CLINICAL PROTOCOL

Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Safety, and Tolerability of Two Fixed Doses (15 mg and 30 mg QD) of CVL-231 in Participants With Schizophrenia Experiencing an Acute Exacerbation of Psychosis
Trial Number:	CVL-231-2002
Trial Phase:	2
Compound:	Emraclidine (CVL-231)
Sponsor Name:	Cerevel Therapeutics, LLC
Legal Registered Address:	222 Jacobs Street, Suite 200 Cambridge, MA 02141 US
Health Authority Identifier Numbers	IND 144,666 EudraCT 2022-000581-17

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

MEDICAL MONITOR NAME AND CONTACT INFORMATION IS PROVIDED IN THE TRIAL OPERATIONS MANUAL

CONFIDENTIAL – PROPRIETARY INFORMATION

Version 3.0: 15 Mar 2023

Version 2.0: 23 Feb 2022

Version 1.0: 07 Dec 2021

SPONSOR SIGNATORIES

PROTOCOL VERSION 3.0 SUMMARY OF CHANGES TABLE

Document History	
Protocol Version	**Date**
3.0	15 Mar 2023
2.0	23 Feb 2022
1.0	07 Dec 2021

A summary of the protocol amendment issued prior to the present amendment is provided in Section 10.9.

Amendment: Protocol Version 3.0 (15 Mar 2023)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the trial.

Overall Rationale for the Amendment:

The overall rationale for the amendment is to clarify trial procedures.

Section # and Name[a]	Description of Change	Brief Rationale
Signature Page	Updated sponsor signatories	Change in internal responsibilities
1.1 Synopsis	In sentence referring to extending enrollment due to higher anticipated early terminations, removed language “due to COVID-19 or other reasons”	Modification due to impacts from COVID-19 pandemic no longer necessary
1.1 Synopsis 9.3.2 Primary Endpoint/Estimand Analyses 9.3.3 Second Endpoint/Estimand Analyses	In description of statistical method, the strategies for addressing intercurrent events and missing values due to discontinuations were revised to provide further delineation of the intercurrent events of different nature.	[redacted]
1.3 Schedule of Assessments	Modified language in footnotes y and z regarding PK sampling	Clarify site procedures
5.2 Exclusion Criteria	Relaxed entry criterion (Exclusion Criterion #12) regarding COVID-19/ SARS-CoV-2 testing	Allows flexibility to follow COVID-19 procedures employed by each individual site

Section # and Name[a]	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Removed exclusion of participants with positive result for hepatitis B core antibody at Screening and updated wording of "Note" in Exclusion Criterion #15	Focus on risk due to active hepatitis B virus rather than any past exposure; wording updated per Cerevel standard
5.2 Exclusion Criteria	Allowed enrollment of participants who were involved in a long-term follow-up period of an interventional trial with no treatment within 12 months of signing ICF upon approval of medical monitor	Clarify exclusion regarding prior trial participation in Exclusion Criterion #29
6.7.2 Prohibited Therapy	Reduced washout period for depot or long-acting injectable antipsychotic agents from 2 full cycles to 1.5 cycles	Matches washout period for other trials in participants with acute schizophrenia
8.2.3 Vital Sign Measurements 10.3.3 Recording and Follow-Up of AEs and/or SAEs/AESIs	Added instruction and table describing CTCAE grading of blood pressure-related adverse events	Provide additional guidance and clarification for grading of AEs of increased blood pressure
10.2 Clinical Laboratory Tests	Added in clarification that "additional tests" for SARS-CoV-2 can be done at investigator discretion	Clarification of trial procedures
10.4.2.2 Female Participants Who Become Pregnant	Modified language to specify that follow-up not required for longer than 12 weeks beyond estimated delivery date	Match duration required for follow-up period for pregnant partners of male participants
10.7 Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A (not exhaustive)	Updated table	Reflect current medication use and updates made per Cerevel standards
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors or provide further clarification

Abbreviations: AE=adverse event; AESI=adverse event of special interest; COVID-19=coronavirus disease-2019; CTCAE=Common Terminology Criteria for Adverse Events; FDA= Food and Drug Administration; PK=pharmacokinetic; SAE=serious adverse event; SARS-CoV-2=severe acute respiratory virus syndrome coronavirus-2.

a. Numbering (eg, section numbers and numbered lists) refers to current version of the protocol.

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1.1 Synopsis

Protocol Title:

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

Short Title:

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

Rationale:

Emraclidine (previously referred to as CVL-231) is a brain penetrant muscarinic acetylcholine receptor (mAChR) activator that selectively binds to the M4 muscarinic receptor subtype while sparing other muscarinic receptor subtypes (M1, M2, M3, and M5). Emraclidine is being developed for treatment of psychosis in schizophrenia.

The aim of this trial is to investigate the efficacy, safety, and tolerability of 2 fixed doses of emraclidine (15 mg and 30 mg once daily [QD]) in participants with schizophrenia who are experiencing an acute exacerbation of psychosis.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	Primary Endpoint: • Change from Baseline at Week 6 in the PANSS total score Key Secondary Endpoint: • Change from Baseline at Week 6 in the CGI-S score Secondary Endpoints: • Change from Baseline at all time points in PANSS total score • Change from Baseline at all time points in CGI-S score • Percentage of responders at Week 6 (responders defined as ≥30% reduction from Baseline in PANSS total score) Exploratory Endpoints: • CGI-I at Weeks 3 and 6 • Change from Baseline at all time points in PANSS positive, negative, and general psychopathology subscale scores • Change from Baseline at all time points in PANSS Marder Factor scores
Secondary	
• To evaluate the safety and tolerability of 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	• Treatment-emergent adverse events • Clinically significant changes in electrocardiograms, clinical laboratory assessments and metabolic parameters, standard vital sign measurements, and physical and neurological examination results, including body weight • Clinically significant findings in suicidality assessed using the C-SSRS • Extrapyramidal symptoms evaluated using the change from Baseline in SAS, AIMS, and BARS assessments

Objectives	Endpoints
Exploratory	
• To evaluate the plasma pharmacokinetics of emraclidine and its metabolite, CV-0000364, following 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	• Pharmacokinetic parameters for emraclidine and its metabolite, CV-0000364 (C_{max} and AUC_{tau})
• To evaluate quality of life and cognition following 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	• Change from Baseline at Week 6 in BACS symbol coding test • Change from Baseline at Week 6 in SF-6D

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

Brief Summary (Lay Language):

The purpose of this trial is to measure the efficacy, safety, and tolerability of 2 fixed doses of emraclidine (15 mg QD and 30 mg QD) compared with placebo in participants with schizophrenia who are experiencing an acute exacerbation of psychosis. Trial details include the following:

- Trial duration: up to approximately 13 weeks
- Treatment duration: up to 45 days
- Visit frequency: all eligible participants will be admitted to the inpatient facility at the time they sign the informed consent form (ICF) and remain in the inpatient facility for the duration of treatment

Overall Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 6-week trial to evaluate the efficacy, safety, and tolerability of 2 fixed doses of emraclidine (15 mg QD and 30 mg QD) in male and female participants aged 18 to 65 years, inclusive, who have schizophrenia and are experiencing an acute exacerbation of psychosis.

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. All participants will be admitted to the inpatient facility at the time they sign the ICF and remain in the inpatient facility for the duration of treatment.

On Day 1 (Baseline), participants will be randomized in a 1:1:1 ratio to the following treatment groups:

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

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

The daily dosing schedule will start on Day 1 with all participants receiving a single daily dose of investigational medicinal product (IMP) in the morning.

Participants are to remain in the inpatient facility for the entire duration of the trial (ie, from ICF signing through Week 6/early termination [ET]); however, beginning at the Week 3 time point, participants who are sufficiently stable (per investigator assessment) may receive day passes for urgent issues. While away from the site, participants must be supervised by hospital/research staff (medical monitor approval for supervision by a family member or caregiver may be obtained). Participants are not permitted to stay away from the inpatient facility overnight; if, in unforeseen circumstances, the participant is unable to return to the facility the same day, the medical monitor should be contacted to discuss continuing participant eligibility. In addition, the participant must agree to submit to testing (ie, urine drug screen and alcohol breathalyzer test) upon return to the site. If the breathalyzer test is positive, the medical monitor should be contacted to determine continued eligibility of the participant. Participants returning from a day pass who have a positive urine drug screen will be discontinued from the trial. Participants with a positive urine drug screen resulting from use of marijuana (any tetrahydrocannabinol [THC]-containing product), prescription, or over-the-counter medications or products that, in the investigator's documented opinion, do not signal a clinical condition that would impact the safety of the participant or interpretation of the trial results may continue in the trial following consultation and approval by the medical monitor.

All participants will continue dosing through Day 45 of Week 6. For the Week 6 time point, trial assessments will be completed on 2 separate days; on Day 42, the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity of Symptoms (CGI-S), and Clinical Global Impression-Improvement of Symptoms (CGI-I) will be completed, and on the last day of the treatment period, Day 45, the remaining scale and safety assessments will be completed. A minimum of 3 days is required between the completion of the Day 42 assessments and the Day 45 assessments, as noted in the Schedule of Assessments. Participants will receive their last dose of IMP on Day 45.

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

Participants may be allowed to stay in the inpatient facility up to 1 week after their last dose of IMP if necessary to achieve stabilization on alternate therapy with review and approval by the medical monitor.

All participants (completers and early withdrawals), with the exception of those entering the optional open-label rollover trial, will have a follow-up safety contact at approximately 28 days after the last dose of IMP.

Number of Participants:

Approximately 600 participants will be screened to achieve approximately 372 participants qualified to be randomized to treatment in the trial (124 per treatment group).

In the event of higher than anticipated early terminations, Cerevel may extend enrollment in order to achieve trial objectives.

Key Entry Criteria:

- Men and women 18 to 65 years of age, inclusive, with a primary diagnosis of schizophrenia per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, as confirmed by the Mini International Neuropsychiatric Interview for Psychotic Disorders, and experiencing an acute exacerbation or relapse of psychotic symptoms, with onset less than 60 days prior to signing the informed consent form

- PANSS total score between 85 and 120, inclusive, and CGI-S ≥4 (moderately to severely ill) at the time of signing the informed consent form and at Baseline

Intervention Groups and Duration:

Participants will receive treatment with 1) emraclidine 15 mg QD, 2) emraclidine 30 mg QD, or 3) placebo during the Treatment Period of the trial.

The trial will include up to a 15-day Screening Period, a 45-day Inpatient Treatment Period, and a 28-day Follow-up Period. Each participant will participate in the trial for up to approximately 13 weeks.

Statistical Considerations:

Sample Size Estimation:

A sample size of approximately 93 participants in each treatment group completing the Week 6 assessments (approximately 279 in total) should provide at least 90% power to detect an effect size of 0.48 in change from Baseline in PANSS total score at Week 6 between either active treatment group versus placebo at the α=0.05 level. The effect size of 0.48 represents a clinically meaningful effect on symptom reduction based on large scale meta-analysis of historical data from several currently approved antipsychotic

medications in common usage. It could be translated into a difference of 7 points versus placebo if the standard deviation of change from Baseline is 14.6 points or a difference of 8 points versus placebo if the standard deviation of change from Baseline is 16.7 points. Both scenarios of the standard deviation are consistent with historical observations. To account for a discontinuation rate of approximately 25% for a 6-week treatment period (as observed in Trial CVL-231-SCH-001), it is planned to randomize approximately 372 participants.

Statistical Methods

The primary estimand has the following attributes:

1. Treatments as randomized

2. Modified intent-to-treat (mITT) population as the primary population of interest

3. Change from Baseline at Week 6 in total PANSS score as the primary endpoint of interest

4. The population level summary of interest is the treatment differences estimated based on the least square mean and the corresponding 95% confidence interval from the mixed model for repeated measures (MMRM) model with treatment, visit, and treatment by visit interaction as fixed effect, participant as a random effect, and baseline PANSS score as a covariate. An unstructured covariance structure will be used for the repeated measures. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. 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. If a reduced covariance matrix becomes necessary, the sandwich variance estimator will be used.

5. To address intercurrent events (ICEs) with the primary outcome data available, a treatment policy strategy will be used to include all collected outcomes in the primary statistical analysis, consistent with the intent-to-treat principle. The only exception will be the cases of concomitant use of protocol prohibited other antipsychotic and, in such cases, the data collected under the influence of confounding ICEs will be treated as missing.

6. To address ICE of trial or treatment discontinuation with no outcome data collected post discontinuation, the primary analysis of MMRM described above will be followed by pattern mixture model (PMM) approach with varying level of shift parameters for missing values due to discontinuations that are potentially missing not at random (MNAR), including discontinuation due to lack of efficacy or due to adverse events. This will be implemented using delta adjustment imputation method. Further details will be described in the statistical analysis plan (SAP).

The statistical hypothesis testing on the primary endpoint (emraclidine 30 mg QD vs placebo and emraclidine 15 mg QD vs placebo) will be based on the estimated treatment difference from the model at Week 6 and will be tested in a hierarchical order with each at 2-sided alpha level 0.05. The evaluation of other time points will also be derived from the same model.

The number and proportion of responders (ie, participants with 30% reduction from Baseline in the PANSS total score at Week 6 or the last assessment before discontinuation) will be summarized. A logistic regression model, with baseline PANSS as a covariate, will be used to compare the proportion of responders in each active arm with placebo. If expected counts are <5, then a Fisher's Exact test will be used.

The secondary estimand has the following attributes:

1. Treatments as randomized

2. mITT population as the primary population of interest

3. Change from Baseline to Week 6 in CGI-S score as the endpoint of interest

4. The population level summary of interest is the treatment differences estimated based on the least square mean and the corresponding 95% confidence interval from the MMRM model with treatment, visit, and treatment by visit interaction as 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. When a reduced covariance matrix is used, the sandwich variance estimator will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

5. ICEs will be addressed using the same strategies as described above for the primary endpoint.

The number and proportion of participants with ≥1 and ≥2 point improvements from Baseline at the last CGI-S assessment (at Week 6 or the last assessment before discontinuation) will be summarized. A logistic regression model, with baseline CGI-S as a covariate, will be used to compare the proportion of responders in each active arm with placebo. If expected counts are <5, then a Fisher's Exact test will be used.

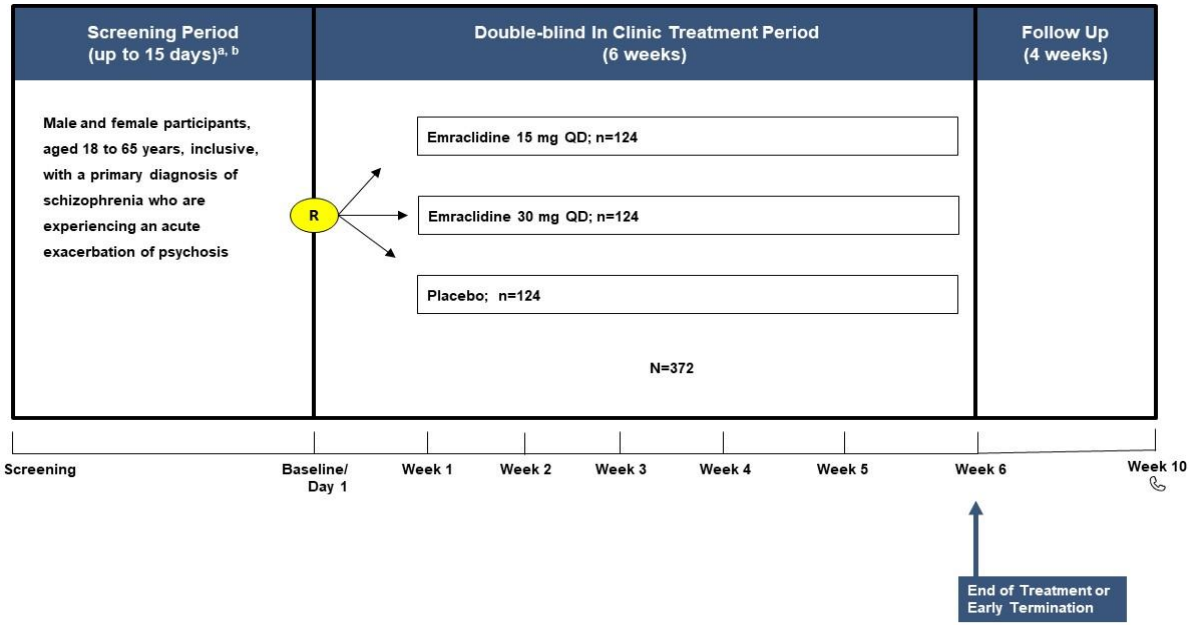
Treatment-emergent adverse events will be coded according to the Medical Dictionary for Regulatory Activities and summarized by treatment group, system organ class, and preferred term. Further summaries will be done by seriousness, severity, and relationship to IMP.

Other safety endpoints will be summarized with descriptive statistics by treatment group, including, vital sign measurements, clinical laboratory assessments and metabolic

parameters, and physical and neurological examination results (including body weight), suicidality assessments using Columbia-Suicide Severity Rating Scale and extrapyramidal symptoms assessed by Abnormal Involuntary Movement Scale, Simpson Angus Scale, and Barnes Akathisia Rating Scale.

1.2 Schema

Figure 1 Trial Schematic



Abbreviations: QD=once daily; R=randomization.
Note: Assessment time points are planned for the last day of the indicated week (eg, Day 7, 14, 21, etc) with a ±2 day window (see Schedule of Assessments in Section 1.3).

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

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

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

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

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

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

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

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

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

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

e. Beginning at the Week 3 time point, participants may receive supervised day passes for urgent issues at the investigator's discretion as described in Section 4.1.2. A breathalyzer test and a urine drug screen must be performed upon return to the inpatient facility for any participant issued a supervised day pass. If the breathalyzer test is positive, the medical monitor should be contacted to determine the next steps. Participants returning from a day pass who have a positive urine drug screen should be discontinued from the trial. However, if the positive urine drug screen results from use of marijuana (any THC-containing product), prescription, or over-the-counter medications or products that, in the investigator's documented opinion, does not signal a clinical condition that would impact the safety of the participant or interpretation of the trial results, the participant may continue in the trial following consultation and approval by the medical monitor.

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

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

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

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

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

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

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

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

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

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

p. 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. At approximately 2 hours following dosing at weekly time points, single 12-lead ECGs will be obtained. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).

q. At Screening and Baseline, blood pressure and heart rate assessments should be performed in order to confirm eligibility (see Exclusion Criterion in Section 5.2). Triplicate supine heart rate and blood pressure measurements should be taken at approximately 1-minute intervals predose (Day 1 only, Baseline), and at approximately 2 hours after dosing on Day 1 and Weeks 1 through 6. The triplicate supine heart rate and blood pressure measurements will be followed by a single measurement after approximately 2 minutes in a standing position to allow for orthostatic assessments. Additional time points can be added at the investigator's discretion (eg, if abnormalities are noted). Further details are provided in Section 8.2.3 and in the Operations Manual.

r. The "Baseline/Screening" C-SSRS form will be completed for all participants 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. The "Since Last Visit" C-SSRS form will also be completed at weekly time points after Baseline.

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

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

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

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

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

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

y. PK samples will be obtained predose (within 15 minutes prior to dosing) and at 1, 4, and 8 hours following dosing on Day 4 and processed for plasma (2 aliquots required [primary/backup]) as described in Section 8.4 and the Lab Manual.

z. PK samples will be obtained predose (within 15 minutes prior to dosing) and at 1, 2, 4, 8, 12, and 24 hours following dosing on Day 24 and processed for plasma (2 aliquots required [primary/backup]) as described in Section 8.4 and the Lab Manual.

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

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

2 INTRODUCTION

2.1 Trial Rationale

Emraclidine (previously referred to as CVL-231) is a brain penetrant mAChR activator that selectively binds to the M4 muscarinic receptor subtype while sparing other muscarinic receptor subtypes (M1, M2, M3, and M5). Emraclidine is being developed for treatment of psychosis in schizophrenia.

The aim of this trial is to investigate the efficacy, safety, and tolerability of 2 fixed doses of emraclidine (15 mg QD and 30 mg QD) in participants with schizophrenia who are experiencing an acute exacerbation of psychosis.

2.2 Background

2.2.1 Disease Overview

Schizophrenia is characterized by positive symptoms (eg, hallucinations and delusions), negative symptoms (eg, emotional blunting and lack of motivation), and deficits in cognitive function (eg, attention, information processing, and working memory) (Shekhar et al, 2008). Treatment of schizophrenia is currently limited to typical and atypical antipsychotic medications that act by blocking various dopamine (D1 and D2) receptors in the brain (Shekhar et al, 2008; Howes and Kapur, 2009). However, these antipsychotics typically also bind to a number of additional receptor subtypes, including other dopaminergic, serotonergic, muscarinic, adrenergic, and histaminergic receptor subtypes (Miron et al, 2014).

The first-generation antipsychotics (eg, chlorpromazine, haloperidol, and fluphenazine) are effective at controlling some symptoms of schizophrenia, especially positive symptoms such as delusions and hallucinations, due to a combination of D2 blockade and anticholinergic and antihistaminergic effects (Buoli et al, 2016; Altamura et al, 2011). However, the use of these first-generation antipsychotics is limited by severe antidopaminergic side effect such as EPS, tardive dyskinesia, and hyperprolactinemia (Schneider et al, 2006; Huybrechts et al, 2012; Foster et al, 2016).

The “atypical” antipsychotics, of which clozapine was the prototype, have reduced extrapyramidal side effects yet retain antipsychotic potency, likely due to a more rapid dissociation from D2 receptors combined with potent serotonergic (5HT2A) blockade (Kapur and Seeman, 2000; Kapur and Seeman, 2001; Solmi et al, 2017). However, these atypical antipsychotics are associated with off-target receptor mediated metabolic effects and weight gain (Nasrallah, 2008).

Recent literature suggests that for xanomeline, an M1/M4 preferring mAChR agonist, its antipsychotic efficacy may be driven primarily by M4 mAChR stimulation (Woolley et al, 2009; Byun et al, 2014; Brannan et al, 2021), and that a selective M4 mAChR activator could convey similar clinical benefits. Presynaptic expression of the

M4 mAChR on cholinergic interneurons regulates striatal acetylcholine and dopamine equilibrium, the imbalance of which is hypothesized to contribute to the symptoms of psychosis observed in schizophrenia. (Howes and Kapur, 2009).

2.2.2 Nonclinical Experience

Emraclidine is a novel, brain penetrant, orally bioavailable, small molecule, reversible activator of M4 mAChR. Presynaptic expression of the M4 mAChR on cholinergic interneurons regulates striatal acetylcholine and dopamine equilibrium, the imbalance of which is hypothesized to contribute to psychosis in schizophrenia (Howes and Kapur, 2009).

Nonadverse treatment-related increases in blood pressure and heart rate, decreases in PR interval and/or RR interval, and shortening of the QT interval (without changes in QTc) were observed in single-dose nonpivotal and pivotal dog cardiovascular safety pharmacology studies with resolution of these findings by 9 hours postdose. In the pivotal 1- and 3-month repeat-dose toxicity studies, similar effects were observed (ie, increased heart rate and decreased PR, RR, and/or QT interval [without changes in QTc]). In the 3-month dog study, the greatest (magnitude) increase in heart rate was observed on Day 1 in the mid- and high-dose groups (≥3.75 mg/kg/day) and was considered adverse based on the magnitude of increase. By Days 43 and 91, heart rate was still increased in these dose groups compared with control animals, but the differences were of small magnitude, and all mean heart rate values were within the normal range for dogs. The reduced magnitude of heart rate increase on Days 43 and 91 are indicative and consistent with the development of tolerance to the emraclidine effects on heart rate. With the exception of Day 1 in the 3-month study, these heart rate increases in the pivotal 1- and 3-month dog toxicity studies were considered nonadverse as there were no corresponding adverse in-life or postmortem findings, including histopathological effects on cardiovascular tissues. Similarly, in the 9-month repeat-dose dog toxicity study, adverse (based on magnitude of increase) heart rates were generally observed at the start of the study (Day 1 for the high dose group and Days 8 and 15 during dose-escalation) and appeared to attenuate as the study progressed (reduced magnitude of heart rate increase generally by Day 22 in previously affected groups). There were no corresponding adverse in-life or postmortem findings, including histopathological effects on cardiovascular tissues. Overall, the cardiovascular effects that were noted in all studies were monitorable, reversible, and not associated with cardiac or vascular pathologies.

The nonclinical safety profile of emraclidine and CV-0000364 metabolite have been adequately characterized to support clinical trials of up to 13 weeks in duration in women of childbearing potential and men with use of highly effective contraception for the duration of systemic exposure.

Please refer to the emraclidine Investigator's Brochure for more detailed information.

2.2.3 Clinical Experience

Safety, tolerability, and PK of emraclidine were evaluated following single doses in healthy participants (Trial C2561001) and following multiple ascending doses in participants with schizophrenia (Trial CVL-231-SCH-001).

In Trial C2561001, emraclidine single oral doses in the range of 0.3 mg to 30 mg were administered under fasted conditions. There were transient changes in heart rate and blood pressure that appeared to be dose related and were most prominent at the 30 mg dose level. These changes returned toward baseline by 24 hours. Two AEs of moderate severity associated with cardiovascular assessments (orthostatic hypotension and sinus tachycardia) were observed at the 30 mg dose level.

In the Phase 1b, 2-part, multiple ascending dose trial in participants with schizophrenia (Trial CVL-231-SCH-001), 39 participants with stable schizophrenia received multiple doses of emraclidine of 5, 10, 20, or 30 mg QD for up to 14 days or 20 mg BID for up to 28 days (7-day titration; 21 days target dose) during Part A. An additional 54 participants with acute exacerbation of psychosis received treatment with emraclidine 30 mg QD (27 participants) or 20 mg BID (27 participants) for up to 42 days in Part B of the trial.

In contrast with healthy participants, the effect of emraclidine on blood pressure in participants with schizophrenia was variable, nonsustained, and had no clear dose relationship. In Part A of Trial CVL-231-SCH-001, emraclidine at doses ≥20 mg QD appeared to be associated with modest, transient increases in both systolic and diastolic blood pressure; none of these increases were associated with TEAEs. emraclidine was also associated with an increase in heart rate that appeared to be dose dependent and persisted throughout the Treatment Period. There were no TEAEs of tachycardia. In Part B of the trial, modest elevations in systolic and diastolic blood pressure and heart rate were observed with emraclidine compared with placebo early in the Treatment Period; these elevations decreased over time. The average change from Baseline during Week 6 in systolic and diastolic blood pressure and heart rate for both the emraclidine 30 mg QD and 20 mg BID groups showing no clinically meaningful difference versus placebo. The average change for the emraclidine 30 mg QD group versus placebo at the 2-hour post morning dose time point during Week 6 were +1.2 mmHg, -0.1 mmHg, and +4.4 bpm for systolic blood pressure, diastolic blood pressure, and heart rate, respectively.

Emraclidine was safe and generally well tolerated in participants with schizophrenia. The most frequently reported TEAEs in emraclidine treated participants (>5% of emraclidine participants) in Part A were headache (4/39 participants; 10%), dizziness (2/39; 5%), insomnia (2/39; 5%), and increased weight (2/39; 5%) and in Part B were headache (15/54; 28%), nausea (4/54; 7%), and back pain, blood creatinine phosphokinase increased, dizziness, dry mouth, increased weight, and somnolence (3/54; 6% each). No clinically meaningful changes were observed in ECGs, except increase in heart rate consistent with vital sign findings. No clinically relevant changes were observed in clinical laboratory findings, or clinical scales for extrapyramidal symptoms or suicidality.

The PK of emraclidine were characterized by rapid absorption and biphasic elimination, with the median T_{max} ranging from 1.0 to 1.8 hours under fasted conditions (3.0 hours in the fed state) and the mean $t_{1/2}$ ranging between 9.4 hours and 12.2 hours across following single doses in healthy participants. Increase in emraclidine C_{max} and AUC appeared to be dose proportional. The results of a pilot food effect trial at the 10 mg dose suggest that administration of the compound immediately following a high-fat diet result in a slight reduction in C_{max} without significantly affecting the overall bioavailability of emraclidine. Pharmacokinetic data from Trial CVL-231-SCH-001 suggest that PK of emraclidine in participants with schizophrenia is similar to that observed in healthy participants. The increase in C_{max} values for emraclidine was roughly dose proportional. However, the high interparticipant variability in emraclidine AUC values, similar to results from the single ascending dose trial, affected accurate dose proportionality assessment.

Both the emraclidine 30 mg QD and the 20 mg BID doses demonstrated clinically meaningful antipsychotic activity compared with placebo in Part B of Trial CVL-231-SCH-001. The emraclidine 30 mg QD dose resulted in a statistically significant and clinically meaningful mean reduction from Baseline of 19.5 points in the PANSS total score (12.7-point difference from placebo group; nominal p=0.023) at Week 6. The emraclidine 20 mg BID dose resulted in a statistically significant and clinically meaningful mean reduction from Baseline of 17.9 points in PANSS total score (11.1-point difference from placebo group; nominal p=0.047) at Week 6. These results were further supported by clinically meaningful improvements versus placebo on the PANSS positive, negative, and general psychopathology subscale scores, as well as on the CGI-S scale score.

Please refer to the emraclidine Investigator's Brochure for more detailed information.

2.3 Benefit/Risk Assessment

This trial is designed primarily to evaluate the efficacy and safety of 2 fixed doses (15 mg QD and 30 mg QD) of emraclidine in the target patient population.

Based on results from Part B of Trial CVL-231-SCH-001, treatment with 30 mg QD emraclidine in patients with schizophrenia experiencing an acute exacerbation of psychosis may be beneficial based on clinically meaningful reductions from Baseline in PANSS and CGI-S scores (see Section 2.2.3).

Doses were chosen for this trial based on nonclinical safety and toxicology data and clinical safety data available to date (see Section 4.3).

There is a potential for an increase in blood pressure and heart rate based on nonclinical findings and findings from the single and multiple ascending dose trials (see Section 2.2.2 and Section 2.2.3). The cardiovascular effects of emraclidine will be carefully monitored on an inpatient basis throughout the trial. The inpatient design will also facilitate careful monitoring of participants during and subsequent to washout from their antipsychotic drug treatment.

More detailed information about the known and expected benefits and potential risks of emraclidine are found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	Primary Endpoint: • Change from Baseline at Week 6 in the PANSS total score Key Secondary Endpoint: • Change from Baseline at Week 6 in the CGI-S score Secondary Endpoints: • Change from Baseline at all time points in PANSS total score • Change from Baseline at all time points in CGI-S score • Percentage of responders at Week 6 (responders defined as ≥30% reduction from Baseline in PANSS total score) Exploratory Endpoints: • CGI-I at Weeks 3 and 6 • Change from Baseline at all time points in PANSS positive, negative, and general psychopathology subscale scores • Change from Baseline at all time points in PANSS Marder Factor scores
Secondary	
• To evaluate the safety and tolerability of 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	• Treatment-emergent adverse events • Clinically significant changes in electrocardiograms, clinical laboratory assessments and metabolic parameters, standard vital sign measurements, and physical and neurological examination results, including body weight • Clinically significant findings in suicidality assessed using the C-SSRS • Extrapyramidal symptoms evaluated using the change from Baseline in SAS, AIMS, and BARS assessments

Objectives	Endpoints
Exploratory	
• To evaluate the plasma pharmacokinetics of emraclidine and its metabolite, CV-0000364, following 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	• Pharmacokinetic parameters for emraclidine and its metabolite, CV-0000364 (C_{max} and AUC_{tau})
• To evaluate quality of life and cognition following 2 fixed oral doses (15 mg QD and 30 mg QD) of emraclidine in adult participants with schizophrenia experiencing an acute exacerbation of psychosis	• Change from Baseline at Week 6 in BACS symbol coding test • Change from Baseline at Week 6 in SF-6D

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

4 TRIAL DESIGN

4.1 Overall Design

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

4.1.1 Screening Period

Participants will enter a Screening Period 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. All participants will be admitted to the inpatient facility at the time they sign the ICF and remain in the inpatient facility for the duration of treatment.

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

4.1.2 Treatment Period

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

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

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

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

Participants are to remain in the inpatient facility for the entire duration of the trial (ie, from ICF signing through Week 6/ET); however, beginning at the Week 3 time point, participants who are sufficiently stable (per investigator assessment) may receive day passes for urgent issues. While away from the site, participants must be supervised by hospital/research staff (medical monitor approval for supervision by a family member or caregiver may be obtained). Participants are not permitted to stay away from the inpatient facility overnight; if, in unforeseen circumstances, the participant is unable to return to the facility the same day, the medical monitor should be contacted to discuss continuing participant eligibility. In addition, the participant must agree to submit to testing (ie, urine drug screen and alcohol breathalyzer test) upon return to the site. If the breathalyzer test is positive, the medical monitor should be contacted to determine the continued eligibility of the participant. Participants returning from a day pass who have a positive urine drug screen should be discontinued from the trial. However, if the positive urine drug screen results from use of marijuana (any THC-containing product), prescription, or over-the-counter medications or products that, in the investigator's documented opinion, does not signal a clinical condition that would impact the safety of the participant or interpretation of the trial results, the participant may continue in the trial following consultation and approval by the medical monitor.

All participants will continue dosing through Day 45 of Week 6. For the Week 6 time point, trial assessments will be completed on 2 separate days; on Day 42, the PANSS, CGI-S, and CGI-I will be completed, and on the last day of the treatment period, Day 45, the remaining scale and safety assessments will be completed. A minimum of 3 days is required between the completion of the Day 42 assessments and the Day 45 assessments, as noted in the Schedule of Assessments (Table 1). Participants will receive their last dose of IMP on Day 45.

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

4.1.3 Follow-up Period

All participants (completers and early withdrawals), with the exception of those entering the optional open-label rollover trial, will have a follow-up safety contact at approximately 28 days after the last dose of IMP.

Participants may be allowed to stay in the inpatient facility up to 7 days after their last dose of IMP if necessary to achieve stabilization on alternate therapy with review and approval by the medical monitor.

4.1.4 Definition of Completed Participant

A participant is considered to have completed the trial if he/she has completed the inpatient Treatment Period of the trial including the last inpatient visit (Day 45), as shown in the Schedule of Assessments in Section 1.3.

4.2 Scientific Rationale for Trial Design

The randomized, double-blind, placebo-controlled, parallel-group trial design minimizes the risk of bias and is considered appropriate for evaluating the effects of a trial treatment for indications in which use of a placebo is ethical (US FDA, 2001). Randomization reduces bias in the assignment of participants to a treatment group, the double-blind design prevents differential treatment and assessments, and the placebo-controlled design controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the drug.

The 6-week duration of the current trial is of sufficient length to show a treatment effect on acute exacerbation of schizophrenia symptoms and has been used for prior trials of antipsychotics evaluated to treat acute psychotic symptoms in patients with schizophrenia (Correll et al, 2020; Correll et al, 2016; Leucht et al, 2013; McEvoy et al, 2007; Kane et al, 2015). As described in Section 2.2.3, emraclidine 30 mg QD demonstrated antipsychotic activity compared with placebo in Part B of Trial CVL-231-SCH-001 based on assessment of PANSS total score and CGI-S score at 6 weeks.

The PANSS is a widely used and validated measure of the severity of core positive and negative symptoms associated with schizophrenia, as defined by the DSM-5. The change from Baseline in the PANSS total score has been the basis of approval for many antipsychotic agents, including Latuda, Rexulti, and Caplyta (Latuda Package Insert, 2013; Rexulti Package Insert, 2018; Caplyta Package Insert, 2019). The CGI-S, which is also widely used and accepted, is included as a supplementary scale to provide a global assessment of clinical status. The BACS is a highly sensitive measure of cognitive defects in patients with schizophrenia; the symbol coding test of the BACS is included in the trial to evaluate the potential effect of emraclidine on attention and processing speed (Keefe et al, 2004; Dickinson et al, 2007).

The safety assessments, including those for assessing EPS, are considered standard for evaluation of an antipsychotic compound in a population with schizophrenia. The C-SSRS is commonly used for stringent monitoring of the risk for suicidality in clinical trials (Posner et al, 2011).

4.3 Justification for Dose

Emraclidine doses and dosing frequency in this trial are based on the safety/tolerability data and PK profile of emraclidine from Trials C2561001 and CVL-231-SCH-001. The targeted maximum dose level of 30 mg QD in this trial represents the top end of the therapeutic dose range for emraclidine. The emraclidine 30 mg QD dose demonstrated clinically meaningful and statistically significant antipsychotic activity compared with placebo as assessed by changes from Baseline at Week 6 in the PANSS total score in a Phase 1b trial in participants with an acute exacerbation of schizophrenia. emraclidine 30 mg QD, dosed for up to 6 weeks without titration, has been deemed safe and well tolerated in participants with schizophrenia. As mentioned above, this dose was associated with a maximum increase of 4.4 bpm in supine heart rate and 1.2 mmHg in supine systolic blood pressure (Week 6 average at 2 hours post morning dose compared with placebo).

The 15 mg QD dose is selected to understand the efficacy at a lower dose. Based on range of doses evaluated in the multiple ascending dose trial (CVL-231-SCH-001), the 15 mg QD dose is expected to be safe and well tolerated. The 2 doses of 30 mg QD and 15 mg QD will facilitate the evaluation of efficacy of emraclidine across a wide exposure range for a thorough understanding of exposure responsiveness of emraclidine effects.

4.4 End of Trial Definition

The end of the trial is defined as the date of the last visit (including follow-up safety contact) of the last participant in the trial globally.

The definition of a completed participant is provided in Section 4.1.4.

5 TRIAL POPULATION

Men and women, 18 to 65 years of age, inclusive, with a primary diagnosis of schizophrenia who are experiencing an acute exacerbation or relapse of psychotic symptoms will be enrolled into the trial.

5.1 Inclusion Criteria

Individuals are eligible for participation in this trial only if all of the following criteria apply:

General	
1.	Male and female participants, ages 18 to 65 years, inclusive, at the time of signing the ICF.
Target Disease Characteristics	
2.	Primary diagnosis of schizophrenia per DSM-5, as confirmed by the MINI for Psychotic Disorders version 7.0.2.
3.	CGI-S ≥4 (moderately to severely ill) at the time of signing the ICF and Baseline.

4.	PANSS Total Score between 85 and 120, inclusive, at the time of signing the ICF and at Baseline. Additionally, participants must meet a score of ≥4 (moderate or greater) for ≥2 of the following Positive Scale items at the time of signing the ICF and at Baseline: • Positive Scale Item 1 (delusions) • Positive Scale Item 2 (conceptual disorganization) • Positive Scale Item 3 (hallucinatory behavior) • Positive Scale Item 6 (suspiciousness/persecution)
5.	Experiencing an acute exacerbation or relapse of psychotic symptoms, with onset less than 60 days prior to signing the ICF. • Participant requires hospitalization for this acute exacerbation or relapse of symptoms • If participant is already an inpatient at the time of signing the ICF, has been hospitalized for ≤14 days for the current episode of psychosis at the time of signing the ICF, excluding hospitalization for psychosocial reasons
6.	Scores as follows (normal to mild symptoms) at the time of signing the ICF and Baseline (Day 1): • All individual items of the SAS <2 • All individual items (Items 1-7) of the AIMS <2 • Clinical global assessment item of the BARS <3
7.	Willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.
8.	Resides in a stable living environment as demonstrated by the ability to provide contact information for themselves and/or family/friend/caregiver.
Other and Administrative Criteria	
9.	Agree to comply with the following contraception requirements during the trial and for 7 days after the last dose of IMP: • Sexually active men must agree to use a condom and practice contraception during treatment and until the end of relevant systemic exposure (ie, 7 days after the last dose of IMP). • Sexually active women of childbearing potential must use highly effective contraception as defined in Section 10.4.1.1 In addition, male participants should not donate sperm for a minimum of 7 days following the last dose of IMP.
10.	Body mass index of 18.0 to 40.0 kg/m^2 and a total body weight ≥50 kg (110 lbs).
11.	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in Section 10.1.3.
12.	Ability, in the opinion of the investigator, to understand the nature of the trial, participate in trial visits, and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, outcomes measures, and other trial procedures.

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; CGI-S=Clinical Global Impression–Severity of Symptoms; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICF=informed consent form; IMP=investigational medicinal product; MINI=Mini International Neuropsychiatric Interview; PANSS=Positive and Negative Syndrome Scale; SAS=Simpson Angus Scale.

5.2 Exclusion Criteria

Individuals are not eligible for participation in this trial if any of the following criteria apply:

Target Disease	
1.	Current DSM-5 diagnosis other than schizophrenia including, but not limited to, intellectual disability; schizoaffective disorder; major depressive disorder; schizophreniform disorder; psychotic depression; bipolar disorder; post-traumatic stress disorder; generalized anxiety disorder, obsessive compulsive disorder, eating disorders (bulimia, anorexia), or other anxiety disorders as a primary diagnosis (note: anxiety symptoms secondary to schizophrenia are allowed); delirium, dementia, amnestic, or other cognitive disorders. Acute depressive symptoms within 30 days prior to signing the ICF that require treatment with an antidepressant are exclusory. Acute manic symptoms within 30 days prior to signing the ICF that require treatment with a mood stabilizer are exclusory. Additional excluded conditions include borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder.
2.	Any of the following: • Schizophrenia considered resistant/refractory to antipsychotic treatment by history (failure to respond to 2 or more courses of adequate pharmacological treatment defined as an adequate dose per label and a treatment duration of at least 4 weeks) • History of response to clozapine treatment only or failure to respond to clozapine treatment for schizophrenia
3.	Any of the following regarding history of schizophrenia: • Time from initial onset of schizophrenia <2 years based on prior records or participant self-report • Presenting with an initial diagnosis of schizophrenia • Presenting for the first time with an acute psychotic episode requiring treatment
4.	Reduction (improvement) in PANSS total score of ≥20% between Screening and Baseline.
5.	Either of the following: • History of tardive dyskinesia • Extrapyramidal symptoms that required medication within 6 months prior to signing the ICF
Other Medical History and Concurrent Conditions	
6.	Current or past history of significant pulmonary, gastrointestinal, renal, hepatic, metabolic, genitourinary, endocrine (including diabetes mellitus), malignancy (except for basal cell carcinoma of the skin and cervical carcinoma in situ, at the discretion of the investigator), hematological, immunological, neurological, or psychiatric disease that, in the opinion of the investigator or medical monitor, could compromise either participant safety or the results of the trial. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the participant to an undue risk of significant AEs or interfere with the assessment of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a participant's medical conditions(s) and the potential impact of the condition(s) on trial participation.

7.	Current or past history of significant cardiovascular disease including any of the following: ischemic heart disease, myocardial infarction, cardiac valvulopathy, cardiac surgery revascularization (coronary artery bypass grafting) or stenting or percutaneous transluminal coronary angioplasty, receiving more than 2 medications to treat hypertension or have not been on stable doses of antihypertensive medications for >3 months, orthostatic hypotension, angina, unstable angina, cerebrovascular accident or stroke or transient ischemic attack, pacemaker, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia, or non-sustained or sustained ventricular tachycardia, pulmonary arterial hypertension, sick sinus syndrome, Type 2 second-degree or third-degree atrioventricular block, congestive heart failure, personal or family history of sudden death or long QT syndrome, unexplained syncope, syncope within the last 3 years regardless of etiology, or symptomatic orthostatic dizziness (by history or observed at the Screening Visit during the vital sign assessments).
8.	Active central nervous system infection, demyelinating disease, degenerative neurological disease, mental retardation, brain tumor, prior hospitalization for severe head trauma, seizures (excluding febrile seizures in childhood), or any central nervous system disease deemed to be progressive during the course of the trial that may confound the interpretation of the trial results.
9.	Diagnosis of moderate to severe substance or alcohol-use disorder (excluding nicotine or caffeine) as per DSM-5 criteria within 12 months prior to signing the ICF. Participants with mild substance or alcohol-use disorder may be included in the trial following consultation and approval by the medical monitor.
10.	"Yes" responses for any of the following items on the C-SSRS (within the past 6 months): • Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) • Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) "Yes" responses for any of the following items on the C-SSRS (within past 2 years): • Any of the Suicidal Behavior items (Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Acts or Behavior) Serious risk of suicide in the opinion of the investigator is also exclusionary.
11.	Any condition or surgery that could possibly affect drug absorption, including, but not limited to, complicated appendectomy or cholecystectomy, bowel resections, bariatric weight loss surgery, gastric banding, or gastrectomy.
12.	Have recently been diagnosed with and hospitalized for symptomatic COVID-19 or test positive for SARS-CoV-2 at Screening.
Prior or Concomitant Therapies	
13.	Use of prohibited medications prior to randomization within the required wash-out period (Table 4) or likely to require prohibited concomitant therapy (Table 5) during the trial.
14.	Transcranial magnetic stimulation or electroconvulsive therapy within 90 days of signing the ICF.
Laboratory Test Results	
15.	Positive result for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody with detectable viral RNA levels at Screening. Note: Positive or indeterminate test result for hepatitis C antibody should follow with hepatitis C virus PCR RNA test. If result is positive, the participant is excluded.

16.	Positive drug screen or a positive test for alcohol (note: individuals who test positive for alcohol may be rescreened). Participants with a positive urine drug screen resulting from use of marijuana (any THC-containing product), prescription, or over-the-counter medications or products that, in the investigator's documented opinion, do not signal a clinical condition that would impact the safety of the participant or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor.
17.	Any of the following clinical laboratory test results at the Screening Visit, confirmed by a single repeat measurement, if deemed necessary: • AST or ALT ≥2 × ULN • Total bilirubin >1.5 × ULN. If Gilbert's syndrome is suspected, total bilirubin >1.5 × ULN is acceptable if the conjugated or direct bilirubin fraction is <20% of total bilirubin
18.	Positive pregnancy test result prior to receiving IMP. Note: female participants who are pregnant, breastfeeding, or planning to become pregnant during IMP treatment or within 7 days after the last dose of IMP are also excluded.
Other Exclusionary Safety Assessments	
19.	12-lead ECG demonstrating any of the following at the Screening Visit and at Baseline: • QTcF interval >450 ms • QRS interval >120 ms (unless right bundle branch block) • PR interval >200 ms • LVH with ST depressions and/or T wave inversions in leads with relatively tall R waves (ie, LVH with associated ST-T wave abnormalities) • Type 2 second-degree or third-degree atrioventricular block • Heart rate <45 bpm or >100 bpm • Abnormal ECG changes (such as clinically significant ST depression or elevation or T wave inversion) • Abnormal heart rhythm (atrial fibrillation and atrial flutter) Note: at Screening, eligibility will be based on the average of a centrally read triplicate set of ECGs. At Baseline Visit, if any of the above criteria are met on the machine read of the ECG, the medical monitor should be consulted to determine whether the participant is eligible for randomization. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the interpretation of ECG results.

20.	Blood pressure measurements demonstrating any of the following at the Screening Visit and/or at Baseline: • Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg ○ Blood pressure will be measured in triplicate at approximately 1-minute intervals in a supine position after at least 3 minutes of rest. The triplicate measures will be individually recorded and the average of the last 2 measurements will be used to determine eligibility. • Orthostatic hypotension, defined as a decrease of ≥20 mmHg in systolic blood pressure and/or ≥10 mmHg in diastolic blood pressure after at least 2 minutes of standing compared with the average of the resting supine blood pressure measurements as measured above
21.	Any other abnormal safety findings unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the participant or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Tests with abnormal results that are potentially exclusionary should be repeated to ensure reproducibility of the result before excluding a potential participant based on criteria provided in the protocol.
Lifestyle or Other Miscellaneous Exclusion	
22.	Refusal to abstain from grapefruit-containing foods or beverages or Seville orange-containing foods or beverages from 7 days prior to dosing through Week 6/ET.
23.	Chronic consumption of >400 mg/day of caffeine-containing drinks or food (eg, >4 cups [8 ounces] of brewed coffee, 9 cans [12 ounces] of diet cola, 12 cans [12 ounces] of cola, 8.5 cups of brewed black tea, 2 energy shot drinks) based on participant self-report.
24.	Considering or scheduled to undergo any surgical procedure during the trial.
25.	Prisoners or participants who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical illness (eg, infectious disease).
26.	Any other condition that would preclude IMP administration or trial participation (eg, difficulty swallowing, poor venous access).
27.	Known allergy or hypersensitivity to emraclidine, closely related compounds, or any of its specified ingredients.
28.	Received IMP in a prior clinical trial of emraclidine.
29.	History of participation in any clinical trial involving an IMP as defined by the following: • Current enrollment or past participation within 90 days prior to signing the ICF, with the exception of a trial with a long-term follow-up period where dosing occurred more than 12 months prior to signing the ICF for this trial (discussion with and approval by the medical monitor required prior to enrollment) • Enrollment in more than 1 interventional trial within 12 months prior to signing the ICF Note: Prior participation in an interventional trial and a rollover extension trial with the same IMP within the last 12 months is permitted
30.	Anyone who should not participate in the trial in the opinion of the sponsor, investigator, or medical monitor, eg, participants who would be considered a risk for violent or destructive behavior.

31.	Employee of the investigator, clinic, or sponsor with direct involvement in the proposed trial or other trials under the direction of the investigator or clinic, as well as family members of the employee or investigator.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG=electrocardiogram; ET=early termination; HIV=human immunodeficiency virus; ICF=informed consent form; IMP=investigational medicinal product; LVH=left ventricular hypertrophy; PANSS=Positive and Negative Syndrome Scale; QTcF=QT interval corrected for heart rate using Fridericia's formula; THC=tetrahydrocannabinol; ULN=upper limit of normal range.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should fast for at least 8 hours prior to screening safety laboratory evaluations, if at all possible. If this is not possible, nonfasting screening laboratory evaluations may be obtained for eligibility determination. Participants must fast for a minimum of 8 hours prior to baseline and Week 6 safety laboratory assessments and should avoid consuming high-fat meals for 8 hours prior to any other safety laboratory assessments.

Participants should refrain from eating or drinking food/food products which are strong/moderate inhibitors of cytochrome P450 3A4 (including but not limited to grapefruit, grapefruit juice, or grapefruit-related citrus fruits/juices [eg, Seville oranges, pomelos]) from 7 days prior to dosing through Week 6/ET.

5.3.2 Caffeine, Alcohol, and Tobacco

Chronic consumption of >400 mg/day of caffeine-containing drinks or food (eg, >4 cups [8 ounces] of brewed coffee, 9 cans [12 oz] of diet cola, 12 cans [12 oz] of cola, 8.5 cups of brewed black tea, 2 energy shot drinks) will be prohibited while participants are in the inpatient facility.

Participants should abstain from alcohol from time of signing ICF (check-in to inpatient facility) until Week 6/ET (check-out of inpatient facility). Participants will undergo an alcohol breath test at Screening (check-in), upon return to the inpatient facility if they leave, and at the discretion of the investigator.

For participants who smoke, the number of cigarettes (or equivalent) smoked per day will be collected at both Screening and Baseline.

5.3.3 Activity

Participants should abstain from strenuous exercise during the trial.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from health authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) at screening may be rescreened once at the discretion of the investigator and after consultation with the medical monitor unless screen failure is due to a positive urine drug screen for illicit substances. Rescreened participants will be assigned a new participant number.

6 TRIAL INTERVENTION AND CONCOMITANT THERAPY

Trial intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial participant according to the trial protocol.

In this protocol, the trial interventions are referred to as IMPs. An IMP is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

6.1 Trial Interventions Administered

A summary of the IMP to be administered during this trial is presented in Table 3.

Table 3 Investigational Medicinal Product

Treatment Group	Emraclidine 15 mg QD	Emraclidine 30 mg QD	Placebo
Type	Drug	Drug	Not applicable
Dose Formulation	Tablet	Tablet	Matching tablet
Unit Dose Strength	15 mg	30 mg	0 mg
Dosage Level	15 mg QD	30 mg QD	0 mg QD
Route of Administration	Oral	Oral	Oral
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	IMP will be provided in bottles. Each bottle will be labeled as required per US requirement.	IMP will be provided in bottles. Each bottle will be labeled as required per US requirement.	Trial treatment will be provided in bottles. Each bottle will be labeled as per country requirement.

Abbreviations: IMP=investigational medicinal product; QD=once daily; US=United States.

Information regarding potential overdose with IMP is provided in Section 8.3.6.

6.2 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit (original shipment and/or moving of IMP supply from 1 office or facility to another within the trial site's network) for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only participants enrolled in the trial may receive IMP and only authorized trial site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized trial site staff.

The investigator is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the preparation, handling, storage, accountability, and disposition of unused IMP are provided in the pharmacy manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Assignment to Treatment

All participants will be centrally randomized in a 1:1:1 ratio to 1 of 3 treatment groups (placebo, emraclidine 15 mg QD, or emraclidine 30 mg QD) on Day 1 via an IRT

according to a computer-generated randomization scheme. Participants will be sequentially assigned to the next available randomization number and will receive the IMP that corresponds to that randomization number. Once a randomization number has been assigned, it will not be reassigned.

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

6.3.2 Blinding

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

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

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

6.4 Trial Intervention Compliance

The date and dose (and time on days with PK assessments) of each IMP administration, along with information on any missed or inappropriately administered dose, will be recorded in source documents and the eCRF. Compliance will be ensured by a hand and mouth check during the oral dosing administration.

6.5 Dose Modification

No dose modifications are permitted during the trial.

6.6 Intervention After the End of the Trial

Participants who complete through Day 45 of the trial may have the opportunity to receive open-label treatment with emraclidine in an open-label extension trial

(Protocol CVL-231-2003) if available. Participants who are ineligible or elect not to enter the open-label extension trial will resume treatment with available antipsychotic medications at the discretion of and as determined by their physician.

6.7 Prior and Concomitant Therapy

6.7.1 Time Period for Recording Prior and Concomitant Therapy

The investigator will record all therapies (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken by the participant from 30 days prior to signing the ICF through the end of the evaluation period (defined as the time period during which participants are evaluated for primary and/or secondary objectives).

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in the eCRF: therapy, indication, start date, and end date.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.2 Prohibited Therapy

All participants must agree to discontinue all prohibited medications during the Screening Period in order to meet the protocol-specified washout periods. Table 4 provides the required duration of washout for selected prohibited medications. All other prohibited medications must be discontinued at least 24 hours before the first dose of IMP.

Table 4 List of Medications Prohibited Before Randomization

Prohibited Prior Medications	Washout (if applicable)
Antipsychotic agents	
Oral (or immediate-release intramuscular) aripiprazole or cariprazine	14 days
Other oral (or immediate-release intramuscular) antipsychotic agents	7 days
Depot or long-acting injectable antipsychotic agents	1.5 cycles (per prescribing information)
Antidepressants	
Fluoxetine or Symbyax	28 days
Monoamine oxidase inhibitors	14 days
Citalopram and escitalopram	7 days
Venlafaxine and desvenlafaxine	7 days
All other antidepressants	14 days
Mood stabilizers (ie, lithium and/or anticonvulsants)	14 days
All other psychoactive substances (except benzodiazepines)	7 days
Varenicline (eg, Chantix)	7 days
Beta receptor antagonists to treat hypertension	Not applicable
Other antihypertensive agents Receiving more than 2 medications to treat hypertension Have not been on stable doses of antihypertensive medications for >3 months	Not applicable

Table 5 lists all medications prohibited during the trial, including exceptions, where appropriate.

Table 5 List of Medications Prohibited During the Treatment Period

Psychotropic agents including, but not limited to, the following: a) Antipsychotics, including depot or long-acting injectable formulations b) Antidepressants (including monoamine oxidase inhibitors) c) Mood stabilizers (ie, lithium and/or anticonvulsants) d) Benzodiazepines, except specific benzodiazepines when used to treat anxiety, agitation, or insomnia secondary to schizophrenia[a] e) Prescription stimulants (including appetite suppressants and treatments for attention-deficit hyperactivity disorder or narcolepsy) f) Opioid analgesics, unless approval is obtained from the medical monitor. Approval for opioid use may be considered for a documented and clinically appropriate indication (eg, episodic pain, tooth extraction) if prescribed at a medically appropriate dose and frequency
Hypnotics, including ramelteon and other non-benzodiazepine sleep aids, except for specific medications when used to manage active insomnia[b]
Antihistamines (except for loratadine and cetirizine)
Varenicline (eg, Chantix)
Vitamins, other nutritional supplements, and non-prescription herbal preparations, unless approved in advance by the medical monitor
Investigational agents

Any drug or product that is a moderate to strong inducer of CYP3A metabolism, which has the potential to lower emraclidine exposure levels. An example list of strong (>80% reduction in AUC) and moderate (50% to 80% reduction in AUC) inducers is provided in Section 10.7. Previous use of a CYP3A inducer must not have been taken at least 8 weeks prior to dosing.
Any drug or product that is classified as a significant (ie, strong or moderate) inhibitor of the CYP3A metabolic pathway, which has the potential to increase emraclidine exposure levels. An example list of strong (eg, >5-fold increase in AUC) and moderate (eg, 2-to 5-fold increase in AUC) inhibitors is provided in Section 10.7. Previous use of a significant inhibitor of CYP3A must not have been taken for at least 2 weeks prior to dosing.
Participants taking a drug that is a substrate for the renal transporters OCT2, MATE1, and MATE2K (eg, metformin).
Anticholinergic agents, beta-receptor antagonists (eg, propranolol), and VMAT2 inhibitors (eg, valbenazine and deutetrabenazine).
Initiation or change in antihypertensive therapy is prohibited during the trial unless discussed with and approved by the medical monitor.

Abbreviations: AUC=area under the concentration-time curve; CYP=cytochrome P450; MATE=multidrug and toxin extrusion transporter; OCT=organic cation transporter; VMAT2=vesicular monoamine transporter 2.

a. See Section 6.7.3 for details on benzodiazepine use during the trial.
b. See Section 6.7.4 for details on non-benzodiazepine sleep aid use during the trial.

6.7.3 Benzodiazepine Use During the Trial

The use of intramuscular benzodiazepines is prohibited during this trial. However, use of oral lorazepam as management for anxiety, agitation, and insomnia secondary to schizophrenia (either as an ongoing comorbidity noted at screening or as an AE) will be allowed both during the washout period between the screening and baseline assessments, and during the treatment phase.

During the washout period, the prior use of other benzodiazepines must be discontinued in favor of oral lorazepam up to a maximum dose of 4 mg/day. In countries where oral lorazepam is not available, equivalent doses (as defined in the Operations Manual) of an alternate short-acting benzodiazepine may be used. As an exception, oral lorazepam (or equivalent) can be used up to a maximum dose of 6 mg/day if needed to treat symptoms of agitation during the Screening Period and on days with intensive PK sampling (ie, Day 24).

The prescribed benzodiazepines should be discontinued as soon as the symptoms for which it was initiated subsides, as per the investigator's discretion, to avoid any withdrawal effects.

Benzodiazepines must not be administered within 12 hours prior to any scheduled efficacy or safety assessments. Investigators are encouraged to delay scale administration until a full 12 hours have elapsed since the last benzodiazepine dose, if at all possible, including at screening and baseline assessments. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the

use of benzodiazepine documented, including a notation of the drug name, dose, and time of administration on the eCRF.

6.7.4 Non-benzodiazepine Sleep Aids

Non-benzodiazepine sleep aids (ie, zolpidem, zaleplon, zopiclone, and eszopiclone only) are permitted for the treatment of insomnia, but not within 10 hours of administration of a benzodiazepine, regardless of indication. For the non-benzodiazepine sleep aids, site personnel should utilize one of the listed medications that are approved for this indication and the specific prescribing information should be used to determine the maximum allowable daily dose for the treatment of insomnia. Non-benzodiazepine sleep aids must not be administered within 12 hours prior to scheduled efficacy and safety assessments, including EPS scales. Investigators are encouraged to delay scale administration until 12 hours have elapsed, if at all possible. However, if delaying the administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the sleep aid documented, including a notation of the drug name, dose, and time of administration on the eCRF.

6.7.5 Psychotherapy

With the exception of group therapy on the unit, newly initiated psychological therapy is prohibited during the trial.

Except for inpatient group therapy, participants may only receive psychological therapy (individual, group, marriage, or family therapy) if they have been participating in therapy regularly for at least 8 weeks prior to screening and can commit to maintain their participation during the course of the trial at the current frequency. Permission for initiation of new therapy may be obtained only from the medical monitor.

7 DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Details on discontinuation of individual trial sites or of the trial as a whole are provided in Section 10.1.8.

7.1 Discontinuation of Trial Intervention

If a participant permanently discontinues IMP, refer to the Schedule of Assessments (Section 1.3) for data to be collected following IMP discontinuation.

If a participant discontinues IMP due to an AE, the investigator or other trial personnel will make every effort to follow the event until it has resolved or stabilized.

7.2 Participant Discontinuation/Withdrawal From the Trial

All participants have the right to withdraw from the trial at any time without prejudice. Participants cannot withdraw consent for use of data already collected as part of the trial,

but can withdraw consent for future participation. The investigator can also discontinue a participant from the trial at any time for safety, behavioral, or compliance reasons. Unless a participant provides written withdrawal of consent or there is other written documentation by the investigator confirming the participant's verbal intent to completely withdraw from the trial, participants should be followed for all protocol-specified evaluations and assessments, if possible.

At the time of discontinuation from the trial, if possible, an early termination visit should be conducted. See the Schedule of Assessments (Section 1.3) for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed. All assessments should be completed prior to reinitiating antipsychotic therapy, whenever possible. If antipsychotic therapy has been initiated, the efficacy scales (PANSS, CGI-S, CGI-I) should not be conducted.

The reason for discontinuation from the trial will be recorded in the eCRF.

7.3 Lost to Follow-up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the trial site personnel. The following actions must be taken if a participant fails to return to the site for a required trial visit:

- Trial site personnel must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Participants who continue to be unreachable will be considered to have withdrawn from the trial.

8 TRIAL ASSESSMENTS AND PROCEDURES

The timing and frequency of trial procedures are provided in the Schedule of Assessments (Section 1.3). Protocol waivers or exemptions are not allowed.

At each time point during the trial, efficacy and health economics assessments should be completed before safety assessments in the following preferred order:

1. PANSS

2. CGI-S/CGI-I

3. Vital sign measurements
4. ECGs
5. Laboratory blood draws (clinical safety laboratory assessments/PK)
6. BACS/SF-6D
7. Safety scale assessments (C-SSRS/SAS/AIMS/BARS)

Immediate safety concerns should be discussed with the medical monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP.

Adherence to the trial design requirements, including those specified in the Schedule of Assessments, is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants who are screened and to confirm eligibility or record reasons for screening failure, as applicable.

The MINI for Psychotic Disorders version 7.0.2 (Sheehan et al, 1998; Sheehan et al, 1997) will be conducted at the Screening Visit to confirm the participant's diagnosis of schizophrenia and to rule out exclusionary comorbid psychiatric diagnoses. Detailed instructions for administration of this structured interview will be provided in the Operations Manual.

8.1 Efficacy Assessments

Trained and qualified (details provided in the Operations Manual) clinicians should administer the efficacy assessments and the number of raters should be kept to a minimum. All efforts should be made to ensure the same clinician administers the scales for a given participant throughout the trial.

All efficacy assessments will be completed using an approved electronic data capture system.

Benzodiazepines and non-benzodiazepine sleep aids are not permitted within 12 hours of administration of clinician-administered scales (see Section 6.7).

The timing and frequency of efficacy assessments are provided in the Schedule of Assessments (Section 1.3).

8.1.1 Positive and Negative Syndrome Scale

The PANSS (Kay et al, 1999) is a clinical scale that has been extensively used as a reliable and valid measure of the negative and positive symptoms of schizophrenia

(Liechti et al, 2017). The scale is used for measuring symptom severity in 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

Although the PANSS is structured as a scale to assess the above 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.

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.

8.1.2 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.

8.1.3 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.

8.1.4 Brief Assessment of Cognition in Schizophrenia – Symbol Coding Test

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

8.2 Safety Assessments

The timing and frequency of safety assessments are provided in the Schedule of Assessments (Section 1.3).

8.2.1 Height and Weight

Height will be measured at Screening 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

8.2.2 Physical and Neurological Examinations

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

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

A full neurological examination will include an assessment of the 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 (or designee) is responsible for performing the physical and neurological examinations. If the appointed designee is to perform these examinations, he or she must be permitted by local regulations and his or her name must be included on the delegation of authority log. Whenever possible, the same individual should perform all physical and neurological examinations.

Any condition present at the post-treatment physical and neurological examinations that was not present at the baseline examination should be documented as an AE and followed to a satisfactory conclusion.

8.2.3 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 1.3). The triplicate values will be individually recorded, and the values will be averaged by the sponsor for all time point assessments following confirmation of eligibility. For determination of eligibility, the average of the last 2 values will be used (see Section 5.2). Additional details are provided in the Operations Manual.

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

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 AE section of the eCRF.

If the increase in blood pressure is clinically significant and therefore reported as an AE, the NCI-CTCAE toxicity grades summarized in Section 10.3.3 (Table 12) should be followed.

Further details on taking vital sign measurements are provided in the appropriate trial specific manuals.

Abnormal vital sign measurements that are defined as AESIs are discussed in Section 8.3.7.

8.2.4 Electrocardiograms

Electrocardiogram 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. The ECG results will be evaluated at the investigational site to determine the participant's eligibility and to monitor safety during the trial. The principal investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. 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. A central ECG service will be used for reading all ECGs in order to standardize interpretations for the safety analysis. Additional guidance on collection of ECGs will be provided in the Operations Manual.

At Screening, 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. If, during screening, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the participant or the interpretation of the trial results) or meets an exclusion criterion (see Section 5.2), the participant should be excluded from the trial. The central ECG service will provide the QTcF corrections and average of the 3 ECGs performed to determine eligibility.

At all other specified time points in the Schedule of Assessments (Section 1.3) where an ECG recording must be performed, only a single ECG is required.

Exclusion criteria for screening do not apply as mandatory discontinuation criteria for participants who are already randomized. A repeat ECG should be performed in case of any clinically significant abnormality that is identified in a randomized participant during the treatment period and, in these cases, the medical monitor should be consulted on the appropriateness of the participant continuing in the trial.

8.2.5 Clinical Safety Laboratory Assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the trial as an AE. The laboratory reports must be filed with the source documents.

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.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the Schedule of Assessments.

8.2.6 Suicidal Ideation and Behavior Risk Monitoring

Suicidality will be monitored during the trial using the C-SSRS. This semi-structured interview was originally developed to evaluate the link between antidepressants and suicidal behavior and ideation in youth and adverse events from pediatric clinical trials (Posner et al, 2011). It was designed to quantify the severity of suicidal ideation and behavior. Trial personnel administering the C-SSRS must have completed the appropriate training and have valid certification. Access to training on the scale will be provided by the sponsor or designee.

This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version will be completed for all participants at Screening to determine eligibility. The exclusion criteria based on the C-SSRS are provided in Section 5.2.

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

8.2.7 Extrapyramidal Symptoms

Trained and experienced clinicians should administer the EPS assessments and the number of raters should be kept to a minimum. All efforts should be made to ensure the same clinician administer the scales for a given participant throughout the trial.

Benzodiazepines and non-benzodiazepine sleep aids are not permitted within 12 hours of administration of EPS scales (see Section 6.7).

8.2.7.1 Simpson-Angus Scale

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.

8.2.7.2 *Abnormal Involuntary Movement Scale*

The AIMS assessment (Guy, 1976) consists of 10 items describing symptoms of dyskinesia. Facial and oral movements (items 1 through 4), extremity movements (items 5 and 6), and trunk movements (item 7) are observed unobtrusively while the 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 participant should be sitting on a hard, firm chair while the scale is administered.

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

8.2.7.3 *Barnes Akathisia Rating Scale*

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 (eg, while engaged in neutral conversation or engaged in other activity) may also be rated. Subjective phenomena are to be elicited by direct questioning.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3. Definitions of AESIs are provided in Section 8.3.7.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE, or AESI and remain responsible for following up AESIs and AEs that are serious, considered related to the IMP or trial procedures, or that caused the participant to discontinue IMP (see Section 7.1).

Further details about AE recording and follow-up are provided in Section 10.3.

8.3.1 Time Period and Frequency for Collecting AE and SAE/AESI Information

All AEs and SAEs/AESIs will be recorded from the first dose of IMP until follow-up contact at the time points specified in the Schedule of Assessments (Section 1.3).

Medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history.

All SAEs/AESIs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE/AESI data to the sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AEs, AESIs, or SAEs after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, or AESI, and he/she considers the event to be related to the IMP or trial participation, the investigator must promptly notify the sponsor.

8.3.2 Method of Detecting AEs and SAEs/AESIs

The method of recording, evaluating, and assessing causality of AEs and SAEs/AESIs and the procedures for completing and transmitting SAE/AESI reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs/AESIs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs/AESIs

After the initial AE/SAE/AESI report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs/AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs/AESIs

Prompt notification by the investigator to the sponsor regarding an SAE/AESI is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local health authority and other health authorities about the safety of an IMP under clinical investigation. The sponsor

will comply with country-specific regulatory requirements relating to safety reporting to the health authority, IRBs/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE/AESI or other specific safety information (eg, summary or listing of SAEs/AESIs) from the sponsor will review, acknowledge, and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants or in female partners of male participants will be collected after the start of IMP and until final contact.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.2.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Treatment of Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a trial participant, at a dose above that which is assigned to that individual participant according to the protocol.

There is no specific antidote for overdose with emraclidine. In the event of an overdose, treatment should consist of general supportive measures.

The investigator should complete the following for any emraclidine overdose:

1. Contact the medical monitor immediately

2. Closely monitor the participant for any AE/SAE and clinically significant vital signs, ECG, or laboratory abnormalities. Additional safety procedures may need to be performed at the investigator's discretion.

3. Document the quantity of the excess dose as well as the duration of the overdose (if multiple time points) in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.3.7 Adverse Events of Special Interest

All AESIs should be reported according to the procedures and timelines for SAEs (see Section 10.3.4).

The following events will be reported as AESIs:

- AEs that result in the discontinuation of IMP including those resulting from elevations in liver test results (see Section 10.6)
- Heart rate >120 bpm
    - Confirm heart rate by ECG
    - Repeat heart rate measurement 30 and 60 minutes after participant is at rest
    - Report as an AESI and notify the medical monitor if heart rate remains >120 bpm 60 minutes after initial elevation OR if it is not sinus tachycardia
    - Continue to follow the participant as clinically appropriate
- QTcF is >500 ms or the QTc value represents a >60 ms increase from Baseline
    - Repeat ECG
    - Report as an AESI and notify the medical monitor
    - Repeat ECGs every 30 minutes until QTcF <450 ms or improves to <30 ms from baseline value
    - Continue to follow the participant as clinically appropriate if QTcF does not improve
- Systolic blood pressure reading (average of triplicates) ≥160 mmHg but <200 mmHg and/or diastolic blood pressure reading ≥100 mmHg but <120 mmHg
    - Repeat blood pressure measurements after 5 minutes of participant at rest in a quiet room. If blood pressure (average of triplicates) reading continues to be ≥160 mmHg systolic and/or ≥100 mmHg diastolic, additional blood pressure measurements should be performed after 30 minutes and 60 minutes from the initial elevation
    - If blood pressure elevation continues to be ≥160 mmHg systolic and/or ≥100 mmHg diastolic 60 minutes after initial elevation, report as an AESI and notify the medical monitor
    - Withhold IMP

- Consider referring participant to a health care facility for further evaluation and treatment as appropriate
- Resume IMP only upon consultation with the medical monitor

- Systolic blood pressure ≥200 mmHg and/or diastolic blood pressure ≥120 mmHg
  - Repeat blood pressure measurements after 5 minutes of participant at rest in a quiet room. If blood pressure (average of triplicates) reading continues to be ≥200 mmHg systolic and/or ≥120 mmHg diastolic, additional blood pressure measurement should be performed after 30 minutes from the initial elevation
  - If blood pressure continues to be ≥200 mmHg systolic and/or ≥120 mmHg diastolic after 30 minutes from initial elevation, report as an AESI and notify the medical monitor
  - If blood pressure does not improve, perform a physical examination and obtain the following tests: serum blood urea nitrogen, creatinine, serum cystatin-C, plasma renin activity, serum catecholamines (metanephrines, normetanephrines), serum aldosterone, endothelin level; urinalysis; and an ECG
  - Refer participant to a health care facility for further evaluation, monitoring, and treatment.
  - Withhold IMP
  - IMP may be resumed only after discussing with the medical monitor

8.4 Pharmacokinetics

Venous blood samples will be collected in appropriately labeled tubes, at the times specified in the Schedule of Assessments (Section 1.3), to evaluate the PK of emraclidine and its metabolite CV-0000354. Additional details about sample collection, processing, and shipment will be provided in the Lab Manual.

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

A fully validated bioanalytical method will be used to quantitate the concentrations of emraclidine and CV-0000364 (metabolite) in plasma. Plasma samples collected in this trial may be used to further development of the bioanalytical method or identification of metabolites. The backup plasma samples may be stored for a duration of approximately up to 1 year after the date of the final clinical study report.

Plasma concentration data from this trial combined with other data may also be used to build and/or update a population PK model for emraclidine for the purpose of further characterizing the PK or PK/pharmacodynamic behavior of the compound. Any population PK assessment will be described in a separate report.

Statistical analyses for PK parameters are summarized in Section 9.3.6.

8.5 Biomarkers

Biomarkers are not evaluated in this trial.

8.6 Future Biospecimen Research

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of participants who respond well and those who respond poorly to treatment may help to better define the most appropriate group of participants in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them at Cerevel makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, pharmacodynamics, tolerability, or safety not anticipated prior to the beginning of this trial.

Future biospecimen research samples will be collected from participants who provide additional consent specifically for this sample collection. Research performed on these samples may include genetic analyses, gene expression profiling, proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial). The objective of collecting these specimens is to explore and identify biomarkers that inform the scientific understanding of diseases or their therapeutic treatments.

Additional details about future biospecimen research samples are provided in Section 10.5.

8.7 Health Economics and Resource Utilization

8.7.1 Short Form – 6 Dimensions 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).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

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

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

Abbreviations: PANSS=Positive and Negative Syndrome Scale; QD=once daily.

9.2 Analysis Sets

The analysis sets that are defined for this trial are described in Table 6.

Table 6 Analysis Set Descriptions

Population	Description	Analysis
ITT	All randomized participants	Demographic and Baseline Characteristics
FAS	All randomized participants who receive at least 1 dose of IMP. This will be the safety analysis set.	Safety analysis
mITT	All randomized participants who receive at least 1 dose of IMP and have both a baseline and at least 1 postbaseline PANSS assessment	Primary analysis set for efficacy
Endpoint completers	All participants in the mITT population who complete the PANSS assessment at Week 6	Sensitivity analysis for efficacy
PK Analysis Set	All randomized participants who receive at least 1 dose of IMP and have at least 1 measurable emraclidine concentration	PK analysis

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

9.3 Statistical Analyses

9.3.1 General Considerations

Descriptive statistical methods will be used to summarize the data from this trial, with statistical testing performed for the efficacy endpoints. All statistical analyses will be conducted with the SAS® System, version 9.4 or higher. The remainder of this section is a summary of the planned statistical analyses of the primary and secondary endpoints as well as a description of planned safety analyses. Full details of these analyses will be included in the statistical analysis plan.

9.3.2 Primary Endpoint/Estimand Analyses

The primary estimand has the following attributes:

1. Treatments as randomized

2. mITT population as the primary population of interest

3. Change from Baseline to Week 6 in total PANSS score as the primary endpoint of interest

4. The population level summary of interest is the treatment differences estimated based on the least square mean and the corresponding 95% confidence interval from the MMRM model with treatment, visit, and treatment by visit interaction as fixed effect, participant as a random effect, and baseline PANSS score as a covariate. An unstructured covariance structure will be used for the repeated measures. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. 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. If a reduced covariance matrix becomes necessary, the sandwich variance estimator will be used.

5. To address ICEs with the primary outcome data available, a treatment policy strategy will be used to include all collected outcomes in the primary statistical analysis, consistent with the intent-to-treat principle. The only exception will be the cases of concomitant use of protocol prohibited other antipsychotic and, in such cases, the data collected under the influence of confounding ICEs will be treated as missing.

6. To address ICE of trial or treatment discontinuation with no outcome data collected post discontinuation, the primary analysis of MMRM described above will be followed by PMM approach with varying level of shift parameters for missing values due to discontinuations that are potentially missing not at random (MNAR), including discontinuation due to lack of efficacy or due to adverse events. This will be implemented using delta adjustment imputation method. Further details will be described in the SAP.

The statistical hypothesis testing on the primary endpoint (H_1 and H_2 above) will be based on the estimated treatment difference from the model at Week 6. The evaluation of other time points will also be derived from the same model.

The number and proportion of responders (ie, participants with 30% reduction from Baseline in the PANSS total score at Week 6 or the last assessment before discontinuation) will be summarized. A logistic regression model, with baseline PANSS as a covariate, will be used to compare the proportion of responders in each active arm with placebo. If expected counts are <5, then a Fisher's Exact test will be used.

9.3.3 Secondary Endpoint/Estimand Analyses

The secondary estimand has the following attributes:

1. Treatments as randomized
2. mITT population as the population of interest
3. Change from Baseline to Week 6 in CGI-S score as the endpoint of interest
4. The population level summary of interest is the treatment differences estimated based on the least square mean and the corresponding 95% confidence interval from the MMRM model with treatment, visit, and treatment by visit interaction as 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. When a reduced covariance matrix is used, the sandwich variance estimator will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.
5. ICEs will be addressed using the same strategies as described above for the primary endpoint

The number and proportion of participants with ≥1 and ≥2 point improvements from Baseline at the last CGI-S assessment (at Week 6 or the last assessment before discontinuation) will be summarized. A logistic regression model, with baseline CGI-S as a covariate, will be used to compare the proportion of responders in each active arm with placebo. If expected counts are < 5, then a Fisher's Exact test will be used.

9.3.4 Other Endpoints

Other endpoints, including change from Baseline in BACS and SF-6D measurements, will be analyzed similarly using MMRM models.

9.3.5 Safety Analyses

Treatment-emergent adverse events will be coded according to MedDRA and summarized by treatment group, system organ class, and preferred term. Further summaries will be done by seriousness, severity, and relationship to IMP.

Heart rate and blood pressure measurements will be taken weekly at approximately 2 hours after IMP administration. The weekly measurements and corresponding changes from Baseline will be summarized by descriptive statistics. The change from Baseline will be analyzed using MMRM with treatment group, visit, and treatment by visit interaction as fixed effects and participant as a random effect, with the baseline value as a covariate. The difference between each emraclidine group versus placebo at each week will be estimated based on the least squares mean from the MMRM with the 95% CIs.

Other safety endpoints will be summarized with descriptive statistics by treatment group, including clinical laboratory assessments and metabolic parameters, and physical and neurological examination results (including body weight), suicidality assessments using C-SSRS, and EPS assessed by AIMS, SAS, and BARS.

9.3.6 Other Analyses

Plasma concentrations of emraclidine and its major metabolite (if required) will be summarized by dose, visit, and nominal time (if applicable). All PK exposure-response analyses will be described in a separate PK analysis plan that will be finalized before database lock.

Plasma concentrations will also be pooled with data from other trials in a population PK analysis to describe the time course of plasma concentrations of emraclidine and the influence of covariates (eg, body weight, age, sex, race, concomitant medications). The results of population PK analysis and response-exposure analyses will be presented separately from the main clinical study report.

9.4 Interim Analyses

No interim analysis is planned.

9.5 Sample Size Determination

A sample size of approximately 93 participants in each treatment group completing the Week 6 assessments (approximately 279 in total) should provide at least 90% power to detect an effect size of 0.48 in change from Baseline in PANSS total score at Week 6 between either active treatment group versus placebo at the α=0.05 level. The effect size of 0.48 represents a clinically meaningful effect on symptom reduction based on large scale meta-analysis of historical data from several currently approved antipsychotic medications in common usage (Leucht et al, 2013). It could be translated into a difference of 7 points versus placebo if the standard deviation of change from baseline is 14.6 points or a difference of 8 points versus placebo if the standard deviation of change from

baseline is 16.7 points. Both scenarios of the standard deviation are consistent with historical observations. To account for a discontinuation rate of approximately 25% for a 6-week treatment period (as observed in Trial CVL-231-SCH-001), it is planned to randomize approximately 372 participants.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU Regulation 536/2014 for clinical trials (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the participant and answer all questions regarding the trial.

Participants must be informed that their participation is voluntary. Participants will be required to agree to (eg, provide electronic agreement or written signature) a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or trial center.

The medical record must include a statement that informed consent was obtained before the participant was enrolled in the trial and the date the consent was obtained. The authorized person obtaining the informed consent must also agree to (eg, provide electronic agreement or written signature) the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the participant.

As described in Section 10.5, additional consent will be required for participants from whom future biospecimen research samples will be collected.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the sponsor or designee. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from health authorities.

10.1.5 Dissemination of Clinical Trial Data

Cerevel fulfills its commitment to publicly disclose clinical trial results through posting trial results on ClinicalTrials.gov, the European Clinical Trials Database, and other public registries in accordance with applicable local laws/regulations.

In all cases, trial results are reported by Cerevel in an objective, accurate, balanced, and complete manner and are reported regardless of trial outcome or the country in which the trial was conducted.

Clinical trial US Basic Results are posted on Clinicaltrials.gov for all Cerevel-sponsored interventional trials conducted in participants that evaluate the safety and/or efficacy of a Cerevel product, regardless of the geographical location in which the trial is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.4 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

Cerevel posts EU Basic Results on EudraCT for all Cerevel-sponsored interventional trials that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.4 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

10.1.6 Data Quality Assurance

All participant data relating to the trial will be recorded on the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of the eCRF will be provided in the CRF Completion Guidelines.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and health authority inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Clinical Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for the longest of the following periods:

- At least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date health authorities were notified of discontinuation)
- At least 3 years after the sponsor notified the investigator that the final report has been filed with health authorities
- A longer period if required by local regulations or institutional policies

No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8 Trial and Site Closure

The sponsor or designee reserves the right to close a trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for early closure of a trial site by the sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Total number of participants included earlier than expected

The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC.

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs/IECs, health authorities in accordance with regulatory requirements.

10.1.9 Publication Policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Clinical Laboratory Tests

Protocol-required tests detailed in Table 7 will be performed by a central laboratory, with the exception of those specified to be done locally in the Operations Manual.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Serology (screening for human immunodeficiency virus, hepatitis B virus, hepatitis C virus) will be done at Screening.

Serum/urine pregnancy tests are required for all women of childbearing potential at the time points indicated in the Schedule of Assessments; however, pregnancy tests can be done anytime during the trial at the investigator's discretion.

Participants must have SARS-CoV-2 testing done with a negative test result prior to admission to the inpatient facility, refer to site procedures for additional details on

testing. Additional SARS-CoV-2 testing may be performed after admission per the investigator's discretion.

Table 7 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters	
Hematology	Platelet count RBC count Hemoglobin Hematocrit Prothrombin time and INR MCH MCHC MCV	WBC count with differential (absolute and %): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Chemistry	BUN Creatinine Glucose Albumin Cholesterol (total, HDL, LDL) Triglycerides Uric acid Potassium Sodium Calcium Bicarbonate Chloride Magnesium Phosphorus	ALT AST Alkaline phosphatase GGT CPK Total bilirubin and direct bilirubin Total protein Glycosylated hemoglobin
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick	
Additional Required Protocol-specific Tests	Serum/urine pregnancy test (as needed in women of childbearing potential) CPK reflex for isoenzymes if CPK >3 × ULN; serum and urine myoglobin collected if CPK >5 × ULN Prolactin	
Other Screening Tests	A confirmatory FSH is required for post-menopausal women Breathalyzer test for alcohol and urine drug screen Serology (HIV, HBsAg, HBcAb, hepatitis C antibody) SARS-CoV-2 testing (Additional testing may be done at investigator discretion) Thyroid-stimulating hormone with reflex to free T4 if abnormal	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CPK=creatine phosphokinase; FSH=follicle-stimulating hormone; GGT=gamma glutamyl transferase; HBcAb=hepatitis B core antibody; HBsAg= hepatitis B surface antigen; HDL=high-density lipoprotein; HIV=human immunodeficiency virus; INR=international normalized ratio; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; T4=thyroxine; WBC=white blood cell; ULN=upper limit of normal.

Investigators must document their review of each laboratory safety report and file appropriately.

10.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

Table 8 Definition of AE

AE Definition
• An AE is 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.

Table 9 Events Meeting the AE Definition

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after trial intervention administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical manifestations of a suspected drug-drug interaction. • Signs, symptoms, or the clinical manifestations of a suspected overdose of either trial intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE/AESI. Such instances will be captured in the efficacy assessments.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

Table 10 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose in the view of either the investigator or sponsor, results in any of the following outcomes:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias.

10.3.3 Recording and Follow-Up of AEs and/or SAEs/AESIs

Table 11 Recording of AEs and/or SAEs/AESIs

Recording

• When an AE/SAE/AESI occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.
• The investigator will then record all relevant AE/SAE/AESI information in the eCRF.
  ○ Nonserious AEs must be recorded on the AE eCRF with the current status noted. All nonserious events (that are not considered AESIs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eCRF. For any AE, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).
  ○ If updated information (eg, resolved status) on SAE/AESI status becomes available after a participant's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor according to the appropriate reporting procedures.
  ○ The investigator will follow SAEs/AESIs until the events are resolved, stabilized, or the participant is lost to follow-up or has died. Resolution means that the participant has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the participant's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the participant is lost to follow-up, or has died.
  ○ Any new SAEs/AESIs reported to the investigator that occur after the last scheduled contact and are determined by the investigator to be related to the use of the IMP, should be reported to the sponsor. This may include SAEs/AESIs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs/AESIs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the participant is lost to follow-up or has died.
• It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE/AESI eCRF page.
• There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

Table 12 Assessment of Severity and Causality of AEs and/or SAEs/AESIs

Severity

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the NCI-CTCAE, version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)

Adverse events not listed by the NCI-CTCAE will be graded according to the criteria defined below.

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the participant.

Note: Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If the investigator determines an increase in blood pressure to be clinically significant and therefore reported as an AE, the CTCAE toxicity grades defined below should be followed.

Grade	Description
1	Systolic blood pressure 120-139 mmHg or diastolic blood pressure 80-89 mmHg
2	Systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99 mmHg
3	Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg
4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
5	Death

Causality
• The investigator is obligated to assess the relationship between trial intervention and each occurrence of each AE/SAE/AESI. • The investigator will assess the relationship as either of the following: ○ **Related**: An AE will be considered "related" to the use of the IMP if there is evidence to suggest a reasonable possibility of a causal relationship between the IMP and the AE. ○ **Not Related**: An AE will be considered "not related" to the use of the IMP if there is no plausible causal relationship between the IMP and the AE. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE/AESI, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AESI and has provided an assessment of causality. • There may be situations in which an SAE/AESI has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE/AESI data to the sponsor or designee.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Table 13 Follow-Up of AEs and SAEs/AESIs

Follow-Up
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE/AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE/AESI data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs/AESIs

Table 14 SAE/AESI Reporting to the Sponsor or Designee via an Electronic Data Collection Tool

Reporting to the Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE/AESI to the sponsor or designee will be the electronic data collection tool. • The site will enter the SAE/AESI data as soon as it becomes available within 24 hours of awareness. • If the electronic data collection tool is unavailable, then the site will use the paper form (see Table 15). • After the trial is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE/AESI from a trial participant or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken offline, then the site can report this information on the paper form (see Table 15) or to the sponsor or designee by telephone.

Table 15 SAE/AESI Reporting to the Sponsor or Designee via Paper Form (if needed)

Reporting to the Sponsor or Designee via Paper Form
• If the electronic data collection tool is unavailable, then the site will use the paper form. The paper form should be used to electronically transmit this information to the sponsor or designee. • Contacts for electronic transmission of the paper form are provided in the Operations Manual. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the appropriate form within the designated reporting time frames.

10.4 Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

10.4.1.1 Highly Effective Form of Contraception (Failure Rate <1%)

A highly effective form of contraception (failure rate of <1%) is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

10.4.1.2 Women of Childbearing Potential, Women of Nonchildbearing Potential, and Fertile Men

A woman is considered to be a woman of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile.

A woman is considered to be of nonchildbearing potential if she fulfills either of the following criteria:

- Underwent permanent sterilization including hysterectomy, bilateral oophorectomy, or bilateral salpingectomy

- Is in a postmenopausal state, which is defined as no menses for 12 consecutive months without an alternative medical cause, and confirmed with an FSH level >40 IU/mL.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

10.4.2 Collection of Pregnancy Information

10.4.2.1 Male Participants With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this trial. This applies only to male participants who receive trial intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 12 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.2.2 Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this trial. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 12 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek

this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the trial will discontinue trial intervention and be withdrawn from the trial.

10.5 Future Biospecimen Research

Use/Analysis of DNA

- Genetic variation may impact a participant's response to IMP, susceptibility to, and severity and progression of disease. Variable response to IMP may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

- DNA samples will be used for research related to emraclidine or schizophrenia and related diseases. They may also be used to develop tests/assays including diagnostic tests related to emraclidine and/or interventions of this drug class and schizophrenia. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- The samples may be analyzed as part of a multitrial assessment of genetic factors involved in the response to emraclidine or interventions of this class to understand trial disease or related conditions.

- The results of genetic analyses may be reported in the CSR or in a separate trial summary.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained while research on emraclidine or trial treatments of this class or schizophrenia continues but no longer than 15 years or other period as per local requirements.

10.6 Liver Safety: Suggested Actions and Follow-up Assessments

10.6.1 Assessment of Elevations in Liver Test Results

Elevations in liver test results occurring during a clinical trial may result from DILI. However, since DILI is a diagnosis of exclusion, it is essential to exclude other etiologies (see Section 10.6.4) that may lead to elevated results in liver tests.

When amionotransferase (ALT or AST) levels increase to ≥3 × ULN during a clinical trial, current US guidance (US FDA, 2009) recommends close observation and diagnostic workup for causes of hepatic injury (see Section 10.6.4) other than the IMP. The International Consensus Criteria for idiosyncratic DILI only uses ALT to define DILI when referring to aminotransferase levels (Watkins, 2019). The CIOMS Working Group on DILI suggests using serum ALT as it is more specific than AST to detect and monitor the liver injury, irrespective of the cause (EASL, 2019; CIOMS, 2020; Kwo et al, 2017).

The medical monitor must be consulted when ALT levels increase to ≥3 × ULN.

Table 16 describes liver test monitoring during the close observation period of elevated liver tests during a clinical trial. Close observation is required until the elevations in liver test results return to baseline levels or normalize.

Table 16 Monitoring of Liver Tests

Result	**Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]) and INR Tests**
If either of the following: • ALT ≥3 × ULN and total bilirubin ≥2 × ULN or INR >1.5 • ALT ≥3 × ULN with symptoms and signs of hepatitis	Every 24 hours until laboratory abnormalities improve
If ALT ≥3 × ULN and total bilirubin or INR are within the normal range	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND participants' symptoms improve or participants are asymptomatic	Frequency may decrease to once weekly

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; ULN=upper limit of normal.

10.6.2 Criteria for Permanent Discontinuation of IMP (Potential Hy's Law Cases)

The following criteria may suggest the presence of severe liver injury regardless of the etiology; "Hy's law" points to advanced and potentially severe DILI when other possible causes of liver injury have been excluded. When all of the following criteria are met, the IMP should be permanently discontinued and not restarted under any condition and the event should be reported as an SAE.

1. ALT increases to ≥3 × ULN
2. Total bilirubin increases to ≥2 × ULN or INR >1.5
3. Alkaline phosphatase value <2 × ULN (ie, absence of significant cholestasis)
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes are included in Table 18.

10.6.3 Criteria for Temporary Withholding or Permanent Discontinuation of IMP

Participants who develop abnormal results in liver tests (AST, ALT, alkaline phosphatase, total bilirubin) during the trial treatment period may meet the criteria for discontinuation of IMP treatment specified in the FDA guidance (Table 17).

Table 17 Criteria for Temporarily Withholding IMP in Association With Abnormalities in Liver Test Results

Baseline ALT Value	ALT Elevation
<3 × ULN	• >8 × ULN • >5 × ULN for more than 2 weeks • ≥3 × ULN and (total bilirubin ≥2 × ULN or INR >1.5) • ≥3 × ULN with the presence of signs and symptoms consistent with acute hepatitis and/or eosinophilia (≥500 eosinophils/µL)

Abbreviations: ALT=alanine aminotransferase; IMP=investigational medicinal product; INR=international normalized ratio; ULN=upper limit of normal.

IMP should be withheld pending an investigation (Table 19) of alternative causes of abnormalities in liver test results (Table 18). Clinical and laboratory follow-up should continue during the withholding period until the abnormalities in liver test results return to baseline values.

Resumption of IMP can only occur with the express consent of the sponsor and/or their medical designee and only if another cause for the liver test abnormalities is identified and liver tests return to within the normal range.

10.6.4 Evaluation of Alternative Causes of Liver Test Result Abnormalities

Table 18 Alternative Causes of Abnormalities in Liver Test Results

Biliary obstruction, focal liver lesions (benign or malignant), vascular liver disease (such as portal vein thrombosis or Budd-Chiari syndrome)
Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
Autoimmune hepatitis
Exposure to hepatotoxic agents/drugs or hepatotoxins (other than IMP), including herbal and dietary supplements, plants, and mushrooms
Alcoholic hepatitis
Nonalcoholic steatohepatitis and hepatic steatosis
Congestive heart failure, hypotension, ischemic hepatitis
Others: sepsis, sinusoidal obstruction syndrome, primary biliary cholangitis, primary sclerosing cholangitis, Wilson disease, hemochromatosis, alpha-1-antitrypsin deficiency

Abbreviations: IMP=investigational medicinal product.

Table 19 Investigation of Alternative Etiologies for Elevated Liver Test Results

Initial set of tests[a]	
Complementary Tests and Parameters	**Etiologies**
Complete blood count with differential (eg, eosinophilia)	Infection (sepsis), immune-related DILI (eosinophilia), high MCV (alcoholic hepatitis)
ALT, AST, GGT, serum PEth	Alcoholic hepatitis (AST:ALT ratio ≥2)
ALP and GGT	Biliary obstruction
CPK, haptoglobin, LDH, and peripheral blood smear	Rhabdomyolysis and hemolysis
HAV IgM	Hepatitis A
HBsAg, anti-HBc IgM, total anti-HBc, anti-HBs, HBV-DNA (by PCR)	Hepatitis B (acute, reactivation of chronic or occult hepatitis B)
anti-HCV, HCV-RNA (by PCR)	Acute hepatitis C
HEV IgM and IgG	Acute hepatitis E
Liver imaging (ultrasound, CT, or MRI)	Biliary obstruction, focal lesions, vascular liver disease, hepatic steatosis
Serum total Ig G, ANA, anti-smooth muscle antibody	Autoimmune hepatitis
Serum acetaminophen (paracetamol) concentration	Acetaminophen (paracetamol) overdose

Obtain a more detailed history as follows: • Prior and concurrent diseases or illness • Exposure to environmental and/or industrial chemical agents • Presence of symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever • Prior and concurrent alcohol use, recreational drug use, and special diets • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms	
Additional set of tests[b]	
Complementary Tests and Parameters	**Etiologies**
Echocardiogram	Congestive heart failure
CMV IgM (CMV-DNA)	Acute CMV infection
EBV IgM (EBV-DNA)	Acute EBV infection
HSV IgM (HSV-DNA)	Acute HSV infection
Anti-mitochondrial autoantibodies	PBC
24 hours urine copper and serum ceruloplasmin	Wilson disease
Iron studies (serum iron and ferritin) and transferrin saturation	Hemochromatosis
Serum alpha-1 antitrypsin	Alpha-1-antitrypsin deficiency
MRI, ERCP, ANA, perinuclear anti-neutrophil cytoplasmic	PSC
Hepatology consult may be requested (a liver biopsy may be considered in consultation with a hepatologist). The medical monitor should be contacted for questions regarding adequate follow-up tests.	

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANA=anti-nuclear antibody; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; anti-HCV=hepatitis C virus antibody; AST=aspartate aminotransferase; CMV=cytomegalovirus; CPK=creatinine phosphokinase; CT=computed tomography; DILI= drug-induced liver injury; DNA=deoxyribonucleic acid; EBV=Epstein-Barr virus; ERCP=endoscopic retrograde cholangiopancreatography; GGT=gamma glutamyltransferase; HAV=hepatitis A virus; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; HSV=herpes simplex virus; Ig=immunoglobulin; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; MRI=magnetic resonance imaging; PBC=primary biliary cholangitis; PCR=polymerase chain reaction; PEth=phosphatidylethanol; PSC=primary sclerosing cholangitis; RNA=ribonucleic acid.

a. To be done for all participants.
b. To be done when clinically indicated.

10.7 Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A (not exhaustive)

Note that this is not a complete list and that the investigator is responsible for ensuring that participants are not receiving any strong or moderate inducers or inhibitors of cytochrome P450 3A during the trial.

CYP 3A Inhibitors/
CYP 3A Inducers

Antivirals	**Antivirals**
Nirmatrelvir/ritonavir[a]	Efavirenz
Indinavir	Nevirapine
Nelfinavir	Etravirine
Ritonavir	Tipranivir
Saquinavir	**Miscellaneous**
Boceprevir	Barbiturates
Lopinavir/ritonavir	Carbamazepine
Amprenavir	Cenobamate
Atazanavir	Eslicarbazepine
Telaprevir	Glucocorticoids (systemic)
Darunavir/ritonavir	Modafinil
Fosamprenavir	Oxcarbazepine
Antibiotics	Phenobarbital
Clarithromycin	Phenytoin
Erythromycin	Rifabutin
Telithromycin	Rifampin
Ciprofloxacin	St. John's wort
Anti-infectives	Bosentan
Itraconazole	
Ketoconazole	
Fluconazole	
Posaconazole	
Voriconazole	
Anti-anginal/hypertensive therapy	
Diltiazem	
Verapamil	
Anti-cancer therapy	
Crizotinib	
Imatinib	
Miscellaneous	
Nefazodone	
Aprepitant	
Grapefruit juice[b]	
Conivaptan	

a. Paxlovid (nirmatrelvir co-packed with ritonavir) is prohibited.
b. A 7-day washout prior to dosing is required if grapefruit juice was being consumed continually.

10.8 Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AIMS	Abnormal Involuntary Movement Scale
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BACS	Brief Assessment of Cognition in Schizophrenia
BARS	Barnes Akathisia Rating Scale
BID	twice daily
bpm	beats per minute
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression-Severity of Symptoms
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum (peak) plasma concentration
COVID-19	coronavirus disease-2019
CRF	case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DILI	drug-induced liver injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
EPS	extrapyramidal symptoms
ET	early termination
EU	European Union
GCP	Good Clinical Practice
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INN	International Nonproprietary Name

Abbreviation	Definition
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
mAChR	muscarinic acetylcholine receptor
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
MNAR	missing not at random
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PANSS	Positive and Negative Syndrome Scale
PK	pharmacokinetic(s)
PMM	pattern mixture model
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SAS	Simpson Angus Scale
SF-6D	Short Form-6 Dimensions
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time of maximum plasma concentration
ULN	upper limit of normal
US	United States

10.9 Protocol Amendment History

The Document History table, which lists all versions of the protocol, and the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Document History	
Protocol Version	**Date**
3.0	15 Mar 2023
2.0	23 Feb 2022
1.0	07 Dec 2021

Amendment: Protocol Version 2.0 (23 Feb 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the amendment is to address feedback from US FDA.

Section # and Name[a]	**Description of Change**	**Brief Rationale**
Overall	Replaced CVL-231 with emraclidine	Updated drug name to newly approved official INN for CVL-231, emraclidine
Title Page	Added EudraCT number	Required for trials conducted in European Union
Signature Page	Updated sponsor signatory	Change in internal responsibilities
1.1 Synopsis 1.2 Schema 4.1 Overall Design 5 Trial Population 5.1 Inclusion Criteria	Increased upper limit of age range from 55 to 65 years	Ensure representation of full age spectrum of adult patients with schizophrenia
1.1 Synopsis 4.1.2 Treatment Period 6.3.1 Participant Assignment to Treatment	Added information regarding stratification by geographic region	Provide additional clarity
1.1 Synopsis 4.1.2 Treatment Period	Added flexibility to contact medical monitor if participant unable to return to facility on the same day as a day pass was given	Provide flexibility in trial procedures to allow for unforeseen circumstances

Section # and Name[a]	Description of Change	Brief Rationale
1.1 Synopsis 4.1.2 Treatment Period 1.3 Schedule of Assessments	Provided additional text to describe that some positive urine drug screen results may not require participant discontinuation after discussion and approval of medical monitor	Provide clarification and ensure consistency with exclusion criteria
1.1 Synopsis 9.3.2 Primary Endpoint/Estimand Analyses 9.3.3 Secondary Endpoint/Estimand Analyses	Provided additional details regarding MMRM model analyses for primary and secondary estimands	Provide additional clarity
1.1 Synopsis 9.3.2 Primary Endpoint/Estimand Analyses 9.3.3 Secondary Endpoint/Estimand Analyses	Provided additional details regarding sensitivity analyses for primary and secondary estimands	Provide additional clarity
1.3 Schedule of Assessments 10.2 Clinical Laboratory Tests	Revised testing procedures for SARS-CoV-2 to require negative test prior to admission and to adhere to site procedures	Add flexibility for different testing procedures across multiple sites and countries
1.3 Schedule of Assessments 5.2 Exclusion Criteria 8.2.3 Vital Sign Measurements	Updated to have triplicate rather than duplicate vital sign measurements with average of last 2 values used for assessment of eligibility	Consistency with American Heart Association requirements
1.3 Schedule of Assessments	Removed footnote regarding timing of respiratory rate and temperature assessments	Provide flexibility as timing of these assessments is not critical
1.3 Schedule of Assessments	Modified wording of footnote bb regarding future biospecimen research sample to indicate only collected from participants who are enrolled in trial	Avoid sampling from participants who are screen failures
2.2.2 Nonclinical Experience	Removed paragraph on nonclinical mechanistic information related to neurobehavioral components associated with neurodegenerative diseases	Not relevant to current trial
2.2.3 Clinical Experience	Minor wording modifications for clarity in describing changes in vital sign and ECG measurements	Additional clarification
2.3 Benefit/Risk Assessment	Minor wording modifications for clarification and removal of inappropriate information	Additional clarification/correction

Section # and Name[a]	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Modified Inclusion Criterion #9 regarding contraception requirements for men	Clarification to indicate all male participants must use a condom, practice contraception, and not donate sperm during trial and for 7 days following last dose of IMP
5.2 Exclusion Criteria	Changed "mental retardation" to "intellectual disability" in Exclusion Criterion #1	Consistency with DSM-5 nomenclature
5.2 Exclusion Criteria	Added "for schizophrenia" to Exclusion Criterion #2 bullet 2	Additional clarity
5.2 Exclusion Criteria 6.7.2 Prohibited Therapy	Added requirement for participants using antihypertensive medications to have been on stable dose for 3 months or more to Exclusion Criterion #7 and Table 4. Added restriction that participants cannot be receiving more than 2 medications to treat hypertension to Table 4 for consistency.	To ensure a population with minimal cardiovascular risk is enrolled in the trial
5.2 Exclusion Criteria	Increased the exclusionary heart rate value from 90 to 100 bpm in Exclusion Criterion #19	Increase generalizability of trial population to overall patient population
5.3.1 Meals and Dietary Restrictions	Added in restriction for grapefruit- or Seville orange-containing foods and beverages while in trial	Inadvertent omission in prior version of protocol; as specified in prohibited medications section, grapefruit- or Seville orange-containing food or beverages are prohibited
6.3.2 Blinding	Removed text indicating information regarding documentation of unblinding is in eCRF	Inaccurate as only limited information on unblinding in eCRF (time blind is broken and name of personnel involved only in medical record)
6.7.2 Prohibited Therapy 10.7 Medications Known to Prolong QT Interval and/or Cause Torsade de Pointes	Removed medications known to prolong QT interval from list of prohibited concomitant medications	Based on lack of evidence suggesting emraclidine increases the QT interval, there is no need to restrict medications that prolong the QT interval
10.4.1.1 Highly Effective Form of Contraception (Failure Rate <1%)	Removed extraneous information regarding abstinence	Consistency with CTFG guidance
10.4.1.2 Women of Childbearing Potential, Women of Nonchildbearing Potential, and Fertile Men	Modified descriptions of women of childbearing potential, women of nonchildbearing potential, and fertile men	Consistency with updated Cerevel standards and CTFG language

Section # and Name[a]	Description of Change	Brief Rationale
10.6.1 Assessment of Elevations in Liver Test Results	Added explanation and supporting references for the use of ALT (rather than ALT and AST) to detect and monitor liver injury	Although the FDA guidance refers to both ALT and AST level elevations as markers for hepatic injury, more recent information suggests ALT is more specific than AST.
10.7 Moderate to Strong Inducers and Inhibitors of Cytochrome P450 3A (not exhaustive)	Updated time period for washout of grapefruit juice to 7 days	Consistency with other sections of protocol
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors or provide further clarification

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTFG=Clinical Trials Facilitation Group; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG=electrocardiogram; eCRF=electronic case report form; IMP=investigational medicinal product; INN=International Nonproprietary Name; MMRM=mixed model for repeated measures.

a. Numbering (eg, section numbers and numbered lists) refers to current version of the protocol.

11 REFERENCES

Altamura AC, Buoli M, Mauri MC. Haloperidol versus second-generation antipsychotics in the long-term treatment of schizophrenia: a 4-year follow-up naturalistic study. J Clin Psychopharmacol. 2011;31(5):661-3.

Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-6.

Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. N Engl J Med. 2021;384(8):717-26.

Brazier JE, Mulhern BJ, Bjorner JB, et al. Developing a new version of the SF-6D Health State Classification System from the SF-36v2: SF-6Dv2. Med Care. 2020;58(6):557-65.

Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92.

Buoli M, Kahn RS, Serati M, Altamura AC, Cahn W. Haloperidol versus second-generation antipsychotics in the long-term treatment of schizophrenia. Hum Psychopharmacol. 2016;31(4):325-31.

Byun NE, Grannan M, Bubser M, et al. Antipsychotic drug-like effects of the selective M4 muscarinic acetylcholine receptor positive allosteric modulator VU0152100. Neuropsychopharmacology. 2014;39(7):1578-93.

Caplyta. Package insert. Intra-Cellular Therapies; 2019.

Correll CU, Davis RE, Weingart M, et al. Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial [published correction appears in JAMA Psychiatry. 2020;77(4):438]. JAMA Psychiatry. 2020;77(4):349-58.

Correll CU, Skuban A, Hobart M, et al. Efficacy of brexpiprazole in patients with acute schizophrenia: Review of three randomized, double-blind, placebo-controlled studies [published correction appears in Schizophr Res. 2017;190:191-4]. Schizophr Res. 2016;174(1-3):82-92.

Council for International Organizations of Medical Sciences (CIOMS). *Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting*. Geneva, Switzerland: A consensus by a CIOMS Working Group; 2020.

Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry. 2007;64(5):532-42.

European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol. 2019;70(6):1222-61.

Foster DJ, Wilson JM, Remke DH, et al. Antipsychotic-like effects of M4 positive allosteric modulators are mediated by CB2 receptor-dependent inhibition of dopamine release. Neuron. 2016;91(6):1244-52.

Guy W. ECDEU Assessment Manual for Psychopharmacology – Revised. Rockville, MD: US Department of Health, Education, and Welfare; 1976:534-7. DHEW Publication ADM 76-338.

Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. Schizophr Bull. 2009;35(3):549-62.

Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ. 2012;344:e977.

Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: results from an international, phase III clinical trial. J Clin Psychopharmacol. 2015;35(4):367-73.

Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. J Psychiatry Neurosci. 2000;25(2):161-6.

Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics?: A new hypothesis. Am J Psychiatry. 2001;158(3):360-9.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.

Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 2004;68(2-3):283-97.

Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112(1):18-35.

Latuda. Package insert. Sunovion Pharmaceuticals Inc; 2013.

Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis [published correction appears in Lancet. 2013;382(9896):940]. Lancet. 2013;382(9896):951-62.

Liechti S, Capodilupo G, Opler DJ, Opler M, Yang LH. A developmental history of the Positive and Negative Syndrome Scale (PANSS). Innov Clin Neurosci. 2017;14(11-12):12-7.

Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials [published correction appears in J Clin Psychiatry 1998;(4):200]. J Clin Psychiatry. 1997;58(12):538-46.

McEvoy JP, Daniel DG, Carson WH Jr, McQuade RD, Marcus RN. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. J Psychiatr Res. 2007;41(11):895-905.

Miron IC, Baroană VC, Popescu F, Ionică F. Pharmacological mechanisms underlying the association of antipsychotics with metabolic disorders. Curr Health Sci J. 2014;40(1):12-7.

Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Mol Psychiatry. 2008;13(1):27-35.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Rexulti. Package insert. Otsuka Pharmaceuticals Co; 2018.

Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006;14(3):191-210.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(suppl 20):22-57.

Sheehan DV, Lecrubier Y, Harnett-Sheehan K, et al. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur Psychiatry. 1997;12(5):232-41.

Shekhar A, Potter WZ, Lightfoot J, et al. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. Am J Psychiatry. 2008; 165(8):1033-9.

Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212(Suppl 44):S11-9.

Solmi M, Murru A, Pacchiarotti I, et al. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. Ther Clin Risk Manag. 2017;13:757-77.

US Food and Drug Administration (FDA). Guidance for Industry: E10 choice of control group and related issues in clinical trials; May 2001.

US Food and Drug Administration (FDA). Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation; Jul 2009.

Watkins PB. Idiosyncratic drug-induced liver injury in patients: Detection, severity assessment, and regulatory implications. Adv Pharmacol. 2019;85:165-93.

Woolley ML, Carter HJ, Gartlon JE, Watson JM, Dawson LA. Attenuation of amphetamine-induced activity by the non-selective muscarinic receptor agonist, xanomeline, is absent in muscarinic M4 receptor knockout mice and attenuated in muscarinic M1 receptor knockout mice. Eur J Pharmacol. 2009;603(1-3):147-9.