STATISTICAL ANALYSIS PLAN

A 52-week, Phase 2, Open-label Trial to Evaluate the Long-term Safety and Tolerability of CVL-231 in Adult Participants With Schizophrenia

Protocol Number: CVL-231-2003

Compound: Emraclidine

Trial Phase: 2

Short Title: A 52-week, Open-label Trial of CVL-231 in Adult Participants With Schizophrenia

Sponsor Name: Cerevel Therapeutics, LLC

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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 safety and tolerability, and efficacy data from Protocol CVL-231-2003. 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).

The statistical analysis plan (SAP) is based on:

- Protocol CVL-231-2003 Amendment 3, dated March 15, 2023
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)
- Discussions with the FDA

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked. Deviations from the final approved plan will be noted in the clinical study report.

1.1. Study Overview

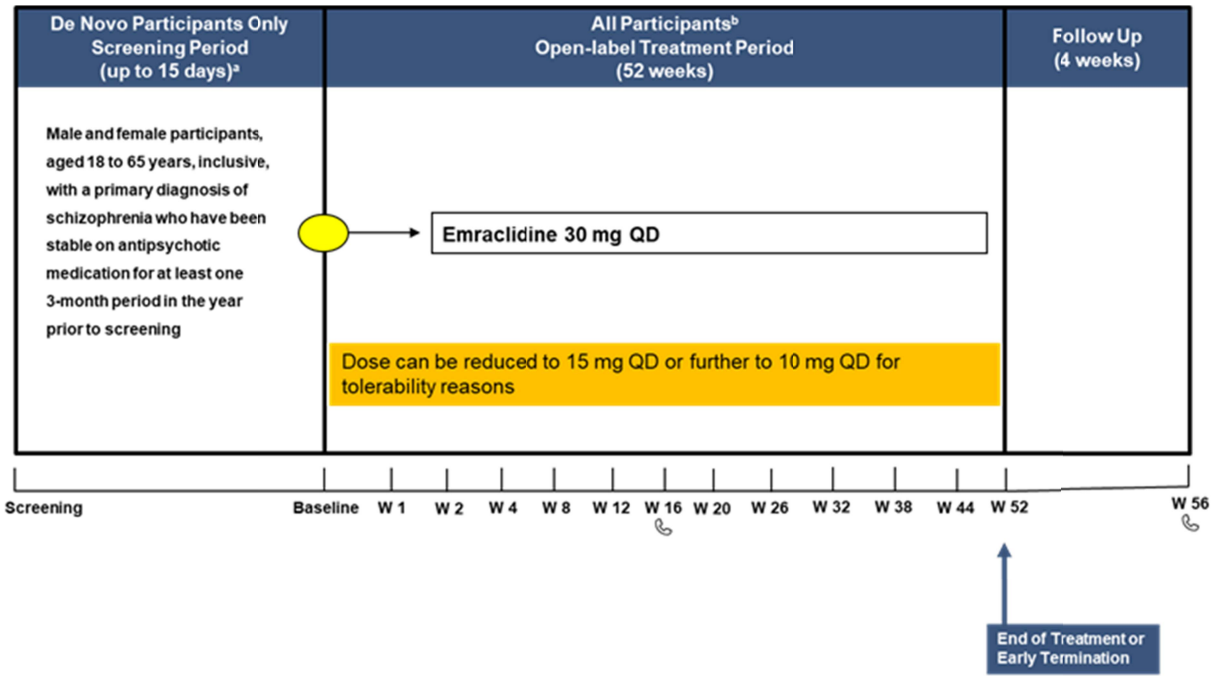
This is a Phase 2, multicenter, open-label, 52-week trial to evaluate the safety and tolerability of emraclidine 30 mg single dose (QD) in adult participants with schizophrenia. The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible participants who, in the investigator's judgment, could potentially benefit from treatment with emraclidine for schizophrenia. There will be 2 groups of participants: 1) participants who completed treatment in one of the double-blind, placebo-controlled Phase 2 efficacy trials (CVL-231-2001 or CVL-231-2002), denoted as "rollover participants" and 2) participants with stable schizophrenia who were not enrolled in either one of the Phase 2 double-blind trials, denoted as "de novo participants." The trial will include up to a 15-day Screening Period (de novo participants only), a 52-week Treatment Period, and a 28-day Follow-up Period. Each participant will participate in the trial for approximately 56 weeks (rollover participants) or 58 weeks (de novo participants). Details of schedule of assessments are provided in Section 9.1.

Rollover participants will be screened for eligibility at the last visit of the double-blind trial (ie, Day 45 of Trials CVL-231-2001 and CVL-231-2002). Rollover participants will sign a new informed consent form (ICF) for participation in Trial CVL-231-2003 before any procedures specific to the open-label trial are performed. For rollover participants, the first dose of investigational medicinal product (IMP) for the open-label trial (ie, Day 1) will occur on the day following baseline assessments. De novo participants will enter a Screening Period of up to 15 days (up to a maximum of 21 days allowed with approval of the medical monitor) to assess eligibility criteria and washout from prior antipsychotic medications and other prohibited medications. The Screening Period begins on the day of signing the ICF. Participants with a "lapse" in antipsychotic treatment (a lapse is defined as no oral antipsychotic medication for 3 or more days immediately prior to signing the ICF) may proceed directly to Baseline Visit (Day 1) of the trial, provided all other eligibility criteria are met, including washout of all other prohibited medications.

Approximately 850 participants total (rollover plus de novo) are planned to be enrolled into this open-label trial in order to fully characterize the safety profile of emraclidine.

The trial design is depicted in Figure 1.

Figure 1: Trial Schematic



Abbreviations: IMP=investigational medicinal product; QD=once daily; W=week.
Note: Assessment time points are planned for the last day of the indicated week (eg, Day 7, 14, 28) with a ±3-day window (see Schedule of Assessments)
a. Separate Screening and Baseline Visits are required for de novo participants to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable. 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. For rollover participants, screening for Trial CVL-231-2003 occurs simultaneously with baseline assessments at the Week 6 (Day 45) time point of Trial CVL-231-2001 or CVL-231-2002.

- For rollover participants, the first dose of IMP for the open-label trial occurs the day following baseline assessments
- For de novo participants, the first dose of IMP for the open-label trial occurs on the same day as baseline assessments

1.2. Sample Size Considerations

The sample size of this trial is not based on statistical hypothesis testing. The trial will enroll eligible participants who completed 1 of the Phase 2, double-blind, placebo-controlled trials (CVL-231-2001 or CVL-231-2002). Additional de novo participants will also be enrolled to achieve approximately 850 participants total (rollover plus de novo) to fully characterize the safety profile of emraclidine.

1.3. Measures to Minimize Bias: Randomization and Blinding

1.3.1. Participant Assignment to Treatment

All participants will begin dosing with emraclidine 30 mg QD. If the participant has tolerability issues at the emraclidine 30 mg dose, the dose may be decreased to 15 mg QD. Further decrease to 10 mg QD is permitted if the participant continues to have tolerability issues following the decrease to 15 mg QD. Dose decreases can occur at any time during the open-label treatment at either a scheduled or an unscheduled visit. Participants unable to tolerate emraclidine 10 mg QD must be withdrawn from the trial.

Rechallenge with the 15 mg QD dose (from 10 mg QD dose) or 30 mg QD dose (from 15 mg QD dose) of emraclidine is permitted a minimum of 7 days after a dose decrease, if clinically warranted based on the investigator's judgement.

1.3.2. Blinding

This is an open-label trial with all participants assigned to receive emraclidine.

1.4. Treatment Period

The daily dosing schedule will start on Day 1 with all participants receiving a single daily dose of IMP, preferably in the morning. Clinic visits will occur as described in the Schedule of Assessments. All participants should continue dosing through Week 52. All participants will have a follow-up safety contact 28±3 days after the last dose of IMP.

2. OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are summarized in Table 1.

Table 1: Objectives and Endpoints

Objective	Endpoint
Primary	
• To assess the long-term safety and tolerability of oral emraclidine in adult participants with schizophrenia	• Treatment-emergent adverse events (TEAEs) • Clinically significant changes in vital sign measurements, body weight, physical and neurological examination results, electrocardiogram (ECG) assessments, clinical laboratory assessments, and metabolic parameters • 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 effect of emraclidine on symptoms of schizophrenia over a 52-week period in adult participants with schizophrenia	• Change from baseline over time in Positive and Negative Syndrome Scale (PANSS) total score • Change from baseline over time in Clinical Global Impression – Severity of Symptoms (CGI-S) score • Clinical Global Impression – Improvement of Symptoms (CGI-I) score • Change from baseline over time in PANSS positive, negative, and general psychopathology subscale scores • Change from baseline over time in PANSS Mader Factor scores • Percentage of responders (responders defined as ≥30% reduction from baseline in PANSS total score)
• To evaluate effect of emraclidine on quality of life over a 52-week period in adult participants with schizophrenia	• Change from baseline over time in Short Form-6 Dimensions (SF-6D)
• To evaluate the effect of emraclidine on work productivity and regular activities over a 52-week period in adult participants with schizophrenia	• Change from baseline over time in the Work Productivity and Activity Impairment (WPAI): Schizophrenia questionnaire

3. KEY ASSESSMENTS AND DERIVATIONS

3.1. Efficacy Assessments

3.1.1. Positive and Negative Syndrome Scale

The PANSS (Kay et al, 1987) 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 participants 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 participant at all time points should be made. The PANSS assessment should be completed prior to all other efficacy scales. Instructions for administering the PANSS will be provided to the site.

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

3.1.1.1. Derivation of PANSS Subscale Score

The subscale score is defined as the sum of scores per participant 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 participants with 30% reduction from baseline in the PANSS total score.

3.1.1.4. Handling of Missing Items from PANSS

If individual items are missing from a given subscale of PANSS for an individual participant 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 participant 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 participant at that time point will be considered missing.

3.1.2. Clinical Global Impression-Severity of Symptoms Scale

The severity of symptoms for each participant will be rated using the 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 participant 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 participants.

3.1.3. Clinical Global Impression-Improvement Scale

The CGI-I is an observer-rated scale that will be used to measure the participant'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 participant's current level of symptoms compared with their symptoms at Baseline (Day 1).

The investigator (or designee) will rate the participant'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.

3.2. Safety Assessments

3.2.1. Vital Signs

3.2.1.1. Height and Weight

Height will be measured at Screening for de novo participants only with a stadiometer, measuring stick, or tape.

The following guidelines will aid in the standardization of body weight measurements:

- Scales should be calibrated and reliable; scales should be at zero just prior to each participant's weigh-in session
- A participant should void prior to being weighed, if possible, and be minimally clothed (ie, no shoes or heavy overgarments)
- Weight should be recorded before a participant's meal and at approximately the same time at each required visit

3.2.1.2. Standard Vital Sign Measurements

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 participant 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 for all time point assessments following confirmation of eligibility.

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.

Any abnormal measurements in vital signs need to be repeated for confirmation. After confirmation, clinically significant measurements occurring during the trial will be recorded in the adverse event (AE) section of the eCRF.

3.2.2. Physical/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 participant'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.

The investigator must review the physical and neurological examination findings and document any clinically significant condition present at the post-treatment physical and neurological examinations that was not present at the baseline examination as an AE. These clinically significant findings should be followed to a satisfactory conclusion.

3.2.3. Electrocardiograms (ECGs)

Electrocardiogram (12 lead) recordings will be obtained after the participant 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. At Screening (de novo participants only), triplicate 12-lead ECGs are required to assess participant eligibility. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period. 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.

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.

3.2.4. 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.

3.2.5. 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, which assesses the lifetime experience of the participant with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all participants at screening to determine eligibility. The "Baseline/Screening" version will be completed for all de novo participants at Screening to determine eligibility.

The "Since Last Visit" C-SSRS form will be completed at all specified visits after the Screening visit for de novo participants and at all specified visits for rollover participants.

3.2.6. Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a patient or clinical trial participant, 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.

3.2.6.1. Adverse Event of Special Interest (AESI)

Adverse events of special interest are defined as described in Protocol (Version 4.0: 30 Apr 2024) Section 8.3.7. All AESIs will be recorded as such on the ADVERSE EVENTS page of the eCRF.

3.2.6.2. Treatment-emergent Adverse Event (TEAE)

Any event reported on the eCRF that occurs on or after the initiation of IMP is considered treatment emergent. Additionally, it is assumed that an AE which was reported to have started on Day 1 without an associated onset time is assumed to be treatment emergent.

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 in the open-label trial. Concomitant medications are those medications taken on or after the initiation of IMP in the open-label trial. 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 of IMP and will not be considered as concomitant. These medications will be recorded in the CONCOMITANT MEDICATIONS eCRF.

3.2.8. Extrapyramidal Symptoms (EPS)

Extrapyramidal Symptoms (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 Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) can be used to assess the severity of the symptoms.

3.2.8.1. 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.

3.2.8.2. Abnormal Involuntary Movement Scale (AIMS)

The AIMS (Guy, 1976) assessment 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 participant is at rest, and the investigator also makes global judgments on the participant'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 participant's dental status.

The AIMS Movement Rating Score is defined as the sum of items 1 through 7 (i.e., items 1 through 4, facial and oral movements; items 5 and 6, extremity movements; and item 7, trunk movements).

3.2.8.3. 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 participant, 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, participants are observed while they are seated and then standing for a minimum of 2 minutes in each position. Symptoms observed in other situations (e.g., while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning.

3.3. Health Economics and Resource Utilization

3.3.1. Short Form – 6 Dimensions (SF-6D) Version 2.0

The 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 patient 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).

3.3.2. Work Productivity and Activity Impairment (WPAI) Questionnaire: Schizophrenia

The WPAI questionnaire (Reilly et al, 1993) is a well-validated instrument to measure impairment in work and activity. The Schizophrenia version consists of 6 questions that evaluate absenteeism, presenteeism, as well as the impairment in unpaid activity because of health problems (physical or emotional problems or symptoms) over a recall period of 7 days. The questions are:

Q1. Are you currently employed?

Q2. During the past seven days, how many hours did you miss from work because of problems associated with your schizophrenia?

Q3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

Q4. During the past seven days, how many hours did you actually work?

Q5. During the past seven days, how much did your schizophrenia affect your productivity while you were working?

Q6. During the past seven days, how much did your schizophrenia affect your ability to do your regular daily activities, other than work at a job?

3.3.2.1. Derivation of Percent Work Time Missed Due to Schizophrenia (Absenteeism)

The percent of work time missed is calculated as 100 multiplied by the number of hours missed due to schizophrenia (Q2) divided by the sum of hours missed due to the schizophrenia plus the number of hours actually worked (Q2+Q4). Subjects who have records with 0 hours for both Q2 and Q4 will not be derived at that given date and visit.

3.3.2.2. Derivation of Percent Impairment While Working Due to Schizophrenia (Presenteeism)

The percent impairment while working is calculated as 100 multiplied by the degree at which the schizophrenia affected productivity while working (Q5) divided by 10.

3.3.2.3. Derivation of Percent Activity Impairment Due to Schizophrenia (Activity Impairment)

The percent activity impairment due to schizophrenia is calculated as 100 multiplied by the degree at which the schizophrenia affected regular daily activities (Q6) divided by 10.

3.3.2.4. Derivation of Percent Overall Work Impairment Due to Schizophrenia (Work Productivity Lost)

The percent overall work impairment is calculated as 100 multiplied by the sum of the percent work time missed (Q2/Q2+Q4) plus 1 minus the percent work time missed (1-[Q2/Q2+Q4]) multiplied by the percent impairment while working (Q5/10). Subjects who have records with 0 hours for both Q2 and Q4 will not be derived at that given date and visit.

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

Day 1 is the day IMP is first initiated in CVL-231-2003.

4.1.3. Study Day of an Event

Study Day of an event is defined relative to 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. Weeks on Study

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

4.1.5. Weeks on IMP

Weeks on IMP is the number of weeks from Day 1 to the date of last dose of IMP as recorded on the OVERALL DOSING – OPEN LABEL eCRF.

4.1.6. Baseline Value – De Novo participants

Baseline will be defined as the last available measurement before the first dose of IMP in the open-label trial. For vitals, baseline is the average of the triplicates at the last visit prior to the IMP administration. If the triplicate value is not available, the last non-missing value obtained prior to the initiation of IMP will be used.

4.1.7. Baseline Value – Rollover Participants from CVL-231-2001/CVL-231-2002

For purposes of analysis, the baseline value is defined as the assessment from the last analysis visit (Week 6) of the double-blind trial, excluding C-SSRS assessments. The "Baseline/Screening" version and all "Since Last Visit" versions of the C-SSRS assessments from the double-blind trial will be used to determine if there was previous suicidal ideation or behavior prior to start in the open-label trial. For vital signs taken in triplicate, the baseline value will be defined as the average of the triplicates will be used. If the triplicate value is not available, then the last non-missing value will be used. For WPAI, the baseline value will be defined as the last available measurement before the first dose of IMP in the open-label trial.

4.1.8. 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.

4.1.9. Percent Change from Baseline

Percent change from baseline for a given endpoint is defined as the value on a given Study Day (Time point) minus the baseline value, divided by the baseline value, and multiplied by 100.

4.1.10. 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 and date, 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 and date will be used.

4.1.11. 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 – OPEN LABEL eCRF. The average daily dose will be calculated as the cumulative dose divided by the expected days on study treatment. For records with partial dosing start and stop dates, average daily dose will not be calculated.

4.1.12. Compliance with Study Drug

Responsible trial personnel will dispense the IMP. Participants will be counseled on the importance of taking the IMP as directed and will be instructed to bring all used and unused IMP to each visit for assessment of accountability and compliance. Compliance will be assessed by direct questioning and by counting returned tablets. Compliance will be documented in the source documents and the eCRF, including any deviations from the prescribed dosage regimen. 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 on the OVERALL DOSING – OPEN LABEL eCRF. For records with partial dosing start and stop dates, compliance will not be calculated.

4.1.13. Handling of Incomplete or Missing Dates

Incomplete or missing start and end dates will be imputed for adverse events to determine treatment-emergence and 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). Similarly, an incomplete or missing date of initial diagnosis of schizophrenia will be imputed to determine time (years) since initial diagnosis. Additionally, dosing start and stop times may be imputed to determine average daily dose of IMP and treatment compliance.

An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a participant. 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 many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (e.g., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For the purposes of handling partially reported start and stop dates for adverse events, medications/non-drug therapies, and diagnosis of schizophrenia, the following algorithm will be applied:

- Missing start day, but month and year present:

  For adverse events and medications/non-drug therapies, 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). For the diagnosis of schizophrenia, if an event occurs in the same year and month as IMP, then the start day and month will be set to the first day of the month.

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

- Missing start day and month, but year present:

  For adverse events and medications/non-drug therapies, if an event occurs in the same year as IMP, then the start date of the event will be assigned to Day 1. For the diagnosis of schizophrenia, if an event occurs in the same year as IMP, then the start day and month will be set to 01 January of that year.

  For all other cases, the start day and month will be set to 01 January.

- In the unlikely event of a completely missing start date (year not present), adverse events and medications/non-drug therapies will have the start date imputed as Day 1. The diagnosis of schizophrenia will be imputed as 01 January of the year dosing started.

- 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 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 participant data listings, start and stop date of events will be displayed as reported on the eCRF (i.e., imputed values will not be listed).

4.1.14. 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. 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.

Table 2: Visit Windows

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Baseline	≤ 1	1
Week 1	2 – 10	7
Week 2	11 – 21	14
Week 4	22 – 42	28
Week 8	43 – 70	56
Week 12	71 – 98	84
Week 16	99 – 126	112

Analysis Visit	Analysis Visit Window	Analysis Visit Target Day
Week 20	127 – 161	140
Week 26	162 – 203	182
Week 32	204 – 245	224
Week 38	246 – 287	266
Week 44	288 – 336	308
Week 52	≥337	364

If assessments are collected multiple times within a given visit window, the result closest to the analysis visit target day will be used for summary presentations. If two measurements have the same distance to the target day, the later value will be used. If a participant has multiple non-missing values on the same date, then the average record will be used (if applicable). If there are multiple average records on the same date, pick the latest as determined by the time from before the average was created. If no averages exist, pick the last record as determined by the time collected.

5. STATISTICAL ANALYSIS METHODS

5.1. GENERAL CONSIDERATIONS

Descriptive statistical methods will be used to summarize the data from this trial. Statistical modelling and testing may be performed for the exploratory endpoints for exploratory purposes. Unless stated otherwise, the term "descriptive statistics" refers to number of participants (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 cohort" refers to the following cohorts:

Table 3: Cohorts

1. CVL-231-2001/2002 Active Rollover
2. CVL-231-2001/2002 Placebo Rollover
3. De Novo
4. Overall

All data collected from participants 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 cohort and participant number and then by date within each participant number. For data listings, treatment cohort will also specify the study and dose level for previously exposed participants, i.e. CVL-231-2001 Active 10 mg Rollover, CVL-231-2002 Active 15 mg Rollover, and CVL-231-2001/2002 Active 30 mg Rollover.

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 in Table 4.

Table 4: Populations for Analysis

Population	Description	Analysis
All Participants Screened	All participants who signed the informed consent form.	Disposition (including Screen Failures) and Inclusion/Exclusion Criteria
ITT	All participants who are enrolled in the trial.	Disposition, Populations for Analysis, and Medical History
Safety Analysis Set	All participants who receive at least 1 dose of emraclidine in Trial CVL-231-2003	Demographics, Safety Analyses, Efficacy Analyses, Health Economics and Resource Utilization Analyses

5.3. Statistical Hypotheses

No formal hypothesis testing is planned for this trial.

5.4. Multiplicity Adjustment

All analyses will be conducted without adjustment for multiple comparisons.

5.5. Strata and Covariates

No strata will be examined. The baseline value of each efficacy variable will be included as a covariate in the exploratory efficacy analyses.

5.6. Participant Disposition, Demographic and Baseline Characteristics

Participant disposition will be based on the ITT population with tabulation of the number of participants who completed study and the number of participants who discontinued from the study and the reasons by treatment cohort. Additionally, the number of weeks on study will be summarized. A separate summary of the number of participants screened, the number of screen failures, and the reason for screen failure will be summarized overall for the All Participants Screened population. Additionally, the number of participants in each analysis population set will be summarized. Kaplan-Meier estimates of time to discontinuation from Day 1 of the study will be plotted for each treatment cohort. Similar plot for time to discontinuation due to AEs will also be presented.

Demographic data and baseline characteristics including age, age categorical distribution, sex, childbearing potential, race, ethnicity, height at screening (Screening for de novo participants and baseline of double blind trial for rollovers), weight at baseline, and body weight index (BMI) at baseline will be summarized for the Safety Analysis Set by treatment cohort.

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 general psychopathology subscale score at baseline, PANSS Marder 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, and CGI-S score at baseline will be summarized by treatment cohort for the Safety Analysis Set.

5.7. Exposure to Treatment

The number of weeks on IMP, reasons for discontinuation of IMP, treatment compliance, average daily dose of IMP, final dose level, and the number of participants who modified dose will be summarized by treatment cohort for the Safety Analysis Set.

5.8. Medical History

Medical history will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher preferred term and system organ class. Medical history will be summarized by treatment cohort, system organ class and preferred term. Medical history will be listed for individual participants showing both verbatim and preferred terms.

5.9. Efficacy Analysis

5.9.1. PANSS

The PANSS total score and corresponding change from baseline will be summarized by visit and treatment cohort for the Safety Analysis Set. A mixed model of repeated measures (MMRM) model will be used to analyze the change from baseline from all timepoints with visit as a fixed effect, participant as a random effect, and baseline PANSS total 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 Least Squares Mean (LSMean) and associated 95% confidence intervals (CI) and p-values will be summarized. PANSS Marder score, PANSS positive, negative, and general psychopathology subscales, PANSS delusions score, PANSS conceptual disorganization score, PANSS hallucinatory behavior score, and PANSS suspiciousness/persecution score will be analyzed similarly.

For PANSS total score, the number and proportion of responders from baseline will be summarized by treatment cohort and study visit.

The mean (±SD) PANSS total score and the mean (±SD) change from baseline will be plotted by treatment cohort and study visit.

5.9.2. CGI-S

The CGI-S scores and corresponding change from baseline will be summarized by visit and treatment cohort for the Safety Analysis Set. An MMRM model will be used to analyze the change from baseline from all timepoints with visit as a fixed effect, participant 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 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 LSMean and associated 95% CIs and p-values will be summarized.

The mean (±SD) CGI-S score and the mean (±SD) change from baseline will be plotted by treatment cohort and study visit.

5.9.3. CGI-I

The CGI-I scores will be summarized by visit and treatment cohort for the Safety Analysis Set. An MMRM model will be used to analyze the data from all timepoints with visit as a fixed effect, participant as a random effect. 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 LSMean and associated 95% CIs and p-values will be summarized.

5.10. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. The treatment as received will be used in the safety presentation.

5.10.1. Adverse Events

Adverse events will be mapped to MedDRA version 26.0 or higher preferred term and system organ class. If a participant 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 3.2.6. Summaries of treatment-emergent AEs (TEAEs) will include any AEs reported beginning with the initiation of study drug on Day 1. An overall summary of the number of participants with a TEAE, TEAE related to IMP, serious TEAE, AESI defined per protocol, TEAE leading to discontinuation of IMP, AESI defined per protocol not leading to discontinuation of IMP or study, TEAE leading to discontinuation of study, and death will be summarized by treatment cohort. The occurrence of TEAEs will be summarized by treatment cohort using preferred terms (PT), system organ classes (SOC), and severity. Separate summaries of TEAEs, treatment-emergent serious adverse events (TESAEs), TEAEs related to IMP, AESIs defined per protocol, events leading to the discontinuation of IMP, and AESIs defined per protocol not leading to discontinuation of IMP or study will be generated respectively by SOC and PT. Additionally, TEAEs will be summarized by PT. TEAE occurrence summaries will be repeated by treatment cohort and 13-week intervals. A summary of treatment-emergent PMQ events will be summarized by PT. Additionally, TEAEs with ≥ 2% incidence in the total overall group will be summarized by PT. All adverse events reported will be listed for individual participants showing both verbatim and preferred terms. A separate listing of AESIs defined per protocol, SAEs, or events leading to discontinuation of IMP or study will be presented. Additionally, separate listings of PMQ events, deaths, AESI and SAE narrative information, and healthcare encounters will be generated.

Missing onset dates will be imputed as previously outlined in Section 4.1.13 as required to determine treatment-emergent events.

5.10.2. 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 will be summarized for the De Novo cohort by drug classification and generic drug name. Concomitant medications and medications taken post last dose of IMP will be summarized by treatment cohort, drug classification, and generic drug name. All medications will be presented in a data listing.

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

5.10.3. 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. 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. Additionally, a listing of participants meeting Hy's law criteria will be generated.

The number and percentage of participants 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 postbaseline value. The "Increase" criteria refer to an increase from baseline to the post-baseline value. Within each laboratory parameter grouping, a participant may be counted once per criteria. Participants will only be included who meet the baseline criteria and have at least one post-baseline value for the parameter.

5.10.4. Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate, and weight. Triplicate blood pressure and heart rate measurements will be obtained after the participant has been supine and at rest for at least 3 minutes. 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. The triplicate values will be individually recorded, and the values will be averaged for the time point assessment. Orthostatic changes will be derived using standing and supine values, prioritizing averages where available. Vital signs and corresponding changes from baseline will be summarized by treatment cohort, position (if applicable), and study visit using descriptive statistics. Additionally, for weight, the number (%) of participants with ≥7% increase and ≥7% decrease in weight from baseline will be summarized by treatment cohort and study visit.

The mean (±SD) blood pressure, heart rate, and weight measurements and the mean (±SD) change from baseline will be plotted by treatment cohort, position (if applicable) and study visit.

In addition, the frequency of out-of-range post- baseline values in vital signs anytime during the treatment period will be summarized according to the criteria below. For supine blood pressure and heart rate, only averages of triplicates will be used. If an average is not available, the single reading will be used for summary.

- 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
- Temperature
  - > 36.0° C
  - < 38.0° C
- Respiratory Rate
  - < 12 breaths/min
  - > 20 breaths/min
- Weight
  - ≥ 7% kg decrease from baseline
  - ≥ 7% kg increase from baseline

5.10.5. Electrocardiograms (ECGs)

Single ECGs will be obtained from all rollover participants at all post- baseline time points. At Screening (de novo participants only), triplicate 12-lead ECGs are required to assess participant eligibility. At all other specified timepoints where an ECG recording must be performed, only a single ECG is required. All ECG recordings will be obtained after the participant has been supine and at rest for approximately 3 minutes. ECGs and corresponding changes from baseline will be summarized by treatment cohort and study visit using descriptive statistics.

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

5.10.6. Physical and Neurological Examinations

Physical and Neurological examination data will be listed.

5.10.7. Extrapyramidal Symptoms (EPS)

The total score of each EPS assessment scale: SAS, AIMS, and BARS, will be listed and summarized by treatment cohort, and visit, with corresponding changes from baseline, using descriptive statistics.

5.10.8. 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 participants 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.

5.11. Protocol Deviations

All protocol deviations will be reviewed by the project team prior to database lock to identify participants 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.

5.12. Other Analyses

5.12.1. SF-6D Version 2.0

The SF-6D measurements and corresponding change from baseline will be summarized by visit and treatment cohort for the Safety Analysis Set. An MMRM model will be used to analyze the change from baseline from all timepoints with visit as fixed effects, participant as a random effect, and baseline SF-6D measurement 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 LSMean and associated 95% CIs and p-values will be summarized.

5.12.2. WPAI Questionnaire

The WPAI numeric question scores and derived parameters and corresponding change from baseline will be summarized by visit and treatment cohort for the Safety Analysis Set. An MMRM model will be used to analyze the change from baseline from all timepoints with visit as fixed effects, participant as a random effect, and baseline WPAI measurement 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 LSMean and associated 95% CIs and p-values will be summarized.

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 Assessment

Table 5: Schedule of Assessments - Screening and Baseline/Day 1 (De Novo Participants)

Trial Periods/Phases	**Screening[a]**	**Baseline/Day 1**
Day	**-15 to -1**	**1**
Entrance and History		
Informed consent[b]	X	
Inclusion/exclusion criteria	X	X[c]
Medical and psychiatric history[d]	←----------	----------→
MINI	X	
Demography	X	
History of drug and alcohol use	X	
Review of birth control methods	X	X
Breathalyzer test for alcohol[e]	X	
Safety Assessments		
Physical/neurological examination[f]	X	X
Height (Screening only) and weight	X	X
ECG[g]	X	X
Heart rate and blood pressure (including orthostatic)[h]	X	X
Respiratory Rate and temperature	X	X
C-SSRS[i]	X	X
EPS (SAS, AIMS, BARS)[j]	X	X
Prior/concomitant treatments[k]	←----------	----------→

Trial Periods/Phases	Screening[a]	Baseline/Day 1
Day	**-15 to -1**	**1**
Adverse event monitoring[l]		X
Laboratory		
Blood for safety laboratory sample	X	X
Urine for safety laboratory	X	X
Serum pregnancy test[m]	X	
Urine pregnancy test[m]		X
Urine drug screen[n]	X	X
Hepatitis B, C, HIV	X	
Blood sample for future biospecimen research[o]		X
Efficacy/Health Economics Assessments		
PANSS		X
CGI-S		X
SF-6D		X
WPAI:Schizophrenia		X
Other		
Register visit in IVR	X	X
IMP dosing[p]		X
IMP dispensing		X

[a] Separate screening and baseline visits are required for de novo participants to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable. Extension of screening (up to a maximum of 21 days total) is allowed following discussion and approval by the medical monitor prior to the expiration of the Screening Period.

[b] Informed consent must be obtained before any trial-related procedures are performed.

[c] For de novo participants, inclusion/exclusion criteria will be assessed at Baseline to ensure ongoing participant eligibility, with the exception of age or assessments that are only scheduled during Screening (eg, height for body mass index calculation).

[d] For de novo participants, 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.

[e] An alcohol test (breathalyzer) is required at Screening for de novo participants. An alcohol test (breathalyzer) can be conducted at any time during the trial for any participant at the discretion of the investigator.
[f] Full physical and neurological examinations should be completed at Screening and Baseline. Symptom-driven physical and/or neurological examinations may be done at any time during the trial at the investigator's discretion.
[g] 12-lead ECG assessments will be performed after the participant 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 participant eligibility; at Baseline, only 1 reading is required for determination of eligibility. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).
[h] 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). At each indicated time point, triplicate supine heart rate and blood pressure measurements will be taken at approximately 1-minute intervals, 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). Further details are provided in Protocol Section 8.2.3 and in the Operations Manual.
[i] For de novo participants, the "Baseline/Screening" C-SSRS form will be completed at Screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at Baseline to ensure that the participant continues to qualify for the trial.
[j] EPS assessments can be completed at any time during the trial, per investigator discretion, if symptoms are present.
[k] Prior and concomitant medications should be recorded from Screening through the participant's last visit/contact.
[l] Adverse events (serious and nonserious) should be recorded from the first dose of IMP.
[m] 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.
[n] 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. The urine drug screen can be conducted at any time during the trial at the discretion of the investigator.
[o] Future biospecimen research sample is optional and is only to be collected if signed consent is obtained from de novo participants only. Sample can be collected at any time following confirmation of participant eligibility and prior to initiation of first dose.
[p] De novo participants will receive their first dose of IMP following completion of baseline assessments.

Table 6: Schedule of Assessments - Screening/Baseline and Day 1 (Rollover Participants)

Trial Periods/Phases	**Screening[a]**	**Baseline/Day 1**
Day	**-15 to -1**	**1**
Entrance History		
Informed consent[b]	X	
Inclusion/exclusion criteria[c]	X	
Medical and psychiatric history[d]	←----------	----------→
Safety Assessments		
Physical/neurological examination	X[e]	
Weight	X[e]	
ECG[f]	X[e]	
Heart rate and blood pressure (including orthostatic)[g]	X[e]	
Respiratory rate and temperature	X[e]	
C-SSRS[h]	X[e]	
EPS (SAS, AIMS, BARS)[i]	X[e]	
Prior/concomitant treatments[j]	←----------	----------→
Adverse event monitoring[k]		X
Laboratory		
Blood for safety laboratory sample	X[e]	
Urine for safety laboratory	X[e]	
Urine pregnancy test[l]	X[e]	
Efficacy/Health Economics Assessments		
PANSS	X[e]	
CGI-S	X[e]	

Trial Periods/Phases	Screening[a]	Baseline/Day 1
Day	**-15 to -1**	**1**
SF-6D	X[e]	
WPAI:Schizophrenia	X	
Other		
Register visit in IVR	X	
IMP dispensing[m]	X	
IMP dosing[m]		X

[a] For rollover participants, screening for Trial CVL-231-2003 occurs simultaneously with baseline assessments at the Week 6 time point of Trial CVL-231-2001 or CVL-231-2002. The first dose of IMP for the open-label trial for rollover participants will occur the day following baseline assessments.
[b] Informed consent for Trial CVL-231-2003 will occur at Screening/Baseline for rollover participants and must be obtained before any trial-related procedures specific to the open-label are performed.
[c] Inclusion and exclusion criteria for rollover participants will be assessed simultaneously with baseline assessments at the Week 6 time point of Trial CVL-231-2001 or CVL-231-2002.
[d] For rollover participants, any ongoing AEs from the double-blind trial will be recorded as medical history until the time of first dose of open-label IMP.
[e] For rollover participants, the screening/baseline assessment will be obtained from the Week 6 time point (Day 42 or Day 45, as appropriate) of the preceding double-blind trial (CVL-231-2001 or CVL-231-2002).
[f] 12-lead ECG assessments will be performed after the participant has been at rest for approximately 3 minutes. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).
[g] Triplicate supine heart rate and blood pressure measurements will be taken at approximately 1-minute intervals, 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). Further details are provided in Protocol Section 8.2.3 and in the Operations Manual.
[h] The "Since Last Visit" C-SSRS form will be completed to ensure that the participant qualifies for the trial.
[i] EPS assessments can be completed at any time during the trial, per investigator discretion, if symptoms are present.
[j] Prior and concomitant medications should be recorded from Screening/Baseline through the participant's last visit/contact.
[k] Adverse events (serious and nonserious) should be recorded from the first dose of open-label IMP.
[l] 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.
[m] Rollover participants will be dispensed IMP and will take their first dose of open-label IMP the day after completion of baseline assessments

Table 7: Schedule of Assessments - Open-Label Treatment (All Participants)

Trial Periods/Phases	**Treatment Period (52 weeks)**												**Follow-up (4 weeks)[a]**
Week	**1**	**2**	**4**	**8**	**12**	**16[a]**	**20**	**26**	**32**	**38**	**44**	**52/ET[b]**	**56**
Day	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**392**
Window (days)	**±3**												
Safety Assessments													
Physical/neurological examination[c]												X	
Limited physical examination[d]				X	X		X	X	X	X	X		
Weight	X	X	X	X	X		X	X	X	X	X	X	
ECG[e]	X	X	X	X	X		X	X	X	X	X	X	
Heart rate and blood pressure (including orthostatic)[f]	X	X	X	X	X		X	X	X	X	X	X	
Respiratory rate and temperature	X	X	X	X	X		X	X	X	X	X	X	
C-SSRS[g]	X	X	X	X	X		X	X	X	X	X	X	
EPS (SAS, AIMS, BARS)[h]			X	X	X		X	X	X	X	X	X	
Concomitant treatments[i]	←----------											----------→	
Adverse event monitoring[j]	←----------											----------→	
Laboratory													
Blood for safety laboratory sample[k]		X	X	X	X		X		X		X	X	
Urine for safety laboratory sample[k]		X	X	X	X		X		X		X	X	
Urine pregnancy test[l]	X	X	X	X	X		X	X	X	X	X	X	
Urine drug screen[m]	X	X	X	X	X		X	X	X	X	X	X	

Trial Periods/Phases	Treatment Period (52 weeks)												Follow-up (4 weeks)[a]
Week	**1**	**2**	**4**	**8**	**12**	**16[a]**	**20**	**26**	**32**	**38**	**44**	**52/ET[b]**	**56**
Day	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**392**
Window (days)	**±3**												
Breathalyzer test for alcohol[n]	←----------→												
Efficacy/Health Economics Assessments													
PANSS		X		X	X		X	X	X	X	X	X	
CGI-S		X		X	X		X	X	X	X	X	X	
CGI-I[o]		X		X	X		X	X	X	X	X	X	
SF-6D		X						X				X	
WPAI:Schizophrenia		X		X	X		X	X	X	X	X	X	
Resource Utilization[p]	X	X	X	X	X		X	X	X	X	X	X	
Other													
Dose adjustment[q]	X	X	X	X	X		X	X	X	X	X		
Contact[a]						X							X
IMP dispensing	X	X	X	X	X		X	X	X	X	X		
IMP accounting	X	X	X	X	X		X	X	X	X	X	X	

[a] Contact with participant via phone call or other means of communication to check on their status.
[b] All Week 52 assessments should be completed for any participant who discontinues early from the trial. All assessments should be completed prior to reinitiation of antipsychotic therapy.
[c] Full physical and neurological examinations should be completed at Screening, Baseline, and Week 52/ET. Symptom-driven physical and/or neurological examinations may be done at any time during the trial at the investigator's discretion.
[d] Details for limited physical examination are provided in Protocol Section 8.2.2.
[e] 12-lead ECG assessments will be performed after the participant has been at rest for approximately 3 minutes. At all time points, single 12-lead ECGs will be obtained. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).

[f] At each indicated time point, triplicate supine heart rate and blood pressure measurements will be taken at approximately 1-minute intervals, 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). Further details are provided in Protocol Section 8.2.3 and in the Operations Manual.

[g] The "Since Last Visit" C-SSRS form will be completed for all participants (rollover and de novo) at all indicated time points.

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

[i] Concomitant medications should be recorded through the participant's last visit/contact.

[j] Adverse events (serious and nonserious) should be recorded from the first dose of IMP in Trial CVL-231-2003 through the participant's last visit/contact.

[k] See Protocol Section 10.2 for more details on clinical laboratory tests.

[l] 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.

[m] The urine drug screen (dipstick) can be conducted at any time during the trial, including unscheduled visits, at the discretion of the investigator.

[n] An alcohol test (breathalyzer) can be conducted at any time during the trial for any participant at the discretion of the investigator.

[o] For rollover participants, improvement should be based on the participants status at the last visit of the double-blind trial (ie, Week 6, Day 45). For de novo participants, improvement should be based on the participants status at Baseline (Day 1); the first CGI-I assessment will be at Week 2 for all participants.

[p] Document health care resource utilization (eg, emergency department or non-trial-related office visits).

[q] Adjustment of emraclidine dose can be made at scheduled and unscheduled visits to optimize efficacy and tolerability as described in Protocol Section 4.1.2. Participants must return to the clinic for an unscheduled visit if the dose adjustment is required between scheduled visits.

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 participant will be categorized as having self-injurious behavior without suicidal intent if there is an occurrence of non-suicidal self-injurious behavior on the C-SSRS – SINCE LAST VISIT eCRF at any postbaseline 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). For rollover participants, C-SSRS assessments from the CVL-231-2001 or CVL-231-2002 parent study will be used to determine baseline score.

Treatment-Emergent Suicide-Related Event

A participant 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 participant 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. Lifetime scores are not considered for baseline suicidal ideation responses.

Treatment-Emergent Serious Suicidal Ideation Compared to Recent History

A participant 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. Lifetime scores are not considered for baseline suicidal ideation responses.

Emergence of Serious Suicidal Ideation Compared to Recent History

A participant 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. Lifetime scores are not considered for baseline suicidal ideation responses.

Emergence of Suicidal Behavior Compared to all Prior History

A participant 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. '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. Listings will be prepared for all participants.
- 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 participants actually summarized within any given summary module; some participants 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 participants actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of participants 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 participant number (including study) 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.
- 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. Abbreviations

Abbreviation	Definition
AE	Adverse events
AESI	Adverse event of special interest
AIMS	Abnormal involuntary movement scale
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BARS	Barnes akathisia rating scale
BMI	Body mass index
CGI-I	Clinical global impression-improvement of symptoms
CGI-S	Clinical global impression-severity of symptoms
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 forms
EPS	Extrapyramidal symptoms
ICF	Informed consent form
IMP	Investigational medicinal product
ITT	Intent to treat
LLN	Lower limit of normal
LSMean	Least squares mean
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model for repeated measures
N	Number of participants
n	Number of observations
PANSS	Positive and negative syndrome scale
PT	Preferred term
Q1	First quartile
Q3	Third quartile
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula

Abbreviation	Definition
SAP	Statistical analysis plan
SAS	Simpson angus scale
SD	Standard deviation
SE	Standard error
SF-6D	Short form-6 dimensions
SF-6Dv2	Short form-6 dimensions version 2.0
SOC	System organ class
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
ULN	Upper limit of normal
WHO	World health organization
WHODrug	World health organization drug dictionary
WPAI	Work productivity and activity impairment