectively. Details of the analysis and output are specified in Section 9.1 and Section 9.2.1.

9.4.4 Additional Efficacy Endpoints and Analyses

The additional efficacy endpoints for DBP are:

- PANSS responder (subjects with SCI-PANSS total score improved by ≥ 30% at Week 6 compared with Baseline)

For the PANSS responder, the number, percent and 2-sided 95% CI will be provided using the LOCF approach, the OC approach or the NRI approach, respectively. Details on the analysis, output are specified in Section 9.1 and Section 9.2.2.

9.4.5 Efficacy Endpoints for BEP and Analyses

The efficacy endpoints for BEP are:

- Change in SCI-PANSS total score from baseline and Week 6 to Week 24

- Change in CGI-S score from baseline and Week 6 to Week 24
- Change in SCI-PANSS positive score from baseline and Week 6 to Week 24
- Change in NSA-16 total score from baseline and Week 6 to Week 24
- Change in SCI-PANSS negative symptom score from baseline and Week 6 to Week 24
- Change in SCI-PANSS negative factor score from baseline and Week 6 to Week 24

Descriptive statistics and figures from baseline to Week 24, and from Week 6 to Week 24 will also be provided using the LOCF approach or the OC approach by modal daily dose and by time point, respectively. Details on the analysis, output are specified in Section 9.1 and Section 9.2.1. Subjects will be grouped according to their modal (most frequent) daily dose during the BEP.

9.5 Efficacy Subgroup Analyses

To evaluate the consistency of the efficacy over demographic and other specific baseline characteristics, subgroup analysis will be performed using the descriptive statistics for the primary endpoints for the subgroups below.

For subgroup analysis, descriptive statistics for each treatment group as well as mean and its 95% CI for treatment differences between cariprazine group and placebo group will be presented using the LOCF approach or the OC approach. No p-value will be provided.

- Age category (< 40 years or ≥ 40 years)
- Sex (Male or Female)
- Region (Japan or Taiwan)
- SCI-PANSS total score at Baseline (<100 or >= 100)
- Negative symptom at Baseline (Applicable or Not applicable)
  - The patients with SCI-PANSS negative factor score >= 24 and the score of at least two items out of three items for N1, N4, and N6 >= 4 at Screening or Day 1 will be regarded as “Applicable”.

For each subgroup for SCI-PANSS total score and Negative symptom, if there are no applicable subjects for any category, its subgroup analysis will not be performed.

10.0 Safety Analyses

10.1 General Considerations

Safety data during the DBP and BEP will be summarized for the safety population and BEP population, respectively. Safety summaries during the DBP and BEP will be presented by treatment group (modal daily dose for BEP), including a total group for all subjects on active study treatment, respectively.

Safety data during the Safety Follow-up Period will be summarized for the safety population. The double-blind treatment subjects actually received during the DBP and modal daily dose during the BEP correspond to the treatment groups that will be used for summaries of safety data during the Safety Follow-up Period for subjects who did not enter the BEP and subjects who entered the BEP, respectively. The Safety Follow-up Period starts the day after the last dose of study drug in the study (either during the DBP or BEP).

Unless otherwise specified, safety data will be summarized by period.

For all safety endpoints, the data from subjects who were randomized to cariprazine 3 mg/day prior to removal of this dose arm from the DBP will be included in analyses of the DBP.

10.2 Adverse Events

AEs will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific AEs will be counted once for each subject for calculating percentages,

unless stated otherwise. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship to study drug will be reported.

10.2.1 Treatment-Emergent Adverse Events and Newly Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any AE with an onset date that is on or after the first dose of study treatment and no more than 30 days after the last dose of study drug. TEAEs for the DBP will be defined as any AE with an onset date that is on or after the first dose of DBP study drug and before the first dose of BEP study drug for subjects who participate in the BEP, or on or before the last dose of DBP study drug for subjects who participate in the Safety Follow-up Period (and not in BEP), or within 30 days after the last dose of DBP study drug for subjects who do not participate in neither BEP nor Safety Follow-up Period. TEAEs for the BEP will be defined as any AE with an onset date that is on or after the first dose of BEP study drug and on or before the last dose of BEP study drug for subjects who participate in the Safety Follow-up Period, and within 30 days after the last dose of BEP study drug for subjects who do not participate in Safety Follow-up Period. AEs during Safety follow-up are defined as any AE with an onset date during the Safety Follow-up Period after the DBP and BEP. All TEAEs will be summarized overall, as well as by primary MedDRA SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. All AEs during Safety follow-up will also be summarized in the same manner as TEAEs.

Unless otherwise specified, TEAEs will be summarized during the DBP and BEP, respectively, and AEs during Safety follow-up will be summarized during the Safety Follow-up Period.

The number and percentage of subjects experiencing TEAEs will be summarized. The number and percentage of subjects experiencing AEs during Safety follow-up will be summarized.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE/AEs during Safety follow-up
- Any TEAE/AEs during Safety follow-up with a reasonable possibility of being related to study drug according to the investigator
- Any severe TEAE/AEs during Safety follow-up
- Any serious TEAE/AEs during Safety follow-up
- Any TEAE leading to discontinuation of study drug (for the DBP and BEP)
- Any TEAE/AEs during Safety follow-up leading to death
- All deaths
- Deaths occurring ≤ 30 days after last dose of study drug (for the Safety Follow-up Period only)
- Deaths occurring > 30 days after last dose of study drug (for the Safety Follow-up Period only)
- Any TEAE/AEs during Safety follow-up of Special Interest

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

TEAEs and AEs during Safety follow-up will be summarized by SOC and PT; SOC and PT with a reasonable possibility of being related to study drug as assessed by the investigator; by maximum severity and SOC and PT. Specific AEs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same AE (SOC or PT) occurs multiple times within a subject, the highest severity and level of relationship to study drug will be reported.

In addition, TEAEs will be summarized by PT and treatment group (modal daily dose for BEP) and sorted by decreasing frequency for the total active group. AEs during Safety follow-up will also be summarized.

10.2.4 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Drug Discontinuation

Treatment-emergent serious AEs (SAEs), TEAEs leading to premature discontinuation of study drug, and TEAEs leading to death will be summarized by SOC and PT and in listing format. AEs during Safety follow-up will also be summarized in the same manner as TEAEs except for AEs leading to premature discontinuation of study drug.

10.2.5 Adverse Events of Special Interest

AEs of special interest (AESIs) will be summarized overall and by PT and will be identified using the search criteria provided in Appendix B. Any extrapyramidal symptoms (EPS) TEAEs excluding akathisia/restlessness and any TEAE of akathisia/restlessness will also be summarized for the AESI of EPS.

Tabular listings of selected TEAEs of special interest will be provided.

10.3 Analysis of Laboratory Data

The clinical laboratory tests defined in the protocol operations manual (e.g., hematology, clinical chemistry, and urinalysis) will be summarized.

Each continuous laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each planned time point and to the minimum, maximum, and final post-baseline value will be summarized with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group (modal daily dose for BEP).

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table will be provided to summarize shifts from baseline to the final post-baseline value.

The criteria for potentially clinically significant (PCS) laboratory values will be determined by list in Appendix C. For each laboratory PCS criterion, the number and percentage of subjects who have at least 1 post-baseline observation that meets the PCS criterion and is more extreme than their baseline value will be summarized by treatment group (modal daily dose for BEP). Listings of subject-level laboratory data will be provided for subjects meeting the criteria.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and body weight will be summarized. Vital sign variables during the DBP, BEP and Safety Follow-up Period will be summarized, respectively.

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each planned time point, to the minimum, maximum, and final post-baseline value will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group (modal daily dose for BEP).

Both the observed value and the change from baseline for vital sign variables will be evaluated based on PCS criteria (Appendix C). For each vital sign PCS criterion, the number and percentage of subjects who have at least 1 post-baseline observation that meets the PCS criterion will be summarized by treatment group (modal daily dose for BEP). A post-baseline value will be considered as a PCS value if it meets both the observed value and the change from baseline criteria. Listings of subject-level vital sign data will be provided for subjects meeting the criteria.

10.5 Other Safety Analyses

Other safety parameters include electrocardiograms, ophthalmologic examination, C-SSRS, and EPS scales (Simpson-Angus Scale [SAS], Abnormal Involuntary Movement Scale [AIMS] and Barnes Akathisia Rating Scale [BARS]).

10.5.1 Analysis of Electrocardiograms

ECG parameters of heart rate, PR interval, RR interval, QRS duration, QT interval, QTcB, and QTcF will be summarized.

Each ECG parameter will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each planned time point, to the minimum, maximum, and final post-baseline value will be summarized with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group (modal daily dose for BEP).

The criteria for PCS ECG parameters will be determined by list in Appendix C. For each ECG PCS criterion, the number and percentage of subjects who have at least 1 post-baseline observation that meets the PCS criterion and is more extreme than their baseline value will be summarized by treatment group (modal daily dose for BEP). Listings of subject-level ECG data will be provided for subjects meeting the criteria.

A listing of subjects with post-baseline significant ECG abnormalities as reported by the central laboratory will be provided.

A summary will also be provided showing subjects who have an increase in QTcB or QTcF from baseline of more than 30 msec but not exceeding 60 msec and subjects who have an increase of 60 msec or higher.

10.5.2 Ophthalmologic Examination

Ophthalmologic parameters include best corrected visual acuity (logMAR of each eye and the lower logMAR of 2 eyes) and the observed results of slit-lamp assessment (examination for abnormalities of the eyelid, conjunctiva, anterior chamber, cornea, vitreous chamber, iris, pupil, optic disc, retinal vessels, and macula). Ophthalmologic parameters during the DBP, BEP and Safety Follow-up Period will be summarized, respectively.

Each continuous ophthalmologic parameter and its change from baseline will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum.

A shift table from normal baseline to abnormal post-baseline in slit-lamp assessment results will be provided for all time points.

The criteria for potentially clinically significant (PCS) ophthalmologic parameters will be determined by list in Appendix C. For each ophthalmologic PCS criterion, the number and percentage of subjects who have at least 1 post-baseline observation that meets the PCS criterion and is more extreme than their baseline value will be summarized by treatment group (modal daily dose for BEP). Listings of subject-level ophthalmologic data will be provided for subjects meeting the criteria.

10.5.3 Columbia–Suicide Severity Rating Scale

For the C-SSRS, the number and percentage of subjects with any suicidal ideation or suicidal behavior as recorded on the C-SSRS will be presented by treatment group (modal daily dose for BEP) and by period (the lifetime history, DBP, BEP, and Safety Follow-up Period). The number and percentage of subjects with the most severe suicidal ideation and suicidal behavior during the lifetime history, DBP, BEP, and the Safety Follow-up Period will also be presented by treatment group (modal daily dose for BEP) and period. In addition, the number of percentage of subjects with non-suicidal self-injurious behavior will be summarized by treatment group (modal daily dose for BEP) and each period.

10.5.4 Extrapyramidal Symptom Scales

EPS parameters including SAS (total score), AIMS (total score) and BARS (total score) will be summarized.

These total scores are derived using the following formula: (total number of items in the scale) × (sum of non-missing items divided by number of items with non-missing values).

- The SAS 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.
- The AIMS 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, the total score will be set to missing.
- The BARS 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.

Each EPS parameter will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Mean change from baseline to each planned time point will be summarized with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group (modal daily dose for BEP).

A subject will be considered to have treatment-emergent parkinsonism if the subject's SAS total score was ≤ 3 at baseline and > 3 at any post-baseline assessment.

A subject will be considered to have treatment-emergent akathisia if the subject's BARS total score was ≤ 2 at baseline and > 2 at any post-baseline assessment.

The number and percentage of subjects with treatment-emergent parkinsonism or akathisia will be tabulated by treatment group (modal daily dose for BEP). Listings of subjects with treatment-emergent parkinsonism or treatment-emergent akathisia will be provided.

11.0 Interim Analyses

Due to early termination of this study, all analyses will be performed only once at the final database lock.

11.1 Data Monitoring Committee

A data monitoring committee is not planned for this study. Given that the safety and AE profile of cariprazine has been characterized extensively in studies of both global and Japanese populations, the emergence of new AEs affecting subject safety are not anticipated.

A population PK analysis demonstrated about 34% increase in steady-state exposure (area under the concentration time curve from time 0 to 24 hours [AUC0-24]) of total cariprazine in Asian subjects (mostly subjects from studies that were conducted in India) compared to Caucasian subjects. Japanese subjects had on average 21% greater steady-state AUC0-24 than Caucasian subjects (Study RGH-MS-08). These differences are within the observed cariprazine PK variability, are relatively small, and are not clinically relevant. The well characterized safety profile, coupled with data specific to the population of this study, mean new safety AEs are not anticipated, and a Data Monitoring Committee is therefore not indicated.

12.0 Overall Type-I Error Control

Due to early termination of this study and the low number of randomized subjects, only descriptive statistics for all efficacy endpoints will be provided. Therefore, overall type-I error control is not applicable.

13.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	25 Aug 2022	Initial version
2.0	11 Oct 2023	• Changed study design from 3-arm to 2-arm. • Amended sample size design and randomization according to the change of study design. • Amended overall type-1 error rate from a gatekeeping method to a fixed sequence method according to the change of study design. • Added handling and analysis of data from subjects who were randomized to cariprazine 3 mg/day prior to removal of this dose arm from the DBP. • Replaced NEAEs by "AEs during Safety Follow-up." • Amended AESI list in Appendix B due to update of MedDRA version to 26.0.

3.0	01 Aug 2024	Along with study termination, changed planned analyses in the protocol as follows. • No interim database lock for primary analysis will be conducted and a database lock will occur after the evaluation of all enrolled subjects in BEP has been completed. • The cariprazine 3 mg/day group will be included for all efficacy and safety analysis in the DBP. • For all efficacy endpoints in the DBP, the descriptive statistics for continuous variables will be provided using several approaches for missing data, and the number and percent for discrete variables as well. In addition, figures of mean/standard deviation for primary and secondary continuous variables will be presented using several approaches for missing data. The descriptive statistics and figures for all efficacy endpoints in BEP will be also provided using several approaches for missing data. • No statistical tests and no model analysis will be performed for comparison with placebo group and the control of type I error rate will not be considered. • The analysis for comparison between the pooled cariprazine group and placebo group will be performed. • Subgroup efficacy analyses for PANSS total score at Baseline and Negative symptom at Baseline will be performed. Removed the pooling process for small site and the sensitivity analysis for primary and key secondary endpoint. Amended AESI list in Appendix B due to update of MedDRA version to 27.0.

13.1 Changes to Planned Analyses in the Protocol

- No interim database lock for primary analysis will be conducted and a database lock will occur after the evaluation of all enrolled subjects in BEP has been completed.
- The cariprazine 3 mg/day group will be included for all efficacy and safety analysis in the DBP.
- Target sample size for statistical power is 250 subjects, however actual number of randomized subjects will be 34 subjects.

- For all efficacy endpoints in the DBP, the descriptive statistics for continuous variables will be provided using several approaches for missing data, and the number and percent for discrete variables as well. The 2-sided 95% confidence interval (CI) will be provided for the difference between cariprazine group and placebo group. In addition, figures of mean/standard deviation for primary and secondary continuous variables will be presented using several approaches for missing data. The descriptive statistics and figures for all efficacy endpoints in BEP will be also provided using several approaches for missing data.

- No statistical tests and no model analysis will be performed for comparison with placebo group and the control of type I error rate will not be considered.

- The analysis for comparison between the pooled cariprazine group and placebo group will be performed.

- Subgroup efficacy analyses for PANSS total score at Baseline and Negative symptom at Baseline will be performed.

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]	[redacted]	Author
		Author
		Clinical Statistics
		Statistical Programming
		Medical/Scientific Monitor

Appendix B. Definition of Adverse Events of Special Interest

Table B-1. AESI for Ocular Events with PTs

AESI Category	MedDRA Preferred Terms (v 27.0)	Preferred Term Codes
Blindness	Amaurosis	10001902
	Amaurosis fugax	10001903
	Blindness	10005169
	Blindness day	10005178
	Blindness transient	10005184
	Blindness unilateral	10005186
	Diabetic blindness	10012646
	Sudden visual loss	10042441
Cataract	Atopic cataract	10069649
	Cataract	10007739
	Cataract cortical	10007748
	Cataract diabetic	10007749
	Cataract nuclear	10007759
	Cataract subcapsular	10007764
	Toxic cataract	10044135
Color vision decrease, abnormality or change	Chloropsia	10008585
	Chromatopsia	10008795
	Colour blindness	10010050
	Colour blindness acquired	10010051
	Colour vision tests abnormal	10010056
	Colour vision tests abnormal blue-yellow	10010057
	Colour vision tests abnormal red-green	10010058
	Cyanopsia	10051819
	Dyschromatopsia	10013892
	Erythropsia	10015290
Lens opacity, opacification or opalescence	Lens discolouration	10070549
	Lenticular opacities	10024214
	Posterior capsule opacification	10036346

AESI Category	MedDRA Preferred Terms (v 27.0)	Preferred Term Codes
Lens or lenticular abnormality	Acquired lenticonus	10064659
	Anterior capsular rupture	10081725
	Aphakia	10002945
	Lens disorder	10061219
	Posterior capsule neovascularisation	10081651
Macular degeneration, abnormality or change	Age-related macular degeneration	10064930
	Diffuse uveal melanocytic proliferation	10078228
	Dry age-related macular degeneration	10075567
	Macular cyst	10025407
	Macular degeneration	10025409
	Macular detachment	10075873
	Macular fibrosis	10071392
	Macular hole	10051058
	Macular opacity	10025416
	Macular pigmentation	10071041
	Macular rupture	10065319
	Macular thickening	10084571
	Maculopathy	10025425
	Neovascular age-related macular degeneration	10071129
	Pigmentary maculopathy	10054856
Night blindness	Delayed dark adaptation	10072729
	Night blindness	10029404
Optic nerve degeneration, abnormality or change	Myopic disc	10069088
	Optic atrophy	10030910
	Optic disc disorder	10061321
	Optic disc drusen	10030917
	Optic discs blurred	10030923
	Optic nerve cup/disc ratio decreased	10057513
	Optic nerve cup/disc ratio increased	10057567
	Optic nerve cupping	10030931
	Optic nerve disorder	10061322
	Papilloedema	10033712
	Pseudopapilloedema	10037141

AESI Category	MedDRA Preferred Terms (v 27.0)	Preferred Term Codes
Retinal degeneration, abnormality or change	Acute macular neuroretinopathy	10086444
	Central serous chorioretinopathy	10086644
	Myopic chorioretinal degeneration	10079959
	Pars plana cyst	10034051
	Retinal cyst	10038839
	Retinal degeneration	10038845
	Retinal depigmentation	10038846
	Retinal deposits	10038847
	Retinal detachment	10038848
	Retinal disorder	10038853
	Retinal drusen	10062776
	Retinal dystrophy	10038857
	Retinal fibrosis	10071391
	Retinal infiltrates	10064833
	Retinal microangiopathy	10087077
	Retinal pallor	10038891
	Retinal pigment epithelial tear	10062971
	Retinal pigment epitheliopathy	10038893
	Retinal pigmentation	10038894
	Retinal tear	10038897
	Retinal thickening	10077890
	Retinal toxicity	10048955
	Retinal white without pressure	10079569
	Retinoschisis	10061492
	Rhegmatogenous retinal detachment	10065569
	Serous retinal detachment	10040114
	Subretinal fibrosis	10062958
	Subretinal fluid	10069356
	Subretinal hyperreflective exudation	10082240
	Tractional retinal detachment	10080316

AESI Category	MedDRA Preferred Terms (v 27.0)	Preferred Term Codes
Retinal pigment epithelium detachment, abnormality or change	Acquired hypertrophy of the retinal pigment epithelium	10086462
	Chorioretinal disorder	10061763
	Chorioretinopathy	10063118
	Detachment of macular retinal pigment epithelium	10071004
	Detachment of retinal pigment epithelium	10052501
	Retinal dystrophy	10038857
Vision decreased, abnormality or change	Accommodation disorder	10000389
	Acute myopia	10078300
	Altered visual depth perception	10053549
	Aniseikonia	10002534
	Anisometropia	10002537
	Antimetropia	10059397
	Astigmatism	10003569
	Cortical visual impairment	10076660
	Delayed light adaptation	10079805
	Hemianopia	10019452
	Hemianopia heteronymous	10019455
	Hypermetropia	10020675
	Low luminance best-corrected visual acuity decreased	10074928
	Myopia	10028651
	Pathologic myopia	10073286
	Presbyopia	10036628
	Pseudomyopia	10075919
	Quadrantanopia	10077820
	Tunnel vision	10045178
	Visual field defect	10047555
	Visual impairment	10047571
	Visual snow syndrome	10079450
Visual acuity decreased, abnormality or change	Refraction disorder	10038264
	Visual acuity reduced	10047531
	Visual acuity reduced transiently	10047532

AESI Category	MedDRA Preferred Terms (v 27.0)	Preferred Term Codes
Visual acuity test abnormality or change	Retinoscopy abnormal	10082017
	Visual acuity tests abnormal	10047534

Table B-2. AESI for EPS with PTs

AESI Category	MedDRA Preferred Terms (v 27.0)	Preferred Term Codes
-	Akathisia	10001540
	Restlessness	10038743
Dystonia cluster	Dystonia	10013983
	Myoclonus	10028622
	Oculogyric crisis	10030071
	Oromandibular dystonia	10067954
	Tongue spasm	10043981
	Torticollis	10044074
	Trismus	10044684
Parkinsonism cluster	Akinesia	10001541
	Bradykinesia	10006100
	Cogwheel rigidity	10009848
	Drooling	10013642
	Dyskinesia	10013916
	Extrapyramidal disorder	10015832
	Hypokinesia	10021021
	Muscle rigidity	10028330
	Muscle tightness	10049816
	Parkinsonism	10034010
	Reduced facial expression	10078576
	Salivary hypersecretion	10039424
	Tremor	10044565
-	Musculoskeletal stiffness	10052904
	Tardive dyskinesia	10043118

Table B-3. AESI for Suicidality with PTs

MedDRA Preferred Terms (v 27.0)	Preferred Term Codes
Completed suicide	10010144
Depression suicidal	10012397
Intentional overdose	10022523
Intentional self-injury	10022524
Poisoning deliberate	10036000
Self-injurious ideation	10051154
Suicidal behaviour	10065604
Suicidal ideation	10042458
Suicide attempt	10042464

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The criteria for Potentially Clinically Significant (PCS) laboratory findings are described in Table C-1, Table C-2 and Table C-3, and the PCS criteria for vital sign findings are described in Table C-4, and the PCS criteria for ECG findings are described in Table C-5, and the PCS criteria for ophthalmologic findings are described in Table C-6.

Table C-1. Criteria for Potentially Clinically Significant Hematology Values

Hematology Variables	SI Units	Conversion Factor[a]	Conventional Unit	Definition of Potentially Clinically Significant	
				Very Low[b]	Very High[b]
Hemoglobin	g/L	0.1	g/dL	$< 0.9 \times LLN$	—
Hematocrit	Volume fraction	100	%	$< 0.9 \times LLN$	—
Eosinophils	%	1	%	—	> 10
Neutrophils	%	1	%	< 30	> 90
Basophils	%	1	%	—	> 6
Monocytes	%	1	%	—	> 20
Lymphocytes	%	1	%	< 10	> 60
Absolute neutrophils	10^9/L	1	$1000/\mu L$	< 1.0	—
Platelet count	10^9/L	1	$1000/\mu L$	≤ 75	≥ 700
White blood cell count	10^9/L	1	$1000/\mu L$	≤ 2.5	≥ 15

LLN = lower limit of normal value provided by the laboratory; SI = Le Système International d'Unités (International System of Units); ULN = upper limit of normal value provided by the laboratory

a. Conversion factor from SI units to conventional units.

b. Criteria refer to SI units.

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table C-2. Criteria for Potentially Clinically Significant Chemistry Values

Chemistry Variables	SI Units	Conversion Factor[a]	Conventional Unit	Definition of Potentially Clinically Significant	
				Very Low[b]	Very High[b]
Albumin	g/L	0.1	g/dL	$< 0.9 \times LLN$	$> 1.1 \times ULN$
Alkaline phosphatase	U/L	1	U/L	—	$\geq 3 \times ULN$
ALT	U/L	1	U/L	—	$\geq 3 \times ULN$
AST	U/L	1	U/L	—	$\geq 3 \times ULN$
GGT	U/L	1	U/L	—	$\geq 3 \times ULN$
LDH	U/L	1	U/L	—	$\geq 3 \times ULN$
Blood urea nitrogen	mmol/L	2.8011	mg/dL	—	$> 1.2 \times ULN$
Calcium	mmol/L	4.008	mg/dL	$< 0.9 \times LLN$	$> 1.1 \times ULN$
Chloride	mmol/L	1	mg/dL	$< 0.9 \times LLN$	$> 1.1 \times ULN$
Total cholesterol	mmol/L	38.6698	mg/dL	—	$> 1.3 \times ULN$
HDL cholesterol	mmol/L	39	mg/dL	$< 0.8 \times LLN$	—
LDL cholesterol	mmol/L	39	mg/dL	—	$> 1.2 \times ULN$
CPK	U/L	1	U/L	—	$> 1.5 \times ULN$
Creatinine	μmol/L	0.0113	mg/dL	—	$> 1.3 \times ULN$
Glucose, fasting	mmol/L	18	mg/dL	$< 0.8 \times LLN$	$> 1.2 \times ULN$
Potassium	mmol/L	1	mEq/L	$< 0.9 \times LLN$	$> 1.1 \times ULN$
Sodium	mmol/L	1	mEq/L	$< 0.9 \times LLN$	$> 1.1 \times ULN$
Total bilirubin	μmol/L	0.0585	mg/dL	—	$> 1.5 \times ULN$
Total protein	g/L	0.1	g/L	$< 0.9 \times LLN$	$> 1.1 \times ULN$
Triglycerides	mmol/L	88.5	mg/dL	—	$> 1.2 \times ULN$
Uric acid	μmol/L	0.0168	mg/dL	—	$> 1.1 \times ULN$

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LLN = lower limit of normal value provided by the laboratory; SI = Le Système International d'Unités (International System of Units); ULN = upper limit of normal value provided by the laboratory

a. Conversion factor from SI units to conventional units.

b. Criteria refer to SI units.

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table C-3. Criteria for Potentially Clinically Significant Urinalysis Values

Urinalysis Variables	SI Units	Conversion Factor[a]	Conventional Unit	Definition of Potentially Clinically Significant	
				Very Low[b]	Very High[b]
Protein	—	—	—	—	At least 2 +
Glucose	—	—	—	—	At least 2 +
Blood	—	—	—	—	At least 2 +

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

a. Conversion factor from SI units to conventional units.

b. Criteria refer to SI units.

Note: A post-baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table C-4. Criteria for Potentially Clinically Significant Vital Sign Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant[a]	
		Observed Value	Change From Baseline
Systolic Blood Pressure (mmHg)	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic Blood Pressure (mmHg)	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse Rate (bpm)	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight (kg)	High	—	Increase of $\geq 7\%$
	Low	—	Decrease of $\geq 7\%$

bpm = beats per minute

a. A post-baseline value is considered as a PCS value if it meets both the observed value and the change from baseline criteria.

Table C-5. Criteria for Potentially Clinically Significant Electrocardiographic Parameters

ECG Variables	SI Units	Conversion Factor	Conventional Unit	High 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 ($QTcB = QT/(RR)^{1/2}$); QTcF = QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)

Table C-6. Criteria for Potentially Clinically Significant Ophthalmologic Parameter

Ophthalmologic Variables	SI Units	Conversion Factor	Conventional Unit	Change from Baseline
Visual Acuity	logMAR	–	–	≥ 0.3