STATISTICAL ANALYSIS PLAN

A Phase 2, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Two Fixed Doses (15 mg and 30 mg QD) of CVL-231 in Subjects With Schizophrenia Experiencing an Acute Exacerbation of Psychosis

Protocol Number: CVL-231-2002

Compound: Emraclidine (CVL-231)

Trial Phase: 2

Short Title: A Placebo-controlled Trial of 15 and 30 mg QD Doses of CVL-231 in Subjects With Schizophrenia Experiencing an Acute Exacerbation of Psychosis

Sponsor Name: Cerevel Therapeutics, LLC

Protocol Version:	**Version 3.0:** 15 Mar 2023
	Version 2.0: 23 Feb 2022
	Version 1.0: 07 Dec 2021
Analysis Plan Version:	**Final 1.0:** 14 Oct 2024

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations planned for the analysis of efficacy, safety, and tolerability data from Protocol CVL-231-2002. Background information is provided for the study designs and objectives. Further details of study conduct, and data collection are provided in the study protocol and electronic case report forms (eCRFs).

1.1. Study Overview

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 6-week trial to evaluate the efficacy, safety, and tolerability of 2 fixed doses of emraclidine (15 mg once daily [QD] and 30 mg QD) in male and female subjects aged 18 to 65 years, inclusive, who have schizophrenia and are experiencing an acute exacerbation of psychosis. The trial will include up to a 15-day Screening Period (up to a maximum of 21 days allowed with approval of the medical monitor), a 45-day Inpatient Treatment Period, and a 28-day Follow-up Period. Each subject will participate in the trial for up to approximately 13 weeks.

Details of schedule of assessments are provided in Section 9.1.

Approximately 600 subjects will be screened to achieve approximately 372 subjects qualified to be randomized to treatment in the trial.

In the event of higher than anticipated early terminations due to COVID-19 or other reasons, Cerevel may extend enrollment in order to achieve trial objectives.

On Day 1 (Baseline), subjects will be randomized in a 1:1:1 ratio to the following treatment groups with approximately 124 subjects per treatment group:

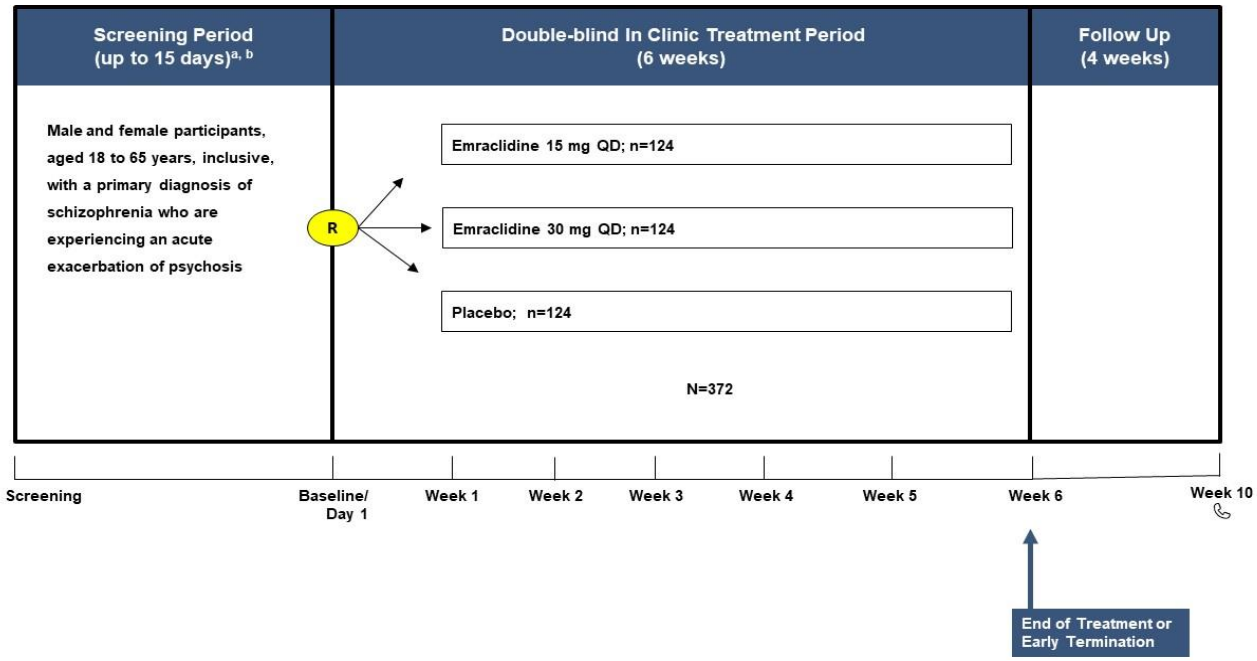
- Emraclidine 15 mg QD
- Emraclidine 30 mg QD
- Placebo QD

The randomization will be stratified by geographic region with 2 strata: United States or all other countries.

The daily dosing schedule will start on Day 1 with all subjects receiving a single, oral, daily dose of investigational medicinal product (IMP) in the morning. All subjects will continue dosing through Day 45 of Week 6.

The trial design is depicted in Figure 1.

Figure 1: Trial Schematic



Abbreviations: QD=once daily; R=randomization.
Note: Assessment time points are planned for the last day of the indicated week (eg, Day 7, 14, 21, etc) with a ±2 day window (see Schedule of Assessments in Section 9.1).

a. Subjects will be admitted to the inpatient facility at the time they sign the ICF and remain in the inpatient facility for the duration of treatment.
b. Extension of screening (up to a maximum of 21 days total) is allowed following discussion and documented approval by the medical monitor prior to the expiration of the Screening Period.

1.2. Sample Size Considerations

A sample size of approximately 93 subjects in each treatment group completing the Week 6 assessments (approximately 279 in total) should provide at least 90% power to detect an effect size of 0.48 in change from Baseline in the Positive and Negative Symptom Score (PANSS) total score at Week 6 between either active treatment group versus placebo at the α=0.05 level. The effect size of 0.48 represents a clinically meaningful effect on symptom reduction based on large scale meta-analysis of historical data from several currently approved antipsychotic medications in common usage (Leucht et al, 2013). It could be translated into a difference of 7 points versus placebo if the standard deviation of change from baseline is 14.6 points or a difference of 8 points versus placebo if the standard deviation of change from baseline is 16.7 points. Both scenarios of the standard deviation are consistent with historical observations. To account for a discontinuation rate of approximately 25% for a 6-week treatment period (as observed in Trial CVL-231-SCH-001), it is planned to randomize approximately 372 subjects.

1.3. Measures to Minimize Bias: Randomization and Blinding

1.3.1. Subject Assignment to Treatment

All subjects will be centrally randomized in a 1:1:1 ratio to 1 of 3 treatment groups (placebo, emraclidine 15 mg QD, or emraclidine 30 mg QD) on Day 1 via an interactive response technology (IRT) according to a computer-generated randomization scheme. Subjects will be sequentially assigned to the next available randomization number and will receive the IMP that corresponds to that randomization number. Once a randomization number has been assigned, it will not be reassigned.

The randomization will be stratified by geographic region with 2 strata: United States or all other countries.

1.3.2. Blinding

During the entire trial, treatment will be blinded such that subjects, the sponsor/designee, raters for clinician-administered scales, the investigator, and other site and trial personnel will not have knowledge of the treatment assignment at any visit. Access to the treatment codes will be restricted to personnel who are responsible for generating and maintaining the randomization code, packaging the IMP, operating the IRT, analyzing the pharmacokinetic (PK) blood samples, or reporting serious adverse events (SAEs) or adverse events of special interest (AESI) to regulatory agencies.

At the initiation of the trial, investigators and site personnel will be instructed on the method for breaking the blind. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of the treatment assignment for an individual subject is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor before unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. The medical monitor must be notified within 24 hours after breaking the blind for a trial subject.

Documentation of unblinding should be recorded in the subject's medical record, including the reason for breaking the blind, the date and time the blind was broken, and the names of the personnel involved. Once the blind is broken for a subject, treatment with the IMP may not be reinitiated for that subject.

1.4. Treatment Period

The daily dosing schedule will start on Day 1 with all subjects receiving a single daily dose of IMP in the morning.

Subjects are to remain in the inpatient facility for the entire duration of the trial (ie, from ICF signing through Week 6/ET); however, beginning at the Week 3 time point, subjects who are sufficiently stable (per investigator assessment) may receive day passes for urgent issues. While away from the site, subjects must be supervised by hospital/research staff (medical monitor approval for supervision by a family member or caregiver may be obtained). Subjects are not permitted to stay away from the inpatient facility overnight; if, in unforeseen circumstances, the

subject is unable to return to the facility the same day, the medical monitor should be contacted to discuss continuing subject eligibility. In addition, the subject must agree to submit to testing (ie, urine drug screen and alcohol breathalyzer test) upon return to the site.

All subjects will continue dosing through Day 45 of Week 6. Subjects will receive their last dose of IMP on Day 45.

Subjects who complete all trial visits, through Week 6 (Day 45), may be offered entry into an optional open-label rollover trial when the trial has been initiated for rollover participation.

2. OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are summarized in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult subjects with schizophrenia experiencing an acute exacerbation of psychosis	Primary Endpoint: • Change from Baseline at Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score Key Endpoint: • Change from Baseline at Week 6 in the Clinical Global Impression-Severity of Symptoms (CGI-S) score Secondary Endpoints: • Change from Baseline at all time points in PANSS total score • Change from Baseline at all time points in CGI-S score • Percentage of responders at Week 6 (responders defined as ≥30% reduction from Baseline in PANSS total score) Exploratory Endpoints: • Clinical Global Impression Improvement of Symptoms (CGI-I) at Weeks 3 and 6 • Change from Baseline at all time points in PANSS positive, negative, and general psychopathology subscale scores • Change from Baseline at all time points in PANSS Marder Factor scores

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult subjects with schizophrenia experiencing an acute exacerbation of psychosis	• Treatment-emergent adverse events (TEAEs) • Clinically significant changes in electrocardiograms (ECGs), clinical laboratory assessments and metabolic parameters, standard vital sign measurements, and physical and neurological examination results, including body weight • Clinically significant findings in suicidality assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) • Extrapyramidal symptoms evaluated using the change from Baseline in Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS) assessments
Exploratory	
• To evaluate the plasma pharmacokinetics of emraclidine and its metabolite, CV-0000364, following 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult subjects with schizophrenia experiencing an acute exacerbation of psychosis	• Pharmacokinetic parameters for emraclidine and its metabolite, CV-0000364 (C_{max} and AUC_{tau})
• To evaluate quality of life and cognition following 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult subjects with schizophrenia experiencing an acute exacerbation of psychosis	• Change from Baseline at Week 6 in Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding test • Change from Baseline at Week 6 in Short Form-6 Dimensions (SF-6D)

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; AUC=area under the concentration-time curve; BACS=Brief Assessment of Cognition in Schizophrenia; BARS=Barnes Akathisia Rating Scale; CGI-I=Clinical Global Impression-Improvement of Symptoms; CGI-S=Clinical Global Impression-Severity of Symptoms; C_{max}=maximum (peak) plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; PANSS=Positive and Negative Syndrome Scale; QD=once daily; SAS=Simpson Angus Scale; SF-6D=Short Form-6 Dimensions.

3. KEY ASSESSMENTS AND DERIVATIONS

3.1. Efficacy Assessments

3.1.1. Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al, 1999) is a clinical scale that has been extensively used as a reliable and valid measure of the negative and positive symptoms of schizophrenia (Liechti et al, 2017). The scale is used for measuring symptom severity in subjects with schizophrenia and is widely used in clinical trials of antipsychotic medications. The PANSS consists of 3 subscales containing a total of 30 symptom constructs. For each symptom construct, severity is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms. The symptom constructs for each subscale are as follows:

1. Positive Subscale – delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility
2. Negative Subscale – blunted affect, emotional withdrawal, poor rapport, passive pathetic withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, stereotyped thinking
3. General Psychopathology Subscale – somatic concern, anxiety, guilt feelings, tension, mannerism and posturing, depression, motor retardation, uncooperative, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance

All efforts to ensure the same rater administers the PANSS for a given subject at all time points should be made. The PANSS assessment should be completed prior to all other efficacy scales.

PANSS total score is defined as the sum of scores for each symptom construct per subject per visit.

3.1.1.1. Derivation of PANSS Subscale Score

The subscale score is defined as the sum of scores per subject per visit for all items included in each subscale described above.

3.1.1.2. Derivation of PANSS Marder Scores

Although the PANSS is structured as a scale to assess the 3 dimensions of schizophrenia, retrospective factor analyses have been performed using scores from the 30 individual PANSS items to categorize symptoms into 5 dimensions, which are collectively referred to as Marder Factor scores (Marder et al, 1997). These 5 dimensions include the following: negative symptoms, positive symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression.

3.1.1.3. Derivation of PANSS Proportion of Responders

The number and proportion of responders is defined as subjects with 30% reduction from Baseline in the PANSS total score at Week 6 or the early termination visit.

For subjects who discontinue and do not have an early termination visit, the subject's last assessment will be considered.

3.1.1.4. Handling of Missing Items from PANSS

If individual items are missing from a given subscale of PANSS for an individual subject at a given time point, the subscale total will be calculated by prorating the total of non-missing items if the number of missing items is no more than one item of the total number of items in the subscale. The PANSS total for an individual subject at a given time point will be similarly calculated by prorating the total of non-missing items if the number of missing items is no more than three items. If the number of missing items exceeds the specifications above, the subscale score or the total score for the individual subject at that time point will be considered missing.

3.1.2. Clinical Global Impression-Severity of Symptoms Scale

The severity of symptoms for each subject will be rated using the Clinical Global Impression-Severity of Symptoms Scale (CGI-S) (Guy, 1976). To perform this assessment, the investigator (or designee) will answer the following question: "Considering your total clinical experience with this particular population, how ill is the subject at this time?" Response choices are 0=not assessed; 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=among the most extremely ill subjects.

3.1.2.1. Derivation of CGI-S Proportion of Responders

The number and proportion of responders is defined as the following:

- Subjects having ≥ 1-point improvements from Baseline in CGI-S score at the Week 6 visit or the early termination visit. For subjects who discontinue and do not have an early termination visit, the subject's last assessment will be considered.
- Subjects having ≥ 2-point improvements from Baseline in CGI-S score at the Week 6 visit or the early termination visit. For subjects who discontinue and do not have an early termination visit, the subject's last assessment will be considered.

3.1.3. Clinical Global Impression-Improvement Scale

The Clinical Global Impression-Improvement Scale (CGI-I) is an observer-rated scale that will be used to measure the subject's symptom severity compared with before initiation of treatment with IMP (Guy, 1976). It is important to note that the observer or rater will provide their assessment of the subject's current level of symptoms compared with their symptoms at Baseline (Day 1).

The investigator (or designee) will rate the subject's change from Baseline in symptom severity using the following response choices: 0=not assessed, 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse.

3.1.4. Brief Assessment of Cognition in Schizophrenia – Symbol Coding Test

The symbol coding test of the Brief Assessment of Cognition in Schizophrenia (BACS) evaluates the cognitive domain related to processing speed, which is identified as important for clinical trials in schizophrenia. The test consists of subjects matching the numerals 1 to 9 to symbols on an electronic platform over a 90-second period. The outcome measure is the number of correct numerals over the time period and ranges from 0 to 110 (Keefe et al, 2004).

3.1.5. Short Form – 6 Dimensions Version 2.0

The Short Form-6 Dimensions (SF-6D) is a new, internationally adopted measure for assessing the cost-effectiveness of health care interventions. The SF-6D was developed by reducing the SF-36 to a 6-dimension classification (physical functioning, role participation, social functioning, bodily pain, mental health, and vitality) and developing an algorithm to generate a continuous index for health (Brazier et al, 2002). The algorithm shows how much value people place on different health limitations, and how they will trade-off between them; for example, how much vitality a subject will sacrifice for a reduction in pain. Version 2.0 of the SF-6D (SF-6Dv2) is an improved version of the SF-6D, the SF-6Dv2 classification system describes more distinct levels of health than SF-6D, changes the descriptions used for a number of dimensions, and provides clearer wording for health state valuation (Brazier et al, 2020).

3.2. Safety Assessments

3.2.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a subject or clinical trial subject, temporally associated with the use of trial intervention, whether or not considered related to the trial intervention. NOTE: Signs and symptoms and/or abnormal laboratory test result indicating a common underlying pathology/diagnosis should be reported as a single AE.

All adverse events will be recorded on the ADVERSE EVENTS eCRF. Adverse events with missing severity will have the severity imputed as ‘Grade 3’ for the AE tabulations. Adverse events with missing relationship to IMP will have the relationship imputed as ‘Related’ for the AE tabulations if the AE started on or after the first dose of IMP. However, in the data listings these missing severity and/or relationship will be presented as missing.

3.2.1.1. Adverse Event of Special Interest (AESI)

AESIs are defined as described in Protocol (Version 3.0: 15 March 2023) Section 8.3.7. All AESIs will be recorded as such on the ADVERSE EVENTS page of the eCRF.

3.2.1.2. Treatment-emergent Adverse Event (TEAE)

Any event reported on the eCRF that occurs on or after the initiation of IMP and up to the completion of follow-up period after discontinuation of IMP is considered treatment emergent. Additionally, it is assumed that an adverse event which was reported to have started on Day 1 without an associated onset time is assumed to be treatment emergent.

3.2.2. Electrocardiograms (ECG)

ECG recordings will be obtained after the subject has been supine and at rest for approximately 3 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an early termination. The ECG will be repeated if any results are considered to be clinically significant. Any clinically significant changes occurring during the trial will be recorded in the AE section of the eCRF.

At Screening, triplicate 12-lead ECGs are required to assess subject eligibility. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period. The central ECG service will provide the QTcF corrections and average of the 3 ECGs performed to determine eligibility.

At all other specified time points in the Schedule of Assessments (Section 9.1), where an ECG recording must be performed, only a single ECG is required.

3.2.3. Clinical Safety Laboratory Assessments

The clinical laboratory tests as listed in the protocol will be performed in accordance with the laboratory manual and the Schedule of Assessments (Section 9.1). All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

3.2.4. Vital Signs

Vital signs include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Triplicate blood pressure and heart rate measurements will be obtained after the subject has been supine and at rest for at least 3 minutes. Measurements will be obtained at approximately 1-minute intervals at the time points indicated in the Schedules of Assessments (Section 9.1). The triplicate values will be individually recorded, and the values will be averaged by the sponsor for all time point assessments following confirmation of eligibility. For determination of eligibility, the average of the last 2 values will be used.

The supine measurements will be followed by a single measurement in the standing position (after standing for approximately 2 minutes) to allow for orthostatic assessments. Orthostatic hypotension is defined as a decrease of ≥20 mmHg in systolic blood pressure and/or ≥10 mmHg in diastolic blood pressure upon standing compared with the average of the resting supine blood pressure measurement (as measured above).

3.2.5. Physical and Neurological Examinations

A full physical examination will include a review of the following body systems: head, ears, eyes, nose, mouth, skin, heart and lungs, lymph nodes, gastrointestinal, and musculoskeletal systems.

A limited physical examination will include evaluation of cardiovascular, pulmonary, and gastrointestinal systems.

A full neurological examination will include an assessment of the subject's mental status (level of consciousness, orientation, speech, memory, etc), cranial nerves, motor (muscle appearance, tone, strength, and reflexes), sensation (including Romberg sign), coordination, and gait.

3.2.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the trial using the C-SSRS.

This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version will be completed for all subjects at Screening to determine eligibility.

The "Since Last Visit" C-SSRS form will be completed after the Screening visit. The investigator will review the results of the "Since Last Visit" C-SSRS during the trial to determine whether it is safe for the subject to continue in the trial. If a subject has any "YES" answers on the C-SSRS for the suicidal ideation or suicidal behavior items, the investigator will evaluate whether a risk assessment by a qualified mental health professional (or the investigator alone if the investigator is a qualified mental health professional) is needed and discuss with the medical monitor whether the subject should continue in or be discontinued from the trial.

Details of C-SSRS categories as well as definition of treatment emerging events are provided in Section 9.2.

3.2.7. Prior Medications, Concomitant Medications and Medications Taken Post Last Dose of IMP

Prior medications are those medications taken prior to and ended prior to the initiation of IMP. Concomitant medications are those medications taken on or after the initiation of IMP. These medications include those medications started before the initiation of IMP and continuing post Day 1. Medications that start after the last dose of IMP will be classified as taken post last dose and will not be considered as concomitant. These medications will be recorded in the CONCOMITANT MEDICATIONS eCRF.

3.2.8. Prior Non-Drug Therapy/Procedures, Concomitant Non-Drug Therapy/Procedures, and Non-Drug Therapy/Procedures Taken Post Last Dose of IMP

Prior non-drug therapy/procedures are those therapies/procedures taken prior to and ended prior to the initiation of IMP. Concomitant non-drug therapy/procedures are those therapy/procedures taken on or after the initiation of IMP. These procedures include those procedures started before the initiation of IMP and continuing post Day 1. Procedures that start after the last dose of IMP will be classified as taken post last dose and will not be considered as concomitant. These procedures will be recorded in the NON-DRUG THERAPY AND PROCEDURES eCRF.

3.2.9. Extrapyramidal Symptoms (EPS)

EPS are serious side-effects of antipsychotic and other drugs. These symptoms can include parkinsonism, akathisia, dyskinesia, and other movement disorders. Rating scales such as the SAS, BARS, and AIMS can be used to assess the severity of the symptoms.

3.2.9.1. Simpson-Angus Scale (SAS)

The SAS (Simpson and Angus, 1970) consists of a list of 10 symptoms of parkinsonism (gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, head rotation, glabella tap, tremor, salivation, and akathisia). Each item is rated on a 5-point scale, with a score of 0 representing absence of symptoms and a score of 4 representing a severe condition. The SAS total score is the sum of the scores for all 10 items.

In case of missing item scores from the SAS, the missing value will be replaced by the sum of the of non-missing scores at the same visit from the same subject multiplied by the expected number of item scores (i.e., 10) and divided by the actual number of item scores contributing to the total score. In case all item scores are missing, the total score will be set as missing.

3.2.9.2. Barnes Akathisia Rating Scale (BARS)

The BARS (Barnes, 1989) consists of 4 items related to akathisia: objective observation of akathisia by the investigator, subjective feelings of restlessness by the subject, subjective distress due to akathisia, and global clinical assessment of akathisia. The first 3 items are rated on a 4-point scale, with a score of 0 representing absence of symptoms and a score of 3 representing a severe condition. The global clinical evaluation is made on a 6-point scale, with a score of 0 representing absence of symptom and a score of 5 representing severe akathisia. To complete this scale, subjects are observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning.

3.2.9.3. Abnormal Involuntary Movement Scale (AIMS)

The AIMS assessment (Guy, 1976) consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) are observed unobtrusively while the subject is at rest, and the investigator also makes global judgments on the subject's dyskinesias (items 8 through 10). Each item is rated on a 5-point scale, with a score of 0 representing absence of symptoms (for item 10, no awareness), and a score of 4 indicating a severe condition (for item 10, awareness, severe distress). In addition, the AIMS includes 2 yes/no questions that address the subject's dental status.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7.

In case of missing item scores from the AIMS, the missing value will be replaced by the sum of the of non-missing scores at the same visit from the same subject multiplied by the expected number of item scores (i.e., 7) and divided by the actual number of item scores contributing to the total score. In case all item scores are missing, the total score will be set as missing.

3.3. Pharmacokinetics

Venous blood samples will be collected in appropriately labeled tubes, at the times specified in the Schedule of Assessments (Section 9.1), to evaluate the PK of emraclidine and its metabolite CV-0000364.

All PK samples should be obtained at the exact nominal time relative to dosing. Samples obtained within 20% of the nominal time point (eg, within 12 minutes of a 60-minute sample) will not be considered a protocol deviation, as long as the exact time of sampling is captured in the source documents.

A fully validated bioanalytical method will be used to quantitate the concentrations of emraclidine and CV-0000364 (metabolite) in plasma.

4. DATA CONVENTIONS AND VISIT WINDOWS

4.1. Data Conventions

4.1.1. Age

Age is the age at the time of informed consent and is as captured on the eCRF.

4.1.2. Day 1 (Baseline)

Day 1 is the day IMP is first initiated.

4.1.3. Study Day of an Event

Study Day of an event is defined relative to Baseline (Day 1) as:

Study Day = event date – date of Day 1 (+ 1, if event date ≥ date of Day 1).

This calculation will result in negative study days for an event occurring prior to the start of IMP and positive study days for an event on or after the start of IMP. There will be no Day 0 value to match the schedule of events.

4.1.4. Days on Study

Days on Study is the number of days from Day 1 to the date of study completion or early termination as recorded on the END OF STUDY eCRF.

4.1.5. Days on IMP

Days on IMP is the number of days from Day 1 to the date of last dose of IMP as recorded on the OVERALL DOSING - BLINDED eCRF.

4.1.6. Baseline Value

For purposes of analysis, the baseline value is defined as the last value obtained prior to initiation of IMP. Should the Day 1 visit value be obtained after the first dose of IMP or if this value is not available at Day 1, then the most recent value obtained prior to earliest initiation of IMP will be used for the baseline value. For ECGs, baseline is the last non-missing value obtained prior to the initiation of IMP. If the last non-missing value is obtained at the screening visit, then the baseline is the average of the triplicates. For vital signs taken in triplicate, the baseline value will be defined as the average of the predose values on Day 1 (calculated separately for each collection position, if applicable). If the triplicate value is not available, then the last non-missing value obtained prior to the initiation of IMP will be used.

4.1.7. Change from Baseline

Change from baseline for a given endpoint is defined as the value on a given Study Day (Time Point) minus the Baseline Value.

4.1.8. Orthostatic Change

Orthostatic change is calculated as the difference in the standing value from the supine value (i.e., supine value – standing value). If an average value is available at a given visit, date, timepoint, it will be used for the calculation of orthostatic change. If an average value is not available, the individual record obtained on a given visit, date, and timepoint will be used.

4.1.9. Average Daily Dose of IMP

The average daily dose of IMP is calculated in milligrams and is based on the daily dose of IMP as recorded in the OVERALL DOSING – BLINDED eCRF. The average daily dose will be calculated as the cumulative dose divided by the expected days on study treatment.

4.1.10. Compliance with Study Drug

The date and dose (and time on days with PK assessments) of each IMP administration, along with information on any missed or inappropriately administered dose, will be recorded in source documents and the eCRF. Compliance will be ensured by a hand and mouth check during the oral dosing administration. Compliance will be calculated as a percentage based on the total number of doses taken relative to the total expected number of doses based on days on treatment as recorded in the OVERALL DOSING – BLINDED eCRF.

4.1.11. Time Since Diagnosis of Schizophrenia

Time (years) since diagnosis of schizophrenia is calculated as the difference in years from date of diagnosis to date of informed consent.

4.1.12. Handling of Incomplete or Missing Dates

Incomplete or missing start and end dates will be imputed for adverse events to determine treatment-emergence, for medications/non-drug therapies to determine when the medication/non-drug therapy was taken (i.e., pre-dose, concomitant, or post last dose of IMP), and for date of initial onset of schizophrenia to determine time since onset.

An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. The database contains data fields for month, day, and year. A date is incomplete if at least one of these three fields is not known.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

- Missing start day, but month and year present:

  If the event occurs in the same month and year as the occurrence of IMP, then the start day of the event will be assigned to the day of first dose of IMP (i.e., Day 1).

  Otherwise, the start day will be set to the first day of the month.

- Missing start day and month, but year present:

  If event occurs in the same year as IMP, then the start date of the event will be assigned to Day 1.

Otherwise, the start day and month will be set to 01 January.

- In the unlikely event of a completely missing start date (year not present), the start date will be imputed as Day 1.
- Missing end day, but month and year present:

  The day will be set to the last day of the month.
- Missing end day and month, but year present:

  The end day and month will be set to the date of study completion.

  However, if study completion year is greater than the year of the event, then the day and month will be set to 31 December.
- Missing all components of an end date and the event is not marked as ongoing:

  The event will be considered as 'ongoing' and will be considered treatment-emergent if the start date is on or after Day 1.

If any imputed start date causes the start date to occur after the end date, the end date will be used for the imputation of the start date. If any imputed end date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date. If the imputed date is later than the date of study withdrawal, then the date of study withdrawal will be imputed for the date. In subject data listings, start and stop date of events will be displayed as reported on the eCRF (i.e., imputed values will not be listed).

4.1.13. Handling of Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, as for example, "<0.1" or ">10", the data will be imputed for quantitative summaries. The actual values as reported in the database will be presented in data listings.

For incorporation in quantitative summaries (except for concentration data), the following imputation rules will be employed:

- The lower limit of quantification will be replaced with ½ the value of the lower limit. For example, < 0.1 will be replaced with 0.05.
- The upper limit of quantitation will be increased by one level of precision that precedes the value. For example, ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1".

Additionally, the upper limit of normal (ULN)/lower limit of normal (LLN) values may be reported as alphanumeric (e.g., '<5', '≤5', '>5', '≥5'). In these cases, if the ULN or LLN is necessary for determination of the laboratory severity grade, the following conventions will be employed:

If the value is in the form of ≤5, the ULN will be populated with the value after removing the symbol (i.e., the ULN is set to 5). If the value is in the form of <5, the ULN will be decreased by two levels of precision in the direction of the symbol (i.e., the ULN is set to 4.99).

If the value is in the form of ≥5, the LLN will be populated with the value after removing the symbol (i.e., the LLN is set to 5). If the value is in the form of >5, the LLN will be increased by two levels of precision in the direction of the symbol (i.e., the LLN is set to 5.01).

4.2. Analysis Visit Windows

Data collected longitudinally across visits will be summarized and analyzed by visit. Assessments made on scheduled visits will be mapped to an appropriate analysis visit that corresponds to the nominal visit. Early termination and unscheduled visits will be assigned to visit windows based on the study day of the event. For unscheduled and early termination vital signs, timepoint will be windowed. For unscheduled and early termination vital signs that occur on study day 1, the time of the last scheduled pre-dose triplicate on Day 1 (nominal visit) will be used to determine if the timepoint should be windowed to a pre-dose or post-dose timepoint. For all other study days, the timepoint will be assumed to be post-dose.

Table 2: Analysis Visit Window

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
PANSS and CGI-S		
≤ 1	Baseline	1
2-10	Week 1	7
11-17	Week 2	14
18-24	Week 3	21
25-31	Week 4	28
32-38	Week 5	35
≥ 39	Week 6	42
ECGs and C-SSRS		
≤ 1 (before Day 1 assessment + 1 hour)	Baseline	1
2-10	Week 1	7
11-17	Week 2	14
18-24	Week 3	21
25-31	Week 4	28
32-40	Week 5	35
≥ 41	Week 6	45
Blood Pressure and Heart Rate		
≤ 1 (before Day 1, Pre-Dose assessment)	Baseline	1
1 (after Day 1, Pre-Dose assessment)	Day 1	1
2-10	Week 1	7

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
11-17	Week 2	14
18-24	Week 3	21
25-31	Week 4	28
32-40	Week 5	35
≥ 41	Week 6	45
Respiratory Rate and Temperature		
≤ 1 (before Day 1, Pre-Dose assessment)	Baseline	1
2-10	Week 1	7
11-17	Week 2	14
18-24	Week 3	21
25-31	Week 4	28
32-40	Week 5	35
≥ 41	Week 6	45
Extrapyramidal Symptoms (SAS, AIMS, BARS), Laboratory Assessments (Chemistry, Hematology, Urinalysis, and Coagulation) and Weight		
≤ 1	Baseline	1
2 - 32	Week 3	21
≥ 33	Week 6	45
CGI-I		
1 - 32	Week 3	21
≥ 33	Week 6	42
BACS, SF-6D, and Laboratory Assessments (Prolactin and Urine Pregnancy Test)		
≤ 1	Baseline	1
≥ 2	Week 6	45

If assessments are collected multiple times within a given visit window, the scheduled visit, if available, will be used for summary presentations. If no scheduled visit is available, then the result closest to the scheduled visit date will be used for summary presentations. If two unscheduled measurements (early termination or unscheduled visit) have the same distance to the target date, the later value will be used. If a subject has multiple non-missing unscheduled values on the same date, then the last one is used, as determined by the time collected, if available.

5. STATISTICAL ANALYSIS METHODS

5.1. GENERAL CONSIDERATIONS

Descriptive statistical methods will be used to summarize the data from this trial, with statistical testing performed for the efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (N), number of observations (n), arithmetic mean, median, standard deviation (SD), coefficient of variation (CV%) (for concentration data only), first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous data, and frequencies and percentages for categorical data. Certain figure presentations will include the standard error of the mean (SE). The term "treatment group" refers to treatment assignment: treatment with 15 mg QD emraclidine, treatment with 30 mg emraclidine or placebo. All data collected from subjects who sign the informed consent form, including screen failures, will be included in data listings. Unless otherwise noted, the data listings will be sorted first by treatment group and subject number and then by date within each subject number.

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher.

5.2. Populations for Analyses

The analysis populations are defined (Table 3). [redacted]

Table 3: Populations for Analysis

Population	Description	Analysis
All Subjects Screened	All subjects who signed informed consent.	Disposition summary, Inclusion/Exclusion Criteria listings, and Demography listings
ITT	All randomized subjects	Demographic and Baseline Characteristics summaries, Patient History listings
FAS	All randomized subjects who receive at least 1 dose of IMP. This will be the safety analysis set.	Safety analysis
mITT	All randomized subjects who receive at least 1 dose of IMP and have both a baseline and at least 1 postbaseline PANSS assessment	Primary analysis set for efficacy
[redacted]	[redacted]	Demographic and Baseline Characteristics summaries, select safety and efficacy outputs
Endpoint completers	All subjects in the mITT population who complete the PANSS assessment at Week 6	Sensitivity analysis for efficacy
PK Analysis Set	All randomized subjects who receive at least 1 dose of IMP and have at least 1 measurable emraclidine concentration	PK analysis

Abbreviations: FAS=full analysis set; IMP=investigational medicinal product; ITT=intent-to-treat; mITT=modified intent-to-treat; PANSS=Positive and Negative Syndrome Scale; PK=pharmacokinetic.

5.3. Statistical Hypotheses

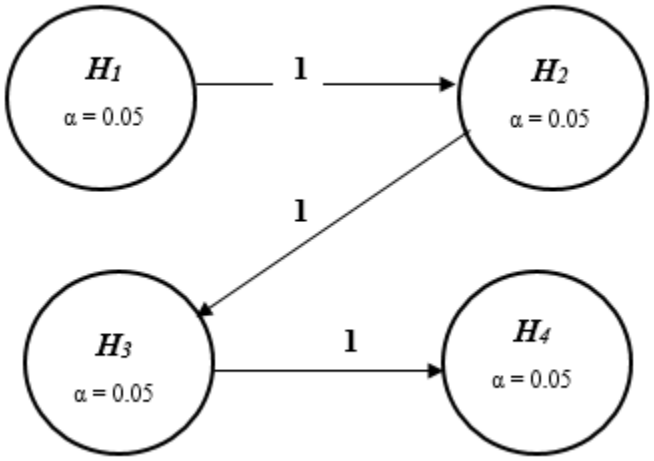
The primary hypotheses are summarized below. The tests will be conducted in hierarchical order from H_1 to H_2 at a 2-sided α level of 0.05. If both primary hypotheses H_1 and H_2 are successful, the key secondary endpoint of change from baseline CGI-S at Week 6 will be similarly tested in hierarchical order with respect to the 2 doses. The overall type I error rate thus is maintained at the 0.05 level.

Primary Endpoint	Emraclidine 30 mg QD vs Placebo	Emraclidine 15 mg QD vs Placebo
Change from Baseline to Week 6 in PANSS total score	$H_1: \mu_{active}=\mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$	$H_2: \mu_{active}=\mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$
Secondary Endpoint	**Emraclidine 30 mg QD vs Placebo**	**Emraclidine 15 mg QD vs Placebo**
Change from Baseline to Week 6 in CGI-S total score	$H_3: \mu_{active}=\mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$	$H_4: \mu_{active}=\mu_{placebo}$ vs $\mu_{active} \neq \mu_{placebo}$

Abbreviations: PANSS=Positive and Negative Syndrome Scale; QD=once daily; CGI-S=Clinical Global Impression-Severity of Symptoms Scale

5.4. Multiplicity Adjustment

A graphical approach depicted below illustrates the hierarchal multiple testing strategy planned for the hypotheses described above to control the overall Type I error rate. The primary endpoint of the emraclidine 30 mg QD will be compared with that of placebo (H_1) with full α of 0.05 and, if successful, the available α will be passed along fully (r=1) to the comparison of the primary endpoint of emraclidine 15 mg QD with placebo (H_2). If H_2 is successful, the full α will be available to the secondary hypothesis H_3. The sequence will continue until H_4 or until the sequence breaks with no α remaining available.



5.5. Strata and Covariates

Randomization was stratified by geographic region with two strata: United States or Other Countries.

The baseline value of each efficacy variable will be included as a covariate in the efficacy analyses.

5.6. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition will be based on the ITT population with tabulation of the number of subjects who complete the study and the number of subjects discontinued from the study and the reasons by treatment group. Additionally, the number of days on study will be summarized.

Further tabulation by region (United States, Other Countries) and country will also be presented. Subject disposition data will also be tabulated for all subjects screened to include the number of subjects screened, the number of screen failures, and the reason for screen failure.

Number of subjects in each analysis population set will be summarized.

Additionally, the number of subjects randomized at each site and overall will be summarized by country, treatment group, and overall. Summaries will be presented for randomized subjects and completed subjects.

Demographic data and baseline characteristics including age, age group, sex, fertility status, race, ethnicity, smoking status (smoker vs. non-smoker) at Baseline, height at screening, weight at screening and baseline, BMI at screening and baseline, will be summarized using descriptive statistics for the ITT population. Further tabulation by region and country also will be presented. [redacted]

Baseline disease characteristics including time (years) since diagnosis of schizophrenia, number of hospitalizations in the last 5 years, PANSS total score at Baseline, PANSS positive subscale score at Baseline, PANSS negative subscale score at Baseline, PANSS Marder Negative score at Baseline, PANSS delusions score at Baseline, PANSS conceptual disorganization score at Baseline, PANSS hallucinatory behavior score at Baseline, PANSS suspiciousness/persecution score at Baseline, CGI-S score at Baseline, change in PANSS total score from Screening to Baseline (Screening – Baseline), and percent change in PANSS total score from Screening to Baseline will be summarized by treatment group. Further tabulation by region and country also will be presented. [redacted]

5.7. Medical and Psychiatric History

Medical and psychiatric history events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher by preferred term and system organ class. Medical and psychiatric history will be summarized by treatment group using preferred terms and system organ classes. All events will be listed.

5.8. Exposure to Treatment

The duration of treatment, the number of subjects who prematurely discontinued IMP, the reasons for treatment discontinuation, treatment compliance, and average daily dose of IMP will be summarized by treatment group for the FAS population. [redacted]

5.9. Primary Efficacy Analysis

5.9.1. Primary Estimand

The key research question for the primary endpoint will be addressed with an estimand based on the following attributes:

1. Treatments: treatments as randomized regardless of the actual treatment received.
2. Target study population of interest: subjects in the mITT population.
3. Endpoint of interest: Change from Baseline to Week 6 in total PANSS score.
4. Population level summary of interest: the treatment differences estimated based on the least square mean and the corresponding 95% confidence interval from the mixed model of repeated measures (MMRM) model of the emraclidine groups and placebo group in the endpoint of interest.

5. Strategy for Intercurrent events (ICEs): A hypothetical strategy to address ICEs of potential death, treatment discontinuations, missed visits, and start of prohibited concomitant medications will be utilized. The data after the start of prohibited concomitant medications (ATC classifications of BUTYROPHENONE DERIVATIVES, INDOLE DERIVATIVES, and OTHER ANTIPSYCHOTICS) after the first dose of IMP and prior to the last dose of IMP with use duration of use of at least 4 days will be censored under the hypothetical strategy. The hypothetical strategy allows the study to assess the effect of emraclidine treatment without the confounding effect of prohibited concomitant treatments.

5.9.2. Main Analytical Approach

The change from baseline to each study visit in total PANSS score will be summarized by visit and treatment group. A MMRM analysis will be used to analyze the data from all post-randomization timepoints up to Week 6 with treatment, geographic region, visit, and treatment by visit interaction as fixed effect, subject as a random effect, and baseline PANSS score as a covariate. An unstructured covariance structure will be used for the repeated measures. If the unstructured covariance matrix results in convergence issue, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive (AR(1)) structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The difference between each emraclidine dose group and placebo at Week 6 will be estimated based on the Least Squares Mean (LSMean) difference between the treatment groups at Week 6 from the MMRM with the associated 95% confidence interval (CI) and P-value. A Cohen's D value will be derived as the ratio of the estimated difference to the population standard deviation at each visit estimated from the model (the square root of the diagonal elements of the estimated covariance matrix). The missing values are assumed to be missing at random for the main analysis, including missing due to missed visits or early termination due to COVID-19 control measures. The LSM (±SE) from the model will be plotted for change in PANSS total score by visit and treatment group. Similarly, the mean (±SD) of absolute values and change from Baseline PANSS total score will be presented by visit and treatment group.

5.9.3. Sensitivity Analyses

5.9.3.1. Treatment Effect based on Actual Treatment Received

Should a discrepancy between the study treatment received and the randomized treatment assignment occurred in 4 or more subjects, a sensitivity analysis may be conducted based on the study treatments that subjects actually received using the MMRM analysis method described in Section 5.9.2.

5.9.3.2. Impact of Missing Values Handling

Whilst every effort will be made to prevent avoidable missing values during the study conduct (National Research Council, 2010), it is unrealistic to expect no missing values in clinical trials. The impact of missing values on the analysis results will be assessed by the sensitivity analyses described below.

Under Missing at Random (MAR) Assumption

Multiple imputation (MI) will be performed to replace each missing value with a set of plausible values that represent the uncertainty about the correct value to impute. The Markov chain (MCMC) method will be utilized for the mITT set. SAS PROC MI will be used with MCMC method, assuming multivariate normality, to generate 25 possible imputed datasets: Each of these datasets will be analyzed using PROC MIXED in SAS using the MMRM model as described in Section 5.9.2. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

Considerations of Data Potentially Missing Not at Random (MNAR)

A pattern mixture model (PMM) approach will be used to address potential MNAR patterns. The following three patterns of subjects in the mITT set will be considered:

1. Subjects with no missing values from discontinuation or from initiation of prohibited concomitant medication during treatment period (No missing)
2. Subjects with missing values from the types of ICEs below will be considered having MNAR:
    a. Subjects who discontinue due to reasons, as recorded on the eCRF, of lack of efficacy, adverse events related to schizophrenia defined by AEHLGT of Schizophrenia and other psychotic disorders, physician decision, and withdrawal by subject
    b. Subjects who initiated concomitant prohibited medications (ATC classifications of BUTYROPHENONE DERIVATIVES, INDOLE DERIVATIVES, and OTHER ANTIPSYCHOTICS) after the first dose of IMP and prior to the last dose of IMP with use duration of use of at least 4 days will be considered having a potential confounding ICE. The efficacy data post the start of ICE will be treated as missing with the missing pattern of MNAR.

    The MNAR cases will be identified and documented prior to database lock and unblinding (Section 9.5).
3. Subjects with missing values from the type of ICEs below will be considered as having MAR
    a. Missing values after discontinuation due to reasons, as recorded on the eCRF, of death, pregnancy, loss to follow-up, adverse event unrelated to schizophrenia, non-compliance, site termination, and COVID-19 control measures will be considered as MAR.

The missing data with MNAR pattern #2 above in the active treatment groups will be imputed tipping point analysis. A set of shift parameters to encapsulate the change in efficacy associated with MNAR due to ICEs for each of the active treatment groups will be applied in the tipping point multiple imputation analysis as described in Ratitch et al. (2013). It is noted, however, MNAR in the placebo group will be imputed as MAR using the standard multiple imputation method.

The MAR pattern #3 above will be imputed using the standard multiple imputation method described above.

Other missing values due to missed visits/assessments before endpoint or discontinuation will also be assumed as MAR and imputed using the standard multiple imputation method for all three patterns.

Core codes for MAR and MNAR imputations are provided in Section 9.6.

Under Missing Completely at Random (MCAR) Assumption

An additional sensitivity analysis will be conducted on the Endpoint Completer set using the MMRM analysis method described in Section 5.9.2.

5.9.4. Subgroup Analyses

Subgroup analyses of the primary endpoint will be made based on the mITT set to assess consistency of the intervention effect across the following subgroups:

- Age group: < 40 vs ≥ 40 years
- Sex: Male vs Female
- Baseline PANSS Total Score: ≤ baseline median vs > baseline median (median of the mITT set regardless treatment group)
- Baseline CGI-S: ≤ baseline median vs > baseline median (median of the mITT set regardless treatment group)
- Race: White vs Black
- Region: United State vs Other Countries

If the number of subjects within a subgroup is too small (less than 10% of the mITT set), the subgroup categories may be redefined prior to unblinding the study. Provided that the sample sizes in the subgroups allow, the MMRM analysis method described in Section 5.9.2 will be applied to the subgroup analysis. Cohen's D will not be summarized for the subgroup analysis. The treatment effect across subgroups will be summarized by forest plots.

5.10. Key Secondary Efficacy Analyses

5.10.1. Secondary Estimand

The key research question for the first secondary efficacy variable will be addressed with an estimand based on the following attributes:

1. Treatments: treatments as randomized regardless of the actual treatment received.
2. Target study population of interest: mITT population.
3. Endpoint of interest: Change from Baseline to Week 6 in CGI-S score.
4. Population level summary of interest treatment differences estimated based on the least square mean and the corresponding 95% confidence interval from the MMRM model of the emraclidine groups and placebo group in the endpoint of interest.

5. Strategy for Intercurrent events (ICEs): A hypothetical strategy to address ICEs of potential death, treatment discontinuations, missed visits, and start of prohibited concomitant medications will be utilized. The data after the start of prohibited concomitant medications (ATC classifications of BUTYROPHENONE DERIVATIVES, INDOLE DERIVATIVES, and OTHER ANTIPSYCHOTICS) after the first dose of IMP and prior to the last dose of IMP with use duration of use of at least 4 days will be censored under the hypothetical strategy. The hypothetical strategy allows the study to assess the effect of emraclidine treatment without the confounding effect of prohibited concomitant treatments.

5.10.2. Main Analytical Approach

Similar to the analysis of the primary efficacy variable, the change from baseline to each study visit in CGI-S score will be summarized by visit and treatment group. A MMRM analysis will be used with treatment, geographic region, visit, and treatment by visit interaction as fixed effect, subject as a random effect, and baseline CGI-S score as a covariate. An unstructured covariance structure will be used for the repeated measures. If the unstructured covariance matrix results in convergence issue, the heterogeneous Toeplitz covariance structure followed by the AR(1) structure will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The difference between each emraclidine dose group and placebo at Week 6 will be estimated based on the LSMean difference between the treatment groups at Week 6 from the MMRM with the associated 95% CI and p-value. A Cohen's D value will be derived as the ratio of the estimated difference to the population standard deviation at each visit estimated from the model (the square root of the diagonal elements of the estimated covariance matrix). The missing values are assumed to be missing at random for the main analysis, including missing due to missed visits or early termination due to COVID-19 control measures. The LSM (±SE) from the model will be plotted for change in CGI-S score by visit and treatment group. Similarly, the mean (±SD) of absolute values and change from Baseline CGI-S score will be presented by visit and treatment group.

5.10.3. Sensitivity Analyses

The sensitivity analyses described in Section 5.9.3 for the primary estimand will also be performed for the key secondary efficacy estimand.

5.10.4. Subgroup Analyses

The subgroup analyses described in Section 5.9.4 for the primary estimand will also be performed for the key secondary efficacy estimand and secondary endpoints.

5.11. Summary of Primary and Key Secondary Efficacy Analyses

ICE Strategy	Primary Analysis	Sensitivity Analysis	Subgroup Analysis
Primary Endpoint: Change from Baseline to Week 6 in the PANSS total score			
Hypothetical strategy with data after treatment discontinuations or after the start of prohibited concomitant medications censored	• mITT population • Treatment as randomized • MMRM described in Section 5.9.2	• Treatment effect based on actual treatment received, if applicable • Missing values imputation using multiple imputations (MI) • Missing values imputation using pattern mixture model (PMM) • Endpoint completer analysis • [redacted]	• Age • Sex • Baseline PANNS Total Score • Baseline CGI-S • Race • Region
Key Secondary Endpoint: Change from Baseline to Week 6 in the CGI-S score			
Hypothetical strategy with data after treatment discontinuations or after the start of prohibited concomitant medications censored	• mITT population • Treatment as randomized • MMRM described in Section 5.9.2	• Treatment effect based on actual treatment received, if applicable • Missing values imputation using multiple imputations (MI) • Missing values imputation using pattern mixture model (PMM) • Endpoint completer analysis • [redacted]	• Age • Sex • Baseline PANNS Total Score • Baseline CGI-S • Race • Region

5.12. Other Secondary Efficacy Analyses

5.12.1. Change From Baseline at All Time Points In PANSS Total Score

The MMRM analysis described in Section 5.9.2 will also be the basis for evaluating the change from baseline at all time points.

5.12.2. Change From Baseline at All Time Points In CGI-S Score

The MMRM analysis described in Section 5.9.2 will also be the basis for evaluating the change from baseline at all time points.

5.12.3. Percentage of PANSS Responders at Week 6/Early Termination Visit

The binary outcome will be defined as having at least 30% reduction from baseline or not having a 30% reduction at Week 6 or the early termination visit. If a subject discontinues and does not have an early termination visit, the subject's last assessment will be used. Subjects who do not achieve a 30% reduction will be considered a non-responder.

A logistic regression model, with baseline PANSS and geographic region as a covariate, will be used to compare the proportion of responders in each active arm with placebo. Odd ratios will be constructed for each emraclidine treatment dose group compared with placebo and will be summarized with a 95% confidence interval. If expected counts are <5, then a Fisher's Exact test will be used.

Similarly, the analysis will be repeated by the subgroups defined in Section 5.9.4.

5.13. Summary of Analyses of Other Efficacy and Exploratory Endpoints

Endpoint	Analysis Population	Analysis Method
CGI-I at Weeks 3 and 6	mITT	MMRM described in Section 5.9.2.
Change from Baseline at all time points in PANSS positive, negative, and general psychopathology subscale scores	mITT	MMRM described in Section 5.9.2.
Change from Baseline at all time points in PANSS Marder Factor scores	mITT	MMRM described in Section 5.9.2.
Change from Baseline at all time points in PANSS delusions and hallucinatory behavior scores	mITT	MMRM described in Section 5.9.2.
Percentage of CGI-S responders (≥ 1-point improvement) at Week 6/ET visit	mITT	Logistic regression described in Section 5.12.3
Percentage of CGI-S responders (≥ 2-point improvement) at Week 6/ET visit	mITT	Logistic regression described in Section 5.12.3
Change from Baseline at Week 6 in BACS symbol coding test	mITT	MMRM described in Section 5.9.2.
Change from Baseline at Week 6 in SF-6D	mITT	MMRM described in Section 5.9.2.

5.14. Interim and Final Analysis

No interim analysis is planned.

A final analysis will be conducted once the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, the pre-analysis meeting has occurred, and the database has been locked.

5.15. Safety Analyses

All safety analyses will be performed on the FAS population. Should any subjects receive a treatment other than their randomized treatment, the treatment as received will be used in the safety presentation.

5.15.1. Adverse Events

Adverse events will be mapped to MedDRA version 26.0 or higher preferred term and system organ class. If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest investigator assessment of relation to IMP will be assigned to the preferred term for the appropriate summaries. Events with missing severity or relationship will be classified as outlined in Section 3.2.1. Summaries of treatment-emergent AEs will include any AEs reported beginning with the initiation of study drug on Day 1 through the follow up contact. An overall summary of TEAEs, including the number of subjects with a TEAE, TEAE related to IMP, AESI, serious TEAE, serious TEAE related to IMP, TEAE leading to discontinuation of

IMP, and TEAE leading to death will be summarized. [redacted] The occurrence of treatment emergent adverse events (TEAEs) will be summarized by treatment group using preferred terms, system organ classes, and severity. Separate summaries of TEAEs, treatment-emergent serious adverse events (TESAEs), TEAEs related to IMP, AESIs, events leading to discontinuation of IMP will be generated by system organ class and preferred term.

Treatment-emergent adverse events with ≥ 2% incidence in either one of the emraclidine arms and a greater incidence than the placebo arm will be summarized by preferred term. The most common TEAEs in either one of the emraclidine arms, defined as an incidence ≥5% and greater than 2 times of the incidence in the placebo group, will also be summarized by treatment group using preferred term. [redacted] All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. All adverse events that occurred prior to the initiation of study treatment will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.1.12 as required to determine treatment-emergent events.

5.15.2. Medications and Non-Drug Therapy/Procedures

Prior medications, concomitant medications, and medications taken post last dose of IMP will be coded using the World Health Organization (WHO) drug dictionary (WHODrug) (Version: Global B3 September 2023 or later). Prior medications, concomitant medications and medications taken post last dose of IMP will be summarized by treatment group, frequency of drug classification, and generic drug name. All medications will be presented in a data listing.

Prior non-drug therapy/procedures, concomitant non-drug therapy and procedures, and non-drug therapy/procedures taken post last dose of IMP will be coded using MedDRA Version 26.0 or higher. Concomitant non-drug therapy/procedures and non-drug therapy/procedures taken post last dose of IMP will be summarized by treatment group, frequency of system organ class and preferred term. All non-drug therapy/procedures will be presented in a data listing.

5.15.3. Clinical Laboratory Assessments

Descriptive summaries of selective (quantitative) clinical laboratory results and change from baseline will be presented by study visit. Additionally, for hematology, blood chemistry, coagulation, and urinalysis parameters, toxicity grade will be determined for laboratory tests with toxicity grade specified in Section 9.3. Shifts from baseline to greatest (worst) post-baseline laboratory grade will be presented. For parameters not graded as described above, laboratory values outside the normal range for each systematically collected hematology, blood chemistry, and urinalysis parameters defined in Protocol Section 10.2 will be identified using shift tables. Each subject's hematology, blood chemistry, and quantitative urinalysis values will be flagged as "low" (below the lower limit of normal/LLN), "normal" (within the normal range), or "high" (above the upper limit of normal/ULN) relative to the normal ranges of the central laboratory. Each subject's qualitative urinalysis values will be flagged as "normal" or "abnormal". Shifts from baseline to high/normal/low status for the hematology, blood chemistry, and urinalysis parameters will be presented to for the maximum post-baseline value and the minimum

post-baseline value for each laboratory test. Shifts from baseline to normal/abnormal status for urinalysis parameters will be presented to the maximum post-baseline value and the minimum post-baseline value for each laboratory test.

The number and percentage of subjects who have post-baseline elevations in transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or bilirubin abnormalities in relation to fold above the upper limit of normal will be summarized according to the Food and Drug Administration's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry (FDA 2009). Abnormal hepatic laboratory values will be categorized and evaluated for any occurrence among all post-baseline assessments. [redacted] Within each laboratory parameter grouping, a subject may be counted once per elevation criteria using the worst-case result. That is, a subject with a worst-case ALT elevation >5 × the ULN would be counted once in the ALT > 3 × ULN category and once in the ALT > 5 × ULN category, regardless of how many ALT elevations the subject had that met the > 5 × ULN and > 3 × ULN elevation criteria.

- ALT and/or AST > 3 × ULN and total bilirubin > 1.5 or 2 × ULN at the same visit
- ALT and/or AST > 3 × ULN and alkaline phosphatase (ALP) < 2 × ULN and total bilirubin > 1.5 or 2 × ULN at the same visit
- AST > 3, 5, 10, 20 × ULN
- ALT > 3, 5, 10, 20 × ULN
- Total bilirubin > 1.5, 2 × ULN
- ALP > 1.5 × ULN, > ULN to 2.5 × ULN, > 2.5 to 5 × ULN, > 5 to 20 × ULN, > 20 × ULN

In addition, an eDISH plot, a shift plot showing liver safety panel tests over time (baseline vs. post-baseline), and distribution plots of ALT, AST, ALP, and bilirubin over time will be produced to aid identification of any potential cases (Merz M. et. al. 2014). The plots to be included are the scatter plot of maximum transaminase versus maximum bilirubin, the liver test safety panel over time, and the distribution of ALT by time. The distribution plots for AST, ALP, and bilirubin will use the same format as used for ALT.

The number and percentage of subjects who have glucose and lipid abnormalities will be summarized. The criteria are defined as follows:

- Glucose
  - Normal (< 100 mg/dL) to High (≥ 126 mg/dL)
  - Borderline (≥ 100 mg/dL and < 126 mg/dL) to High (≥ 126 mg/dL)
- Triglycerides
  - Increase by ≥ 50 mg/dL
  - Normal (< 150 mg/dL) to High (≥ 200 mg/dL)
  - Borderline (≥ 150 mg/dL and < 200 mg/dL) to High (≥ 200 mg/dL)

- Total Cholesterol
  - Increase by ≥ 40 mg/dL
  - Normal (< 200 mg/dL) to High (≥ 240 mg/dL)
  - Borderline (≥ 200 mg/dL and < 240 mg/dL) to High (≥ 240 mg/dL)
- LDL Cholesterol
  - Increase by ≥ 30 mg/dL
  - Normal (< 100 mg/dL) to High (≥ 160 mg/dL)
  - Borderline (≥ 100 mg/dL and < 160 mg/dL) to High (≥ 160 mg/dL)
- HDL Cholesterol
  - Normal (≥ 40 mg/dL) to Low (< 40 mg/dL)

The "Normal" and "Borderline" criteria refer to the value at baseline. The "High" and "Low" criteria refer to the post-baseline value. The "Increase" criteria refer to an increase from baseline to the post-baseline value. Within each laboratory parameter grouping, a subject may be counted once per criteria. Subjects will only be included who meet the baseline criteria and have at least one post-baseline value for the parameter.

5.15.4. Vital Signs

5.15.4.1. Blood Pressure and Heart Rate

Blood and heart rate measurements and corresponding changes from baseline will be listed and summarized by treatment group, and visit using descriptive statistics.

An MMRM analysis as described in Section 5.9.2, excluding Cohen's D, will be used to compare the changes from baseline in supine blood pressures and heart rate of each dose group with the placebo group as summarized below.

Endpoint	Analysis Population	Analysis Method
Change from Baseline at all time points of supine heart rate	FAS	MMRM described in Section 5.9.2.
Change from Baseline at all time points of supine blood pressure	FAS	MMRM described in Section 5.9.2.

In addition, out of range vital signs occurring post-baseline will be summarized. For supine blood pressure and heart rate, records are eligible if they are post-baseline and are records chosen for analysis or if they are post-baseline and an average record. All post-baseline records are eligible for orthostatic blood pressure.

- Systolic Blood Pressure (Supine)
  - < 90 mmHg
  - > 140 mmHg and ≤ 160 mmHg

  - > 160 mmHg and ≤ 200 mmHg
  - > 200 mmHg
- Orthostatic Change in Systolic Blood Pressure
  - ≥ 20 mmHg decrease upon standing compared with supine position
- Diastolic Blood Pressure (Supine)
  - < 50 mmHg
  - > 90 mmHg and ≤ 100 mmHg
  - > 100 mmHg and ≤ 120 mmHg
  - > 120 mmHg
- Orthostatic Change in Diastolic Blood Pressure
  - ≥ 10 mmHg decrease upon standing compared with supine position
- Heart Rate (Supine)
  - < 50 bpm
  - ≥ 50 bpm and < 60 bpm
  - > 100 bpm and ≤ 120 bpm
  - > 120 bpm

[redacted] Blood pressure and heart rate results, including orthostatic changes, will be listed.

5.15.4.2. Body Weight

Body weight and corresponding changes from baseline will be listed and summarized by treatment group, and visit using descriptive statistics.

An MMRM analysis as described in Section 5.9.2, except Cohen's D, will be used to compare the changes from baseline in body weight of each dose group with the placebo group. In addition, the frequency of subjects with ≥ 7% increase from baseline anytime during the treatment period will also be summarized. The highest weight increase from baseline across visits will be evaluated against the criterion ≥ 7% increase and summarized in the vital sign out of range table.

5.15.4.3. Respiratory Rate and Temperature

Other vital sign measurements including respiratory rate and temperature will be listed. The frequency of subjects with out-of-range temperature and respiratory rate occurring post-baseline will be summarized. All post-baseline records are eligible for respiratory rate and temperature.

- Temperature
  - < 36°C

  - > 38°C
- Respiratory Rate
  - < 12 breaths/min
  - > 20 breaths/min

5.15.5. Electrocardiograms (ECGs)

ECGs and corresponding changes from baseline will be summarized by treatment group and visit using descriptive statistics.

The number and percentage of subjects who experience any post-baseline occurrence of potentially clinically significant corrected QT values using Fridericia's method (QTcF) will be summarized by treatment group. These presentations will include QTcF values > 450 to ≤ 480, > 480 to ≤ 500, and > 500 msec; or changes of > 30 to ≤ 60 or > 60 msec. [redacted]

5.15.6. Physical and Neurological Examinations

Physical and neurological examination data will be listed.

5.15.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

The maximum post-baseline results from the C-SSRS will be summarized. The maximum of each subscale (suicidal ideation [Categories 1-5], suicidal behavior [Categories 6-10], suicidal ideation or behavior [Categories 1-10], and self-injurious behavior without suicidal intent) will be presented. The number of patients with suicide-related treatment-emergent events, treatment-emergent suicidal ideation, and suicidal behavior, based on a comparison of the C-SSRS at baseline and/or previous lifetime experience to maximum C-SSRS scores across all post-baseline assessments will be provided for each treatment. All C-SSRS elements will be reflected in a listing.

5.15.8. Extrapyramidal Symptoms (EPS)

The total score of each EPS assessment scale: Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS), will be listed and summarized by treatment group, and visit, with the corresponding changes from baseline, using descriptive statistics.

An MMRM analysis as described in Section 5.9.2, except Cohen's D, will be used to compare the changes from baseline in the total score of each scale of each dose group with the placebo group.

5.16. Pharmacokinetics

All PK listings and individual plasma concentration-time profiles will be presented using the FAS population. PK summary tables, mean figures and all statistical analyses will be presented using the PK analysis set.

Serial venous blood samples were collected as described in Section 3.3 and the Schedule of Assessments (Section 9.1) for PK assessment. PK collections that have an actual sampling time that deviates from the predefined collection time window (i.e., within 20% of the nominal time point [eg, within 12 minutes of a 60-minute sample]) will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Individual plasma concentrations will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV%, median, minimum, and maximum) by analyte, day, treatment, and time point. Individual plasma concentrations will be plotted by actual sample times on both linear and semi-logarithmic scales, by analyte, day, and treatment. Mean (+SD) plasma concentrations will be plotted with nominal sample times on both linear and semi-logarithmic scales with both treatments overlaid on the same plot by analyte.

5.16.1. Data Handling

5.16.1.1. Pharmacokinetic Profile Exclusions

Changes to the procedures or events which may impact the quality of the PK data, will be considered important protocol deviations or events and will be described within the clinical study report body text. These events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, vomiting following oral dosing occurring within the time frame of 2 times the median T_{max}, sample processing errors that lead to inaccurate bioanalytical results, and/or inaccurate dosing on the day of PK. In the case of an important event, PK data collected during the affected treatment day will be evaluated on a case-by-case basis, be listed but may be excluded from descriptive statistics. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered important events. All exclusions will be documented throughout the affected data listings.

5.16.1.2. Data Rounding

Data rounding specifications for PK data are documented in the PK Table, Listing, and Figure (TLF) shells. Pharmacokinetic parameters will be rounded for reporting purposes both in the summary tables and individual listings. The unrounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. All concentration data will be reported and analyzed with the same precision as the source data regardless of how many significant figures or decimals the data carry. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., C_{max}) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., T_{max}) will be reported in hours with 2 decimal places.

For the reporting of descriptive statistics for concentrations and PK parameters, the mean (arithmetic or geometric) and SD will be presented to 1 digit more precision than the source data. The minimum, median, and maximum will be presented to the same precision as the source data.

Coefficient of variation and GeoMean CV% will be reported to 1 decimal place. Percentage will be reported using 1 decimal place, if not otherwise specified. N and n will be presented to 0 decimal place.

5.16.1.3. Below the Limit of Quantification Values

Plasma concentrations that are below the limit of quantification (BLQ) will be reported as the source data on the data listings. Plasma concentrations that are BLQ will be treated as zero for calculation of concentration descriptive statistics. Mean concentrations will be reported as zero if all values are BLQ, and no other descriptive statistics will be reported. If the calculated mean concentration is below the limit of quantitation, the mean will be reported as BLQ and the SD and CV% shall be reported as not determined (ND). Minimum, median, and maximum may be reported and, if any are BLQ, they shall be reported as such and indicated as BLQ.

For PK analysis, all BLQ values will be treated as zero, with the exception of BLQ values observed between 2 quantifiable concentrations which will be set to missing. Missing values will not be imputed. Additionally, if consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the plasma concentration-time curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

5.16.1.4. Missing Data

All missing concentration data will be presented as missing in concentration data listings and excluded from the concentration summary statistics. However, for the estimation of PK parameters for Day 24, missing predose concentrations will be imputed as the end of dosing interval (tau) concentration, where measurable. This imputation will be performed programmatically in the PK analysis input file.

Otherwise, missing results will be treated as missing and not imputed.

5.16.1.5. Predose Samples Collected Postdose

Predose samples collected in error after dosing will be listed, flagged and excluded from the calculation of concentration summary statistics; however, will be included in the estimation of PK parameters using the actual time relative to dosing.

5.16.1.6. Summary Statistics

Quantitative variables will be summarized using descriptive statistics as follows:

- Plasma concentrations: number of subjects, number of non-missing observations, arithmetic mean, standard deviation, percent coefficient of variation, median, minimum, and maximum.
- Plasma PK parameters: N, n, arithmetic mean, SD, CV%, geometric mean, geometric mean CV%, median, minimum, and maximum. T_{max} will be summarized using N, n, median, minimum, and maximum only.

A minimum of n=3 is required for all descriptive statistics to be generated. If n is less than 3, only N, n, minimum, and maximum will be reported.

5.16.2. Pharmacokinetic Analysis

Plasma concentration-time data will be analyzed by non-compartmental methods using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ) or SAS® (SAS Institute Inc., Cary, North Carolina) Version 9.4 or higher. The following PK parameters will be calculated on Day 24 for CVL-231 (emraclidine) and its metabolite (CV-0000364), where data permit:

PK Parameter	Definition
C_{max}	Maximum (peak) observed concentration.
T_{max}	Time of maximum (peak) observed concentration.
$AUC_{0\text{-}last}$	AUC from time 0 to the last measurable concentration (C_{last}), calculated using the linear up log down trapezoidal rule.
$AUC_{0\text{-}tau}$	Area under the plasma concentration time curve over the dosing interval, calculated using the linear up log down trapezoidal rule.

$AUC_{0\text{-}tau}$ will not be calculated if λ_z cannot be determined or is not reliable to extrapolate to tau.

Additional PK parameters may be calculated.

Actual sampling times will be used for the estimation of all plasma PK parameters, and all concentrations associated with scheduled sampling times will be included in the analysis (including concentrations collected outside predefined collection windows). Unscheduled PK samples will not be included in the estimation of PK parameters.

Plasma PK parameters for CVL-231 (emraclidine) and metabolite CV-0000364 will be presented in data listings and summarized using descriptive statistics (see Section 5.16.1.6) by analyte and treatment. Any excluded parameters will be flagged and included in the individual listings.

5.17. Protocol Deviations

All protocol deviations will be reviewed by the project team prior to unblinding to identify subjects with important protocol deviations. Summaries of important deviations will be presented by category of deviation. All deviations from the protocol will be listed by category along with a description and any additional comments.

6. CHANGES IN THE PLANNED ANALYSES

Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

7. REVISION HISTORY

Date	Revision	Rationale

8. REFERENCES

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9. APPENDICES

9.1. Schedule of Assessments

Table 4: Schedule of Assessments

Trial Periods/Phases	Screening Period [a,b,c]	Treatment Period											Follow-up[d]
Week	**-2 to -1**	**-**	**-**	**1**	**2**	**3[e]**	**-**	**4**	**5**	**6[f]**		**ET[g]**	**10**
Day	**-15 to -1**	**1/ Baseline[h]**	**4**	**7±2**	**14±2**	**21±2**	**24**	**28±2**	**35±2**	**42±2**	**45±2**	**NA**	**73±3**
Entrance and History													
Informed consent	X												
Inclusion/exclusion criteria	X	X[i]											
Medical and psychiatric history[j]	←----------	----------→											
MINI	X												
Demography	X												
History of drug and alcohol use	X												
Smoking history	X	X											
Review of birth control methods	X												
Breathalyzer test for alcohol[k]	X												
SARS-CoV-2 testing[c]	X												
Randomization		X											
Efficacy/Health Economics Assessments[l]													
PANSS	X	X		X	X	X		X	X	X		X	
CGI-S	X	X		X	X	X		X	X	X		X	
CGI-I[m]						X				X		X	

Trial Periods/Phases	**Screening Period** [a,b,c]	**Treatment Period**											**Follow-up**[d]
Week	**-2 to -1**	**-**	**-**	**1**	**2**	**3**[e]	**-**	**4**	**5**	**6**[f]		**ET**[g]	**10**
Day	**-15 to -1**	**1/ Baseline**[h]	**4**	**7±2**	**14±2**	**21±2**	**24**	**28±2**	**35±2**	**42±2**	**45±2**	**NA**	**73±3**
BACS		X									X	X	
SF-6D		X									X	X	
Safety Assessments													
Physical/neurological examination[n]	X										X	X	
Limited physical examination[o]		X											
Height (Screening only) and weight	X	X				X					X	X	
ECG[p]	X	X		X	X	X		X	X		X	X	
Heart rate and blood pressure (including orthostatic)[q]	X	X		X	X	X		X	X		X	X	
Respiratory rate and temperature	X	X		X	X	X		X	X		X	X	
C-SSRS[r]	X	X		X	X	X		X	X		X	X	
EPS (SAS, AIMS, BARS)[s]	X	X				X					X	X	
Prior/concomitant treatments[t]	←----------												----------→
Adverse event monitoring[u]		←----------											----------→
Laboratory													
Blood for safety laboratory sample	X	X				X					X	X	
Urine for safety laboratory	X	X				X					X	X	

Trial Periods/Phases	**Screening Period** [a,b,c]	**Treatment Period**											**Follow-up**[d]
Week	**-2 to -1**	**-**	**-**	**1**	**2**	**3**[e]	**-**	**4**	**5**	**6**[f]		**ET**[g]	**10**
Day	**-15 to -1**	**1/ Baseline**[h]	**4**	**7±2**	**14±2**	**21±2**	**24**	**28±2**	**35±2**	**42±2**	**45±2**	**NA**	**73±3**
Prolactin level[v]		X									X	X	
Serum pregnancy test[w]	X												
Urine pregnancy test[w]		X									X	X	
Urine drug screen[x]	X	X											
Hepatitis B, C, HIV	X												
PK blood sample			X[y]				X[z]					X[aa]	
Blood sample for future biospecimen research[bb]		X											
Other													
Daily morning dose of IMP		←----------										----------→	

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BACS= Brief Assessment of Cognition in Schizophrenia; BARS=Barnes Akathisia Rating Scale; CGI-I=Clinical Global Impression-Improvement of Symptoms; CGI-S=Clinical Global Impression-Severity of Symptoms; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EPS=extrapyramidal symptoms; ET=early termination; HIV=human immunodeficiency virus; IMP=investigational medicinal product; MINI=Mini International Neuropsychiatric Interview; PANSS=Positive and Negative Syndrome Scale; PK=pharmacokinetic; SAS=Simpson-Angus Scale; SF-6D=Short Form-6 Dimensions.

[a] Extension of screening (up to a maximum of 21 days total) is allowed following discussion and documented approval by the medical monitor prior to the expiration of the Screening Period.

[b] Subjects will be admitted to the inpatient facility at the time they sign the ICF and remain in the inpatient facility for the duration of treatment.

[c] Subjects must have SARS-CoV-2 testing done with a negative test result prior to admission to the inpatient facility; refer to site procedures for additional details on testing. Additional SARS-CoV-2 testing may be performed after admission per the investigator's discretion and according to site procedures.

[d] Contact with subject via phone call or other means of communication to check on their status.

[e] Beginning at the Week 3 time point, subjects may receive supervised day passes for urgent issues at the investigator's discretion as described in protocol Section 4.1.2. A breathalyzer test and a urine drug screen must be performed upon return to the inpatient facility for any subject issued a supervised day pass. If the breathalyzer test is positive, the medical monitor should be contacted to determine the next steps. Subjects returning from a day pass who have a positive urine drug screen should be discontinued from the trial. However, if the positive urine drug screen results from use of marijuana (any THC containing product), prescription, or over the counter

medications or products that, in the investigator's documented opinion, does not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results, the subject may continue in the trial following consultation and approval by the medical monitor.

[f] A minimum of 3 days is required between the Week 6 Day 42 assessments (ie, PANSS, CGI-S, and CGI-I) and the Day 45 assessments (ie, all other scales and safety measures); eg, if the Week 6 Day 42 assessments are done on trial day 43, the earliest the Week 6 Day 45 assessments can be done is trial day 46.

[g] All Week 6 (ie, both Day 42 and Day 45 time points) assessments should be completed on a single day (ie, no need for 3-day separation) for any subject who discontinues early from the trial. All assessments should be completed prior to reinitiation of antipsychotic therapy, whenever possible. If antipsychotic therapy has been initiated, the efficacy scales (PANSS, CGI-S, CGI-I) should not be conducted.

[h] Unless indicated otherwise, all assessments to be completed prior to dosing.

[i] Inclusion/exclusion criteria will be assessed at Baseline to ensure ongoing subject eligibility, with the exception of age or assessments that are only scheduled during Screening (eg, height for body mass index calculation). This includes the PANSS total score assessment to ensure no decrease of ≥20% between Screening and Baseline, as per Exclusion Criterion #4 (see protocol Section 5.2.).

[j] Medical occurrences that begin before the start of dosing with IMP but after obtaining informed consent should be collected as medical and/or psychiatric history.

[k] An alcohol test (breathalyzer) is required at Screening and upon return to the inpatient facility for any subject who leaves the inpatient facility. The medical monitor should be contacted to determine the next steps for subjects returning from a day pass who have a positive breathalyzer test. An alcohol test (breathalyzer) can be conducted at any time during the trial at the discretion of the investigator.

[l] PANSS and CGI-S/CGI-I assessments should be completed before other assessments, following the preferred order described in protocol Section 8.

[m] All responses will be relative to the subject's condition at Day 1, prior to first dose of IMP.

[n] Full physical and neurological examinations should be completed at Screening and Week 6/ET. Symptom-driven physical and/or neurological examinations may be done at any time during the trial at the investigator's discretion.

[o] Details for limited physical examination are provided in protocol Section 8.2.2.

[p] 12-lead ECG assessments will be performed after the subject has been at rest for approximately 3 minutes. At Screening, the average of 3 consecutive ECGs collected 1 to 2 minutes apart will be used to determine subject eligibility; at Baseline, only 1 reading is required for determination of eligibility. At approximately 2 hours following dosing at weekly time points, single 12-lead ECGs will be obtained. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).

[q] At Screening and Baseline, blood pressure and heart rate assessments should be performed in order to confirm eligibility (see Exclusion Criterion in protocol Section 5.2). Triplicate supine heart rate and blood pressure measurements should be taken at approximately 1-minute intervals predose (Day 1 only, Baseline), and at approximately 2 hours after dosing on Day 1 and Weeks 1 through 6. The triplicate supine heart rate and blood pressure measurements will be followed by a single measurement after approximately 2 minutes in a standing position to allow for orthostatic assessments. Additional time points can be added at the investigator's discretion (eg, if abnormalities are noted).

[r] The "Baseline/Screening" C-SSRS form will be completed for all subjects at Screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at Baseline to ensure that the subject continues to qualify for the trial. The "Since Last Visit" C-SSRS form will also be completed at weekly time points after Baseline.

[s] EPS assessments can be completed at any time during the trial, per investigator discretion, if symptoms are present.

[t] Prior and concomitant medications should be recorded from Screening through the subject's last visit/contact.

[u] Adverse events (serious and nonserious) should be recorded from the first dose of IMP through the subject's last visit/contact.

[v] The Week 6 prolactin results will be partially blinded; the investigator will be notified if the prolactin levels exceed a predefined limit with instructions to send the subject for appropriate follow-up.

[w] For women of childbearing potential only. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Any urine pregnancy tests that are positive must be confirmed using a serum test.

[x] A urine drug screen is required at Screening (full panel including opioids) and Baseline (dipstick); see the exclusion criteria for exclusions based on the urine drug screen. In addition, the urine drug screen will be conducted upon return to the inpatient facility for any subject who leaves the inpatient facility as described in protocol Section 4.1.2. Subjects returning from a day pass who have a positive urine drug screen will be discontinued from the trial. The urine drug screen can be conducted at any time during the trial at the discretion of the investigator.

[y] PK samples (1 sample and 1 backup sample) will be taken predose (within 15 minutes prior to dosing) and at 1, 4, and 8 hours following dosing on Day 4.

[z] PK samples (1 sample and 1 backup sample) will be obtained predose (within 15 minutes prior to dosing) and at 1, 2, 4, 8, 12, and 24 hours following administration of emraclidine on Day 24.

[aa] A single PK sample will be collected from subjects at time of discontinuation; the actual date and time of sample collection will be documented.

[bb] Future biospecimen research sample is optional and is only to be collected if signed consent is obtained from the subject. Sample can be collected at any time following confirmation of subject eligibility and prior to initiation of first dose.

9.2. Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior Scores

The C-SSRS is comprised of 10 categories with binary responses. The 10 categories include:

Category 1 – Wish to be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Categories 1-5 represent Suicidal Ideation and categories 6-10 represent Suicidal Behavior. Each category is scored as 1 if there is a positive response in the category and a 0 if there are no positive responses in the category.

Self-Injurious Behavior Without Suicidal Intent During Treatment

A subject will be categorized as having self-injurious behavior without suicidal intent if there is an occurrence of non-suicidal self-injurious behavior at any post-baseline visit.

Baseline C-SSRS Score

Baseline represents the pre-treatment assessment of recent history, with elements of suicidal ideation assessed over the prior 6 months and elements of suicidal behavior assessed over the prior 2 years. It is scaled from 0 (no suicidal ideation or behavior) to 10 (completed suicide).

Treatment-Emergent Suicide-Related Event

A subject will be categorized as having a treatment-emergent suicide-related event if at least one post-baseline suicidal ideation or suicidal behavior score is greater than 0.

Treatment-Emergent Suicidal Ideation Compared to Recent History

A subject will be categorized as having treatment-emergent suicidal ideation compared to recent history when there is at least one post-baseline suicidal ideation score > 0 and is an increase from baseline. Subjects with missing ideation in recent history and at least one post-baseline suicidal ideation score > 0 will be categorized as having treatment-emergent suicidal ideation. Lifetime scores are not considered for baseline suicidal ideation responses.

Treatment-Emergent Serious Suicidal Ideation Compared to Recent History

A subject will be categorized as having treatment-emergent serious suicidal ideation compared to recent history if the baseline score was < 4 and the post-baseline suicidal ideation score increases

to 4 or 5. Subjects with missing ideation in recent history and at least one post-baseline suicidal ideation score of 4 or 5 will be categorized as having treatment-emergent serious suicidal ideation. Lifetime scores are not considered for baseline suicidal ideation responses.

Emergence of Serious Suicidal Ideation Compared to Recent History

A subject will be categorized as having emergence of serious suicidal ideation compared to recent history if baseline score was 0 (no suicidal ideation) and post-baseline C-SSRS suicidal ideation score is either 4 or 5. Subjects with missing ideation in recent history and at least one post-baseline suicidal ideation score of 4 or 5 will be categorized as having emergence of serious suicidal ideation. Lifetime scores are not considered for baseline suicidal ideation responses.

Emergence of Suicidal Behavior Compared to all Prior History

A subject will be categorized as having emergence of suicidal behavior compared to all prior history if there had been no suicidal behavior in Categories 6-10 reported at any pre-treatment assessment, including responses to lifetime history questions, and there is at least one positive post-baseline C-SSRS assessment in Categories 6-10. Subjects with missing suicidal behavior at any pre-treatment assessment, and there is at least one post-baseline suicidal behavior score will be categorized as having emergence of suicidal behavior. 'All Prior History' represents lifetime history.

9.3. CTCAE Based Laboratory Test Results Grading Specifications

Lab Test = Albumin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death

Albumin will have grades 1-3,

- Grade 1 being any values from the LLN to 3 g/dL,
- Grade 2 from 2 to < 3 g/dL and
- Grade 3 < 2 g/dL

Lab Test = Amylase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-

Amylase will have Grades 1, 2 and 3:

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 5.0 x ULN
- Grade 3 from>5 x ULN

Lab Test = Alkaline Phosphatase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Alkaline Phosphatase will have grades 1-4 and grading is based ULN only.

- Grade 1 being any values from the ULN to 2.5 x ULN
- Grade 2 from >2.5 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Alanine Aminotransferase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

ALT will have grades 1-4 and grading is based ULN only. The baseline abnormality will be ignored.

- Grade 1 being any values from the ULN to 3.0 x ULN
- Grade 2 from >3.0 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Aspartate Aminotransferase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

AST will have grades 1-4 and grading is based ULN only.

- Grade 1 being any values from the ULN to 3.0 x ULN
- Grade 2 from >3.0 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Bilirubin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-

Bilirubin will have grades 1-4 and grading is based ULN only

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 3.0 x ULN
- Grade 3 from >3.0 to 10.0 x ULN
- Grade 4 from>10.0 x ULN

Lab Test = Corrected Serum Calcium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death

Calcium will have to be corrected for albumin using the formula previously discussed (NOTE: It should be confirmed with the lab whether or not the correction has already been applied). The grading is in both directions High and Low. Both directions are graded in 4 categories as
Hypercalcemia

- Grade 1 being any values from the ULN to 11.5 mg/dL,
- Grade 2 from >11.5 to 12.5 mg/dL,
- Grade 3 from >12.5 to 13.5 mg/dL,
- Grade 4 >13.5 mg/dL

Hypocalcemia

- Grade 1 being any values from the LLN to 8.0 mg/dL,
- Grade 2 from 7.0 to <8.0 mg/dL,
- Grade 3 from 6.0 to <7.0 mg/dL,
- Grade 4 <6.0 mg/dL

Lab Test = Cholesterol

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-

Cholesterol will have grades 1-4,

- Grade 1 being any values from the ULN to 300 mg/dL,
- Grade 2 from >300 to 400 mg/dL,
- Grade 3 from >400 to 500 mg/dL,
- Grade 4 >500 mg/dL

Lab Test = Creatine Kinase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-

Creatine Kinase will have grades 1-4,

- Grade 1 being any values from the ULN to 2.5 x ULN,
- Grade 2 from >2.5 to 5 x ULN,
- Grade 3 from >5 to 10 x ULN,
- Grade 4 >10 ULN

Lab Test = Creatinine

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-

Creatinine will have grades 1-4 and will be based on the baseline value in some cases. Grading for pre-baseline values will ignore the baseline requirement.

- Grade 1 being any values from the ULN to 1.5 x ULN,
- Grade 2 from >1.5 to 3.0 x ULN or >1.5 - 3.0 x baseline,
- Grade 3 from >3.0 to 6.0 x ULN or >3.0 x baseline,
- Grade 4 >6.0 x ULN

Lab Test = Fibrinogen

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	-

Fibrinogen will have Grades 1- 4:

- Grade 1 <1.0 - 0.75 x LLN
- Grade 2 <0.75 - 0.5 x LLN
- Grade 3 <0.5 - 0.25 x LLN
- Grade 4 <0.25 x LLN

Lab Test = Gamma-Glutamyl Transpeptidase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Gamma-Glutamyl Transpeptidase will have grades 1-4 and based on ULN only

- Grade 1 being any values from the ULN to 2.5 x ULN,
- Grade 2 from >2.5 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from >20.0 x ULN

Lab Test = Glucose

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death

Glucose is graded in 2 directions.

Hypoglycemia will have grades 1-4,

- Grade 1 being any values from the LLN to 55 mg/dL,
- Grade 2 from 40 to <55 mg/dL,
- Grade 3 from 30 to <40 mg/dL,
- Grade 4 <30 mg/dL

Hyperglycemia will have one grade. We discussed using the WHO criterion as noted below

- Grade 1 >200 mg/dL;

Lab Test = Lipase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-

Lipase will have Grades 1, 2 and 3:

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 5.0 x ULN
- Grade 3 from>5 x ULN

Lab Test = Magnesium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death

Hypermagnesemia will have grades 1, 3, and 4,

- Grade 1 being any values from the ULN to 3.0 mg/dL,
- Grade 3 from >3.0 to 8.0 mg/dL,
- Grade 4 from>8.0 mg/dL

Hypomagnesemia will have grades 1 - 4,

- Grade 1 being any values from the LLN to 1.2 mg/dL,
- Grade 2 from 0.9 to <1.2 mg/dL,
- Grade 3 from 0.7 to <0.9 mg/dL,
- Grade 4 <0.7 mg/dL

Lab Test = Potassium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death

Hyperkalemia will have grades 1-4,

- Grade 1 being any values from the ULN to 5.5 mmol/L,
- Grade 2 from >5.5 to 6.0 mmol/L,
- Grade 3 from >6.0 to 7.0 mmol/L,
- Grade 4 from >7.0 mmol/L

Hypokalemia will have grades 1, 3, and 4,

- Grade 1 being any values from the LLN to 3.0 mmol/L,
- Grade 3 from >2.5 to 3.0 mmol/L,
- Grade 4 <2.5 mmol/L

Lab Test = Sodium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death

Hypernatremia will have grades 1-4,

- Grade 1 being any values from the ULN to 150 mmol/L,
- Grade 2 from >150 to 155 mmol/L,
- Grade 3 from >155 to 160 mmol/L,
- Grade 4 from >160 mmol/L

Hyponatremia will have grades 1-4,

- Grade 1 being any values from the LLN to 130 mmol/L,
- Grade 2 from 125 to <130 mmol/L,
- Grade 3 from 120 to <125 mmol/L,
- Grade 4 <120 mmol/L

Lab Test = Triglycerides

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death

Triglycerides will have grades 1-4,

- Grade 1 being any values from the 150 to 300 mg/dL,
- Grade 2 from >300 to 500 mg/dL,
- Grade 3 from >500 to 1000 mg/dL,
- Grade 4 from>1000 mmol/L

Lab Test = Uric Acid

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	Death

- Do not grade based on CTCAE

Lab Test = Bicarbonate or CO2

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-

Do not Grade based on CTCAE

Lab Test = Phosphorus or Phosphate

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death

Do not Grade based on CTCAE

Lab Test = Serum pH [This is not urine pH]

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	-
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	-

Serum pH will be graded in both directions with Grades 1 and 3 only.

Acidosis Grade 1 .<LLN, but >=7.3 Grade 3, pH < 7.3

Alkaosis Grade 1 .>ULN, but <=7.5 Grade 3, pH < 7.5

Lab Test = Activated Partial Thromboplastin Time

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-

APTT will have grades 1-3

- Grade 1 being any values from the >ULN to 1.5 x ULN,
- Grade 2 from >1.5 to 2.5 x ULN,
- Grade 3 from >2.5 x ULN,

Lab Test = International Normalized Ratio

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-

INR will have grades 1-3

- Grade 1 being any values from the >1.2 to 1.5,
- Grade 2 from >1.5 to 2.5,
- Grade 3 from >2.5,

Lab Test = Eosinophils

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-

Do not grade based on CTCAE

Lab Test = Hemoglobin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hemoglobin Increased	Increase in > 0-2	Increase in >2-4g/dL	Increase > 4 g/DL	-	Death

Decreased Hemoglobin will have grades 1-3, with

- Grade 1 being any values from the LLN to 10 g/dL,
- Grade 2 from 8 to < 10 g/dL and
- Grade 3 < 8 g/dL

Increased Hemoglobin will not be graded.

Lab Test = CD4 Lymphocytes

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-

Decreased CD4 count will have grades 1-4, with

- Grade 1 being any values from the LLN to 500/mm3,
- Grade 2 from <500 to 200/mm3 and
- Grade 3 from <200 to 50/mm3 and
- Grade 4 <50/mm3

Lab Test = Lymphocytes

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	Lymphocyte count decreased
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	Lymphocyte count increased

Lymphocytes will be graded in both directions.

Decreased Lymphocytes will have grades 1-4, with

- Grade 1 being any values from the LLN to 800/mm3,
- Grade 2 from <800 to 500/mm3 and
- Grade 3 from <500 to 200/mm3 and
- Grade 4 <200/mm3

Increase Lymphocytes will have grades 2 and 3 only, with

- Grade 2 from >4000 to 20,000/mm3 and
- Grade 3 >20,000/mm3

Lab Test = Neutrophils

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-

Neutrophils will have grades 1-4, with

- Grade 1 being any values from the LLN to 1500/mm3,
- Grade 2 from 1000 to <1500/mm3 and
- Grade 3 from 500 to <1000/mm3 and
- Grade 4 <500/mm3

Lab Test = Platelets

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

Do not grade with CTCAE.

Lab Test = WBC

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death

Decreased WBC will have grades 1-4, with

- Grade 1 being any values from the LLN to 3000/mm3,
- Grade 2 from 2000 to <3,000/mm3 and
- Grade 3 from 1000 to <2,000/mm3 and
- Grade 4 <1000/mm3

High WBC will have grade 1, with

- Grade 1 >11,000/mm3 (https://www.aafp.org/afp/2000/1101/p2053.html),

Lab Test = Urine Glucose

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Glucosuria	Present	-	-	-	-

Urine Glucose will have grade 1

- Grade 1 if not negative or trace

Lab Test = Urine Protein

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	**Adult:** Urinary protein >=3.5 g/24 hrs; 4+ proteinuria; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9	-	-

Urine Protein will have grades 1-3, with

- Grade 1 =1+,
- Grade 2 = 2+ to 3+
- Grade 3 = 4+

Lab Test: Urine RBCs/Blood

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death

Do not grade urine in blood using CTCAE

Lab Test: eGFR or CrCl

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
eGFR decreased/CrCl decreased	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death

Values will be graded using the CTCAE values noted above with Grade 1 – Grade 4 values.

eGFR/CrCl:

Grade 1: < LLN – 60 ml/min/1.73 m2

Grade 2: 30 - < 60 ml/min/1.73 m2

Grade 3: 15 - < 30 ml/min/1.73 m2

Grade 4: < 15 ml/min/1.73 m2

9.4. Programming Conventions

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a 1.0" boundary on the left and right edges. The top and bottom margins are 1.0" for tables and listings but may vary for figures. Output should be printed in Courier New with a point size of 8.
- Identification of analysis population: Every summary table, listing, and figure will clearly specify the analysis population being summarized/listed. Listings will be prepared for all subjects.
- Group headers: In the summary tables, the group headers will identify the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.
  - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations
  - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by treatment, subject number and date, if applicable. If a listing is sorted in a different manner, it will be indicated on the listing shells.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of decimal places as captured electronically or on the eCRFs.
  - Minimums and maximums will be reported to the number of decimal places the original parameter is presented

  - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.
  - Means and quartiles will be reported to the one decimal place beyond the number of decimal places the original parameter is presented.
  - Calculated percentages will be reported with one decimal place.
  - Coefficient of variation will be reported to the same number of decimal places as the standard deviation.
  - In some cases, when the raw measurements are calculated values with 3 or more decimal places, the above guideline may be adjusted for readability

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on eCRFs.
- Time will be presented according to the 24-hour clock (HH:MM).
- Verification of Results: All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

9.5. MNAR Cases Identified Prior to Database Lock

Site	Subject ID	IMP Start Date	IMP End Date	Intercurrent Event
[redacted]				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				LACK OF EFFICACY
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
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				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				PHYSICIAN DECISION
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				ADVERSE EVENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				ADVERSE EVENT

Site	Subject ID	IMP Start Date	IMP End Date	Intercurrent Event
[redacted]				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				ADVERSE EVENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				PHYSICIAN DECISION
				WITHDRAWAL OF CONSENT
				PHYSICIAN DECISION
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				PHYSICIAN DECISION
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				ADVERSE EVENT
				WITHDRAWAL OF CONSENT
				PHYSICIAN DECISION
				WITHDRAWAL OF CONSENT
				LACK OF EFFICACY
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				LACK OF EFFICACY

Site	Subject ID	IMP Start Date	IMP End Date	Intercurrent Event
[redacted]				LACK OF EFFICACY
				LACK OF EFFICACY
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				ADVERSE EVENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
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				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT
				WITHDRAWAL OF CONSENT

9.6. Core Codes for Imputation of MAR and MNAR

9.6.1. Imputation of Missing at Random (MAR) Cases

SAS PROC MI will be used to generate 25 possible imputed datasets using the following SAS code:

```
proc mi data=mcmc1 seed=SEED1 nimpute=25 out=Out1X;
mcmc chain=multiple displayinit initial=em(itprint);
var TRT Y0 Y1 Y2 … Yn;
run;
```

Here, TRT is an indicator variable representing treatment with values of 'Emraclidine' or 'Placebo', Y1 - YN are variables representing the response variable (e.g., PANSS total score or CGI-S severity score) for each visit, Y0 is the baseline score, and SEED1 is a random number.

Each of these datasets will be analyzed using PROC MIXED in SAS using the MMRM model. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

9.6.2. Imputation of Missing Not at Random (MNAR) Cases

The MNAR cases will be imputed using a tipping point analysis. Subjects identified in Section 9.5 who were treated with values of 'Emraclidine' will have their imputed values that occurred following an ICE shifted by delta. Delta will be defined based on a percentage (10%-90%) of the mixed effect repeated measures model least-square means difference estimate at each visit relative to each 'Emraclidine' arm from the primary endpoint analysis.

First, the SAS code in Section 9.6.1 will be used to generate 25 possible imputed datasets using PROC MI. Then, the delta shift will be applied to these imputed datasets using the code below:

```
data ShiftX;
set Out1X;
if CRIT1FL = 'Y' and DCSRELF = 'Y' and TRT ^= 'Placebo' then do;
   if AVISITN > VISITN then do;
      AVAL = AVAL0 + DELTA;
      if AVAL > MAX then AVAL = MAX
      if missing < AVAL < MIN then aval = MIN;
      if ABLFL ^= 'Y' then CHG = AVAL - BASE;
   end;
run;
```

Here, TRT is an indicator variable representing treatment with values of 'Placebo' excluded from the delta adjustment, CRIT1FL is an indicator variable representing imputed records with values

of 'Y' indicating a record was imputed, DCSRELEF is an indicator variable representing type of missingness with values of 'Y' indicating an MNAR case, AVISITN is a variable representing the analysis visit, VISITN is a variable representing the subject's last visit prior to the ICE, AVAL0 is a variable representing the original imputed value for the response variable (e.g., PANSS total score or CGI-S severity score) prior to the delta shift, DELTA is a variable representing the shift applied to each imputed value for subjects with treatment values of 'Emraclidine' that occurred after a subject's ICE, AVAL is a variable representing the new value for the response variable following the delta shift, MAX is a variable representing the maximum possible value for the response variable (e.g., 210 for PANSS total score), MIN is a variable representing the minimum possible value for the response variable (e.g., 30 for PANSS total score), ABLFL is an indicator variable flagging the visit that represents the subject's baseline value, BASE is a variable representing the baseline value for the response variable, and CHG is a variable representing the new calculated response variable based on BASE and AVAL.

Following the delta adjustment, each of these datasets will be analyzed using PROC MIXED in SAS using the MMRM model. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

9.7. Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BLQ	Below limit of qualification
BMI	Body Mass Index
CGI-I	Clinical Global Impression-Improvement Scale
CGI-S	Clinical Global Impression-Severity of Symptoms Scale
CI	Confidence Interval
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
ICE	Intercurrent events
ICF	Informed consent form
IMP	Investigational medicinal product
IRT	Interactive response technology
ITT	Intent to Treat
LLN	Lower limit of normal
MCMC	Markov chain Monte Carlo method
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MMRM	Mixed model repeated measures
N	Number of subjects
n	Number of observations

Abbreviation	Definition
ND	Not determined
PANSS	Positive and Negative Syndrome Score
PK	Pharmacokinetic
Q1	First quartile
Q3	Third quartile
QD	Once daily
QTcF	QT interval corrected for heart rate by Fridericia's formula
SAE	Serious adverse event
SAS	Simpson Angus Scale
SD	Standard deviation
SE	Standard error
SF-6D	Short-Form Six Dimension
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TLF	Table, Listing, and Figure
ULN	Upper limit of normal
WHO	World Health Organization
WHODrug	World Health Organization drug dictionary