CLINICAL PROTOCOL

Title:	A 52-week, Phase 2, Open-label Trial to Evaluate the Long-term Safety and Tolerability of CVL-231 in Adult Participants With Schizophrenia
Trial Number:	CVL-231-2003
Trial Phase:	2
Compound:	Emraclidine
Sponsor Name:	Cerevel Therapeutics, LLC
Legal Registered Address:	222 Jacobs Street, Suite 200 Cambridge, MA 02141 US
Health Authority Identifier Numbers:	IND 144,666 EU CT 2024-511441-19-00

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

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

CONFIDENTIAL – PROPRIETARY INFORMATION

Version 4.0: 30 Apr 2024

Version 3.0: 15 Mar 2023

Version 2.0: 23 May 2022

Version 1.0: 21 Mar 2022

SPONSOR SIGNATORIES

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 30-Apr-2024 | 14:32 EDT
FC9601FCAD3E4131AA5E8835A4556460

30-Apr-2024 | 14:32 EDT

[redacted] PhD
[redacted] Cerevel Therapeutics, LLC

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 30-Apr-2024 | 16:51 EDT
6F76A3C70B6C47D5A2BA7984D5E96B35

30-Apr-2024 | 16:51 EDT

[redacted] PhD
[redacted] Cerevel Therapeutics, LLC

Date

PROTOCOL VERSION 4.0 SUMMARY OF CHANGES TABLE

Document History	
Protocol Version	**Date**
4.0	30 Apr 2024
3.0	15 Mar 2023
2.0	23 May 2022
1.0	21 Mar 2022

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

Amendment: Protocol Version 4.0 (30 Apr 2024)

This amendment is considered to be nonsubstantial based on the criteria set forth in annex IV of the European Union Regulation No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC 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 ensure compliance with European Union Clinical Trial Regulation (EU) No 536/2014.

Section # and Name[a]	Description of Change	Brief Rationale
Title Page	Updated Health Authority Identifier Number with EU CT number	Ensure compliance with EU No 536/2014
[redacted]		

Section # and Name[a]	Description of Change	Brief Rationale
6.1 Trial Interventions Administered	Added row to indicate emraclidine is not authorized for use in any indications in any region	Ensure compliance with EU No 536/2014
[redacted]		
8.3.4 Regulatory Reporting Requirements for SAEs/AESIs and Aggregate Safety Reports	Added information regarding reporting of SUSARs and submission of DSURs; updated section header	Ensure compliance with EU No 536/2014
10.1.3 Informed Consent Process	Provided additional details regarding process	Ensure compliance with EU No 536/2014
10.1.4 Data Protection	Provided additional details	Ensure compliance with EU No 536/2014
10.1.5 Dissemination of Clinical Trial Data	Modified to add that EU trial results will be posted on CTIS	Ensure compliance with EU No 536/2014
10.1.6 Data Quality Assurance	Added that data reporting had to comply with timelines dictated by Article 58 of EU Regulation 536/2014	Ensure compliance with EU No 536/2014
10.2 Clinical Laboratory Tests	Removed HBcAb as a screening serology laboratory test for de novo participants	Inadvertently missed removing during last amendment where this was modified in serology exclusion criterion
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors in original protocol

Abbreviations: AESI=adverse event of special interest; CTFG=Clinical Trial Facilitation Group; CTIS=Clinical Trials Information System; DSUR=Development Safety Update Report; HBcAb=hepatitis B core antibody; EU=European Union; SAE=serious adverse event; SUSAR=suspected unexpected serious adverse reaction.

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

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Short Title:

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

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 [redacted] Emraclidine is being developed for treatment of psychosis in schizophrenia.

The aim of this trial is to assess long-term safety and tolerability for participants who complete the Phase 2 efficacy trials (CVL-231-2001 and CVL-231-2002). In addition, de novo participants (ie, those who did not participate in either of the Phase 2 efficacy trials) may also be enrolled into this trial to better characterize long-term safety of emraclidine.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the long-term safety and tolerability of oral emraclidine in adult participants with schizophrenia	• Treatment-emergent adverse events • Clinically significant changes in vital sign measurements, body weight, physical and neurological examination results, ECG assessments, clinical laboratory assessments, and metabolic parameters • 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
[redacted]	

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; SAS=Simpson Angus Scale[redacted]

Brief Summary (Lay Language):

The purpose of this trial is to measure the long-term safety and tolerability of emraclidine in participants with schizophrenia who have completed the Phase 2 double-blind trials (CVL-231-2001 and CVL-231-2002). In addition, de novo participants (ie, those who did not participate in either of the Phase 2 efficacy trials) may also be enrolled into this trial to better characterize long-term safety of emraclidine. Trial details include the following:

- Trial duration: up to approximately 56 weeks (rollover participants) or 58 weeks (de novo participants)
- Treatment duration: up to approximately 52 weeks
- Visit frequency: all eligible participants will visit the clinical site at regular intervals ([redacted] intervals for majority of trial with more frequent visits during early part of trial)

Overall Design:

This is a Phase 2, multicenter, open-label, 52-week trial to evaluate the safety and tolerability of emraclidine 30 mg once daily (QD) in adult participants with schizophrenia. The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible participants who, in the investigator's judgment, could potentially benefit from treatment with emraclidine for schizophrenia. There will be 2 groups of participants: 1) participants who completed treatment in one of the double-blind, placebo-controlled Phase 2 efficacy trials (CVL-231-2001 or CVL-231-2002), denoted as "rollover participants" and 2) participants with stable schizophrenia who were not enrolled in either one of the Phase 2 double-blind trials, denoted as "de novo participants."

The trial will include up to a 15-day Screening Period (de novo participants only), a 52-week Treatment Period, and a 28-day Follow-up Period. Each participant will participate in the trial for up to approximately 56 weeks (rollover participants) or 58 weeks (de novo participants).

Rollover participants will be screened for eligibility at the last visit of the double-blind trial (ie, Day 45 of Trials CVL-231-2001 and CVL-231-2002). Rollover participants will sign a new informed consent form (ICF) for participation in Trial CVL-231-2003 before any procedures specific to the open-label trial are performed. The final assessments from the double-blind trial ([redacted] for all other scales and safety assessments) will serve as the baseline measures for Trial CVL-231-2003 for any assessment that is not unique to the open-label trial. Medical history for Trial CVL-231-2003 would consist of the previous medical history collected during screening for the double-blind trial and any ongoing adverse events (AEs) from the double-blind trial.

For rollover participants, the first dose of IMP for the open-label trial (ie, [redacted]) will occur [redacted] following baseline assessments.

De novo participants will enter a Screening Period of up to 15 days (up to a maximum of 21 days allowed with approval of the medical monitor) to assess eligibility criteria and washout from prior antipsychotic medications and other prohibited medications. The Screening Period begins on the day of signing the ICF. Participants with a "lapse" in antipsychotic treatment (a lapse is defined as no oral antipsychotic medication for 3 or more days immediately prior to signing the ICF) may proceed directly to Baseline Visit [redacted] of the trial, provided all other eligibility criteria are met, including washout of all other prohibited medications.

[redacted]

Baseline assessments and the first dose of IMP occur on the [redacted] following completion of baseline assessments, participants will receive their first dose of IMP.

All participants will begin dosing with emraclidine 30 mg QD. [redacted]

All participants should continue dosing through Week 52.

All participants will have a follow-up safety contact 28±3 days after the last dose of IMP.

Number of Participants:

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

Key Entry Criteria:

- Rollover Participants: Men and women who have completed 6 weeks of post-randomization treatment in Trial CVL-231-2001 or CVL-231-2002 and who, in the opinion of the investigator, could potentially benefit from treatment with emraclidine for schizophrenia

- De Novo Participants: Men and women, ages 18 to 65 years, inclusive, at the time of signing the ICF with a primary diagnosis of schizophrenia per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as confirmed by the Mini International Neuropsychiatric Interview (MINI) for Psychotic Disorders version 7.0.2

Intervention Groups and Duration:

All participants (both rollover and de novo) in this trial will receive 30 mg QD emraclidine.[redacted]

[redacted]

The trial will include up to a 15-day Screening Period (de novo participants only), a 52-week open-label Treatment Period, and a 28-day Follow-up Period. Each participant will participate in the trial for up to approximately 56 weeks (rollover participants) or 58 weeks (de novo participants).

Statistical Considerations:

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

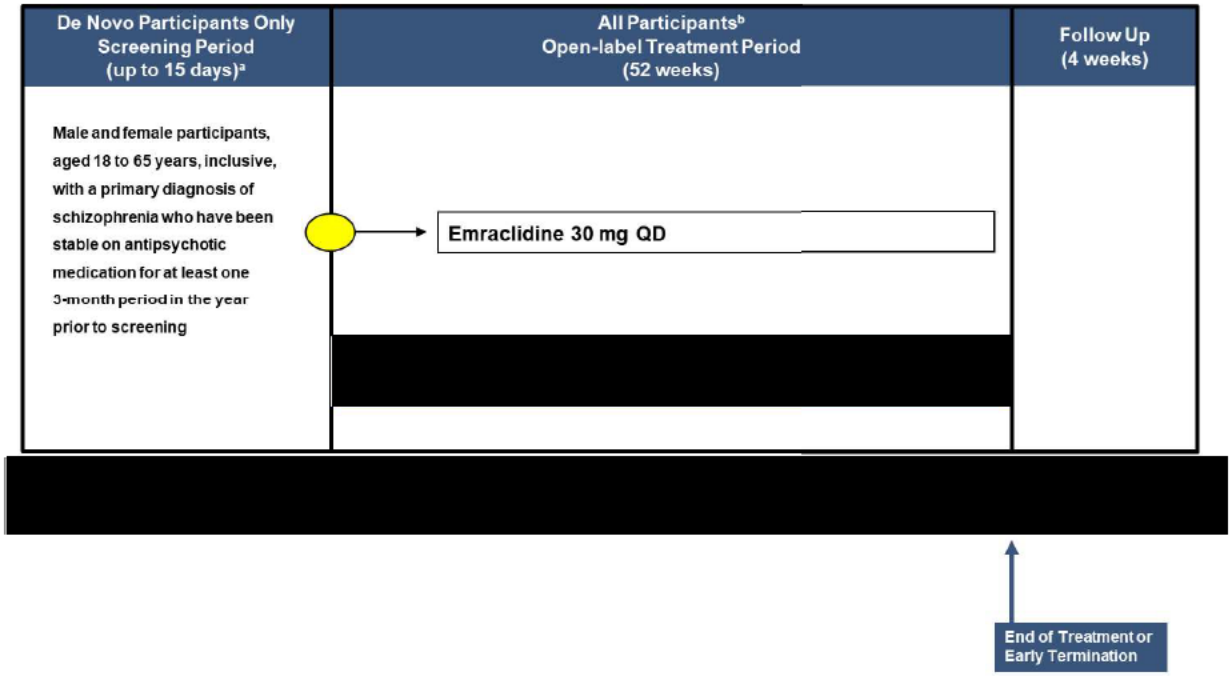
Descriptive statistical methods will be used to summarize the data from this trial. [redacted] Unless stated otherwise, the term "descriptive statistics" includes number of participants (n), mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. All available data for enrolled participants will be listed by participant. All statistical analyses will be conducted with the SAS® System, version 9.4 or higher.

Data Monitoring/Other Committee: No

1.2 Schema

A schematic of the trial design is provided in Figure 1.

Figure 1 Trial Schematic



Abbreviations: IMP=investigational medicinal product; QD=once daily; W=week.
Note: Assessment time points are planned for the last day of the indicated week ([redacted]) with a ±3-day window (see Schedule of Assessments in Table 3).

a. Separate Screening and Baseline Visits are required for de novo participants to allow for completion of eligibility assessments and washout of prohibited concomitant medications, if applicable. Extension of screening (up to a maximum of 21 days total) is allowed following discussion and documented approval by the medical monitor prior to the expiration of the Screening Period.
b. For rollover participants, screening for Trial CVL-231-2003 occurs simultaneously with baseline assessments at the Week 6 (Day 45) time point of Trial CVL-231-2001 or CVL-231-2002.
   - For rollover participants, the first dose of IMP for the open-label trial occurs [redacted] following baseline assessments
   - For de novo participants, the first dose of IMP for the open-label trial occurs on the same day as baseline assessments

1.3 Schedule of Assessments

Table 1 Schedule of Assessments – Screening and Baseline/[redacted] (De Novo Participants)

Trial Periods/Phases	Screening[a]	Baseline[redacted]
[redacted]		
Entrance and History		
Informed consent[b]	X	
Inclusion/exclusion criteria	X	X[c]
Medical and psychiatric history[d]	←----------	----------→
MINI	X	
Demography	X	
History of drug and alcohol use	X	
Review of birth control methods	X	X
Breathalyzer test for alcohol[e]	X	
Safety Assessments		
Physical/neurological examination[f]	X	X
Height (Screening only) and weight	X	X
ECG[g]	X	X
Heart rate and blood pressure (including orthostatic)[h]	X	X
Respiratory rate and temperature	X	X
C-SSRS[i]	X	X
EPS (SAS, AIMS, BARS)[j]	X	X
Prior/concomitant treatments[k]	←----------	----------→
Adverse event monitoring[l]		X
Laboratory		
Blood for safety laboratory sample	X	X
Urine for safety laboratory	X	X
Serum pregnancy test[m]	X	
Urine pregnancy test[m]		X
Urine drug screen[n]	X	X
Hepatitis B, C, HIV	X	
Blood sample for future biospecimen research[o]		X
[redacted]		

Trial Periods/Phases	Screening[a]	Baseline[redacted]
[redacted]		
Other		
Register visit in IVR	X	X
IMP dosing[p]		X
IMP dispensing		X

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EPS=extrapyramidal symptoms; HIV=human immunodeficiency virus; ICF=informed consent form; IMP=investigational medicinal product; IVR=interactive voice response; MINI=Mini International Neuropsychiatric Interview; [redacted] SAS=Simpson-Angus Scale; [redacted]

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

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

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

d. For de novo participants, medical occurrences that begin before the start of dosing with IMP but after obtaining informed consent should be collected as medical and/or psychiatric history.

e. An alcohol test (breathalyzer) is required at Screening for de novo participants. An alcohol test (breathalyzer) can be conducted at any time during the trial for any participant at the discretion of the investigator.

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

g. 12-lead ECG assessments will be performed after the participant has been at rest for approximately 3 minutes. At Screening, the average of 3 consecutive ECGs collected 1 to 2 minutes apart will be used to determine participant eligibility; at Baseline, only 1 reading is required for determination of eligibility. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).

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

i. For de novo participants, the "Baseline/Screening" C-SSRS form will be completed at Screening to determine eligibility and the "Since Last Visit" C-SSRS form will be completed at Baseline to ensure that the participant continues to qualify for the trial.

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

k. Prior and concomitant medications should be recorded from Screening through the participant's last visit/contact.

l. Adverse events (serious and nonserious) should be recorded from the first dose of IMP.

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

n. A urine drug screen is required at Screening (full panel including opioids) and Baseline (dipstick); see the exclusion criteria for exclusions based on the urine drug screen. The urine drug screen can be conducted at any time during the trial at the discretion of the investigator.

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

p. De novo participants will receive their first dose of IMP following completion of baseline assessments.

Table 2 Schedule of Assessments – Screening/Baseline and [redacted] (Rollover Participants)

Trial Periods/Phases	Screening/Baseline[a]	[redacted]
[redacted]		
Entrance and History		
Informed consent[b]	X	
Inclusion/exclusion criteria[c]	X	
Medical and psychiatric history[d]	←----------	----------→
Safety Assessments		
Physical/neurological examination	X[e]	
Weight	X[e]	
ECG[f]	X[e]	
Heart rate and blood pressure (including orthostatic)[g]	X[e]	
Respiratory rate and temperature	X[e]	
C-SSRS[h]	X[e]	
EPS (SAS, AIMS, BARS)[i]	X[e]	
Prior/concomitant treatments[j]	←----------	----------→
Adverse event monitoring[k]		X
Laboratory		
Blood for safety laboratory sample	X[e]	
Urine for safety laboratory	X[e]	
Urine pregnancy test[l]	X[e]	
[redacted]		
Other		
Register visit in IVR	X	
IMP dispensing[m]	X	
IMP dosing[m]		X

Abbreviations: AE=adverse event; AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EPS=extrapyramidal symptoms; IMP=investigational medicinal product; IVR=interactive voice response; [redacted] SAS=Simpson-Angus Scale; [redacted]

a. For rollover participants, screening for Trial CVL-231-2003 occurs simultaneously with baseline assessments at the Week 6 time point of Trial CVL-231-2001 or CVL-231-2002. The first dose of IMP for the open-label trial for rollover participants will occur [redacted] following baseline assessments.
b. Informed consent for Trial CVL-231-2003 will occur at Screening/Baseline for rollover participants and must be obtained before any trial-related procedures specific to the open-label are performed.
c. Inclusion and exclusion criteria for rollover participants will be assessed simultaneously with baseline assessments at the Week 6 time point of Trial CVL-231-2001 or CVL-231-2002.
d. For rollover participants, any ongoing AEs from the double-blind trial will be recorded as medical history until the time of first dose of open-label IMP.
e. For rollover participants, the screening/baseline assessment will be obtained from the Week 6 time point (Day 42 or Day 45, as appropriate) of the preceding double-blind trial (CVL-231-2001 or CVL-231-2002).
f. 12-lead ECG assessments will be performed after the participant has been at rest for approximately 3 minutes. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).
g. Triplicate supine heart rate and blood pressure measurements will be taken at approximately 1-minute intervals, followed by a single measurement after approximately 2 minutes in a standing position to allow for orthostatic assessments. Additional time points can be added at the investigator's discretion (eg, if abnormalities are noted). Further details are provided in Section 8.2.3 and in the Operations Manual.
h. The "Since Last Visit" C-SSRS form will be completed to ensure that the participant qualifies for the trial.
i. EPS assessments can be completed at any time during the trial, per investigator discretion, if symptoms are present.
j. Prior and concomitant medications should be recorded from Screening/Baseline through the participant's last visit/contact.
k. Adverse events (serious and nonserious) should be recorded from the first dose of open-label IMP.
l. For women of childbearing potential only. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Any urine pregnancy tests that are positive must be confirmed using a serum test.
m. Rollover participants will be dispensed IMP and will take their first dose of open-label IMP [redacted] after completion of baseline assessments.

Table 3 Schedule of Assessments – Open-label Treatment (All Participants)

Trial Periods/Phases	Treatment Period (52 weeks)												Follow-up (4 weeks)[a]
[redacted]													
Window (days)	±3												
Safety Assessments													
Physical/neurological examination[c]												X	
Limited physical examination[d]				X	X		X	X	X	X	X		
Weight	X	X	X	X	X		X	X	X	X	X	X	
ECG[e]	X	X	X	X	X		X	X	X	X	X	X	
Heart rate and blood pressure (including orthostatic)[f]	X	X	X	X	X		X	X	X	X	X	X	
Respiratory rate and temperature	X	X	X	X	X		X	X	X	X	X	X	
C-SSRS[g]	X	X	X	X	X		X	X	X	X	X	X	
EPS (SAS, AIMS, BARS)[h]			X	X	X		X	X	X	X	X	X	
Concomitant treatments[i]	←----------											----------→	
Adverse event monitoring[j]	←----------											----------→	
Laboratory													
Blood for safety laboratory sample[k]		X	X	X	X		X		X		X	X	
Urine for safety laboratory sample[k]		X	X	X	X		X		X		X	X	

Trial Periods/Phases	Treatment Period (52 weeks)												Follow-up (4 weeks)[a]
[redacted]													
Window (days)	±3												
Urine pregnancy test[l]	X	X	X	X	X		X	X	X	X	X	X	
Urine drug screen[m]	X	X	X	X	X		X	X	X	X	X	X	
Breathalyzer test for alcohol[n]	←----------→												
[redacted]													
Other													
[redacted]													
Contact[a]						X							X
IMP dispensing	X	X	X	X	X		X	X	X	X	X		
IMP accounting	X	X	X	X	X		X	X	X	X	X	X	

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EPS=extrapyramidal symptoms; ET=early termination; IMP=investigational medicinal product; [redacted] SAS=Simpson-Angus Scale; [redacted]

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

b. All Week 52 assessments should be completed for any participant who discontinues early from the trial. All assessments should be completed prior to reinitiation of antipsychotic therapy.
c. Full physical and neurological examinations should be completed at Screening, Baseline, and Week 52/ET. Symptom-driven physical and/or neurological examinations may be done at any time during the trial at the investigator's discretion.
d. Details for limited physical examination are provided in Section 8.2.2.
e. 12-lead ECG assessments will be performed after the participant has been at rest for approximately 3 minutes. At all time points, single 12-lead ECGs will be obtained. Additional ECGs can be performed at the investigator's discretion (eg, if abnormalities are noted).
f. At each indicated time point, triplicate supine heart rate and blood pressure measurements will be taken at approximately 1-minute intervals, followed by a single measurement after approximately 2 minutes in a standing position to allow for orthostatic assessments. Additional time points can be added at the investigator's discretion (eg, if abnormalities are noted). Further details are provided in Section 8.2.3 and in the Operations Manual.
g. The "Since Last Visit" C-SSRS form will be completed for all participants (rollover and de novo) at all indicated time points.
h. EPS assessments can be completed at any time during the trial, per investigator discretion, if symptoms are present.
i. Concomitant medications should be recorded through the participant's last visit/contact.
j. Adverse events (serious and nonserious) should be recorded from the first dose of IMP in Trial CVL-231-2003 through the participant's last visit/contact.
k. See Section 10.2 for more details on clinical laboratory tests.
l. For women of childbearing potential only. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Any urine pregnancy tests that are positive must be confirmed using a serum test.
m. The urine drug screen (dipstick) can be conducted at any time during the trial, including unscheduled visits, at the discretion of the investigator.
n. An alcohol test (breathalyzer) can be conducted at any time during the trial for any participant at the discretion of the investigator.

[redacted]

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 [redacted] Emraclidine is being developed for treatment of psychosis in schizophrenia.

The aim of this trial is to assess long-term safety and tolerability for participants who complete the Phase 2 efficacy trials (CVL-231-2001 and CVL-231-2002). In addition, de novo participants (ie, those who did not participate in either of the Phase 2 efficacy trials) may also be enrolled into this trial to better characterize long-term safety of emraclidine.

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) ([redacted]). 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 [redacted] 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 [redacted] its antipsychotic efficacy may be driven primarily by M4 mAChR stimulation [redacted]

[redacted]

2.2.2 Nonclinical Experience

[redacted]

[redacted]

[redacted]

The nonclinical safety profile of emraclidine [redacted] have been adequately characterized to support long-term administration in clinical trials in women and men.

[redacted]

2.2.3 Clinical Experience

Safety, tolerability, and PK of emraclidine were evaluated following single doses in healthy participants (Trial C2561001), single doses in healthy participants 21 to 51 years of age (Trial CVL-231-1004), and following multiple ascending doses in participants with schizophrenia (Trial CVL-231-SCH-001). In addition, blood pressure and heart rate were assessed using 24-hour ABPM in participants 30 to 60 years of age with stable schizophrenia (Trial CVL-231-1005) receiving emraclidine.

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.

[redacted]

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.

[redacted]

[redacted]

[redacted]

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 safety and tolerability of emraclidine over a 52-week period 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 acute 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 2.2).

[redacted]

[redacted] Heart rate and blood pressure will be regularly monitored throughout the trial.

The current data suggest a favorable benefit-risk ratio for further evaluation of emraclidine in patients with schizophrenia.

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 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the long-term safety and tolerability of oral emraclidine in adult participants with schizophrenia	• Treatment-emergent adverse events • Clinically significant changes in vital sign measurements, body weight, physical and neurological examination results, ECG assessments, clinical laboratory assessments, and metabolic parameters • Clinically significant findings in suicidality assessed using the C-SSRS • Extrapyramidal symptoms evaluated using the change from Baseline in SAS, AIMS, and BARS assessments
[redacted]	

[redacted]

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; [redacted] C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; [redacted] SAS=Simpson Angus Scale; [redacted]

4 TRIAL DESIGN

4.1 Overall Design

This is a Phase 2, multicenter, open-label, 52-week trial to evaluate the safety and tolerability of emraclidine 30 mg QD in adult participants with schizophrenia. The trial will be conducted on an outpatient basis. Enrollment into the trial will be drawn from eligible participants who, in the investigator's judgment, could potentially benefit from treatment with emraclidine for schizophrenia. There will be 2 groups of participants: 1) participants who completed treatment in one of the double-blind, placebo-controlled Phase 2 efficacy trials (CVL-231-2001 or CVL-231-2002), denoted as "rollover participants" and 2) participants with stable schizophrenia who were not enrolled in one of the Phase 2 efficacy trials, denoted as "de novo participants." Approximately 850 total participants are planned to be enrolled in the trial (rollover plus de novo) in order to fully characterize the safety profile of emraclidine.

The trial will include up to a 15-day Screening Period (de novo participants only), a 52-week Treatment Period, and a 28-day Follow-up Period. Each participant will participate in the trial for up to approximately 56 weeks (rollover participants) or 58 weeks (de novo participants).

Trial procedures and their timing are summarized in the Schedule of Assessments provided in Section 1.3.

4.1.1 Screening/Baseline Period

4.1.1.1 Rollover Participants

Rollover participants will be screened for eligibility at the last visit of the double-blind trial (ie, Day 45 of Trials CVL-231-2001 and CVL-231-2002). Rollover participants will sign a new ICF for participation in Trial CVL-231-2003 before any procedures specific to the open-label trial are performed. The final assessments from the double-blind trial ([redacted] for all other scales and safety assessments) will serve as the baseline measures for Trial CVL-231-2003 for any assessment that is not unique to the open-label trial. Medical history for Trial CVL-231-2003 would consist of

the previous medical history collected during screening for the double-blind trial and any ongoing AEs from the double-blind trial.

For rollover participants, the first dose of IMP for the open-label trial (ie, [redacted]) will occur [redacted] following baseline assessments.

4.1.1.2 De Novo Participants

De novo participants will enter a Screening Period of up to 15 days (up to a maximum of 21 days allowed with approval of the medical monitor) to assess eligibility criteria and washout from prior antipsychotic medications and other prohibited medications. The Screening Period begins on the day of signing the ICF. Participants with a "lapse" in antipsychotic treatment (a lapse is defined as no oral antipsychotic medication for 3 or more days immediately prior to signing the ICF) may proceed directly to Baseline Visit ([redacted] of the trial, provided all other eligibility criteria are met, including washout of all other prohibited medications.

[redacted] (see Table 6). Baseline assessments and the first dose of IMP occur on [redacted] following completion of baseline assessments, participants will receive their first dose of IMP.

4.1.2 Open-label Treatment Period

The daily dosing schedule will start on [redacted] with all participants receiving a single daily dose of IMP, preferably in the morning. Clinic visits will occur as described in the Schedule of Assessments (Section 1.3).

All participants will begin dosing with emraclidine 30 mg QD. [redacted]

[redacted]

All participants should continue dosing through Week 52.

4.1.3 Follow-up Period

All participants will have a follow-up safety contact 28±3 days after the last dose of IMP.

4.1.4 Definition of Completed Participant

A participant is considered to have completed the trial if he/she has completed the last scheduled site visit (ie, Week 52 visit), as shown in the Schedule of Assessments in Section 1.3.

4.2 Scientific Rationale for Trial Design

The open-label, long-term extension trial design is widely accepted as one that is appropriate for evaluating the safety and tolerability of an IMP over an extended period (FDA, 1995).

The safety assessments (vital sign measurements, physical and neurological examinations including those for assessing akathisia and EPS, ECGs, laboratory evaluations, and AEs) are those commonly used to assess the safety and tolerability of trial treatments. The C-SSRS is commonly used for stringent monitoring of suicidality in clinical trials of neurological compounds (Posner et al, 2011).

[redacted]

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

5.1 Inclusion Criteria

5.1.1 Rollover Participants

Individuals entering this trial from the double-blind trials CVL-231-2001 or CVL-231-2002 are eligible for participation in this trial only if all of the following criteria apply at Week 6 of the preceding trial:

General	
1.	Completed 6 weeks of post-randomization treatment in Trial CVL-231-2001 or CVL-231-2002 and who, in the opinion of the investigator, could potentially benefit from treatment with emraclidine for schizophrenia.
Target Disease Characteristics	
2.	Outpatient status at last day of treatment period (Day 45) of the preceding double-blind trial (CVL-231-2001 or CVL-231-2002) defined as follows: • Ability to be discharged from the hospital on Day 45 of Trial CVL-231-2001 or CVL-231-2002 • Hospitalization for psychosocial reasons (eg, homelessness or need for shelter that is unrelated to the participant's underlying psychiatric condition) will be considered outpatient status • Participants remaining in hospital at Day 45 of Trial CVL-231-2001 or CVL-231-2002 (for other than psychosocial reasons) will be permitted to enroll in Trial CVL-231-2003 at Day 45 of the double-blind trial if they are planned to be discharged from the hospital before the Week 1 visit of Trial CVL-231-2003 • Participants not discharged by the Week 1 visit of Trial CVL-231-2003 must be withdrawn
Other and Administrative Criteria	
3.	Agree to comply with the following contraception requirements during the trial and for 7 days after the last dose of IMP: • Sexually active women of childbearing potential must use acceptable (at minimum) contraception as defined in Section 10.4.1.1
4.	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in Section 10.1.3.
5.	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: ICF=informed consent form; IMP=investigational medicinal product.

5.1.2 De Novo Participants

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

General	
6.	Male and female participants, ages 18 to 65 years, inclusive, at the time of signing the ICF.
Target Disease Characteristics	
7.	Primary diagnosis of schizophrenia per DSM-5, as confirmed by the MINI for Psychotic Disorders version 7.0.2.
8.	Participants who have been stable on antipsychotic medication for at least one 3-month period in the year prior to screening (received the same medication or group of medications for at least 3 consecutive months in the prior year and demonstrated stability of symptoms on the antipsychotic medication).
9.	Outpatient status at the time of signing the ICF. Hospitalization for psychosocial reasons (eg, homelessness or need for shelter that is unrelated to the participant's underlying psychiatric condition) will be considered outpatient status. Participants may be hospitalized for not more than 14 days during the conversion to emraclidine with the approval of the medical monitor but must be discharged from the hospital before the Week 1 visit.
10.	Scores as follows (normal to mild symptoms) at the time of signing the ICF and Baseline ([redacted]): • 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
11.	Willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.
12.	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	
13.	Agree to comply with the following contraception requirements during the trial and for 7 days after the last dose of IMP: • Sexually active women of childbearing potential must use acceptable (at minimum) contraception as defined in Section 10.4.1.1
14.	Body mass index of 18.0 to 40.0 kg/m^2 and a total body weight ≥50 kg (110 lbs).
15.	Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in Section 10.1.3.
16.	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; DSM-5= Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICF=informed consent form; IMP=investigational medicinal product; MINI=Mini International Neuropsychiatric Interview; SAS=Simpson Angus Scale.

5.2 Exclusion Criteria

5.2.1 Rollover Participants

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

Other Medical History and Concurrent Conditions	
1.	Participants who, in the judgment of the investigator or medical monitor, had a clinically significant medical, surgical, psychiatric, or laboratory/ECG abnormality during conduct of the previous double-blind trial that could compromise either participant safety or the results of the trial. The medical monitor should be contacted to discuss individual cases, as needed. Abnormal test (eg, clinical laboratory, ECG) results that are potentially exclusionary (as defined in Exclusion Criteria #25 and #27 in Section 5.2.2 for de novo participants) should be repeated to ensure reproducibility of the result before excluding a potential participant. If abnormal results are received from the Week 6 clinical laboratory assessments and confirmed by repeat assessment, the medical monitor should be contacted to determine if the participant is eligible to continue in the open-label trial.
2.	"Yes" responses for any of the following items on the C-SSRS at any time point during the prior double-blind trial (CVL-231-2001 or CVL-231-2002): • 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: • 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.
Prior or Concomitant Therapies	
3.	Likely to require prohibited concomitant therapy during the trial ([redacted]).
Laboratory Test Results	
4.	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.
5.	Blood pressure measurements demonstrating any of the following at the Week 6 Visit (Day 45) of preceding double-blind trial: • 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

Lifestyle or Other Miscellaneous Exclusion	
6.	[redacted]
7.	Considering or scheduled to undergo any surgical procedure during the trial.
8.	In the opinion of the investigator, medical monitor, or sponsor, should not participate in the trial.
9.	Demonstrated substantial noncompliance to IMP dosing and/or trial procedures in the prior double-blind trial, based on the investigator's judgement. The medical monitor should be contacted if the investigator is unsure of a participant's eligibility.
10.	Had previously enrolled in this open-label trial and were subsequently discontinued.

Abbreviations: C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; IMP=investigational medicinal product.

5.2.2 De Novo Participants

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

Target Disease	
11.	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.
12.	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
13.	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	
14.	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.
15.	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).
16.	Active central nervous system infection, demyelinating disease, degenerative neurological disease, intellectual disability, 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.
17.	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.
18.	"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.
19.	Any condition or surgery that could possibly affect drug absorption, including, but not limited to, bowel resections, bariatric weight loss surgery/procedures, and gastrectomy.
20.	This criterion has been removed effective protocol version 3.0.

Prior or Concomitant Therapies	
21.	Use of prohibited medications prior to randomization within the required wash-out period [redacted] or likely to require prohibited concomitant therapy [redacted] during the trial.
22.	Transcranial magnetic stimulation or electroconvulsive therapy within 90 days of signing the ICF.
Laboratory Test Results	
23.	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.
24.	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.
25.	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
26.	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	
27.	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 (such as 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.
28.	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
29.	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	
30.	[redacted]
31.	Considering or scheduled to undergo any surgical procedure during the trial.
32.	Any other condition that would preclude IMP administration or trial participation (eg, difficulty swallowing, poor venous access).

33.	Known allergy or hypersensitivity to emraclidine, closely related compounds, or any of its specified ingredients.
34.	Received IMP in a prior clinical trial of emraclidine, with the exception of Trial CVL-231-1005.
35.	History of participation in any clinical trial involving an IMP as defined by the following: • Current enrollment in another interventional trial, 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 2 interventional trials within 12 months prior to signing the ICF
36.	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.
37.	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, 5th Edition, ECG=electrocardiogram; ET=early termination; HIV=human immunodeficiency virus; ICF=informed consent form; IMP=investigational medicinal product; LVH=left ventricular hypertrophy; QTcF=QT interval corrected for heart rate using Fridericia's formula; RNA=ribonucleic acid; THC=tetrahydrocannabinol; ULN=upper limit of normal range.

5.3 Lifestyle Considerations

[redacted]

5.3.2 Alcohol

Participants should abstain from alcohol from time of signing ICF until Week 52. Participants will undergo an alcohol breath test at Screening (de novo participants only) and anytime during the trial at the discretion of the investigator.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently enrolled. 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 5.

Table 5 Investigational Medicinal Product

IMP	Emraclidine
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength	30 mg[redacted]
Dosage Level	30 mg QD[a]
Route of Administration	Oral
Sourcing	Provided centrally by the sponsor
[redacted]	

Abbreviations: IMP=investigational medicinal product; QD=once daily.
a. All participants will receive treatment with emraclidine 30 mg QD[redacted]

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

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

6.4 Trial Intervention Compliance

Responsible trial personnel will dispense the IMP. Participants will be counseled on the importance of taking the IMP as directed and will be instructed to bring all used and unused IMP to each visit for assessment of accountability and compliance.

Compliance will be assessed by direct questioning and by counting returned tablets. Compliance will be documented in the source documents and the eCRF, including any deviations from the prescribed dosage regimen.

If poor compliance is encountered (eg, multiple missed doses resulting in <80% overall compliance at any point in the trial), discontinuation of the participant from the trial should be considered. Participants who habitually miss visits or habitually attend visits outside of the protocol-defined visit window are also defined as noncompliant and should be considered for discontinuation. The investigator should contact the medical monitor if uncertain whether a participant's lack of compliance merits discontinuation from the trial.

[redacted]

6.6 Intervention After the End of the Trial

There will be no provision of emraclidine for participants after they complete or discontinue treatment in this trial.

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 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.

[redacted]

[redacted]

[redacted]

[redacted]

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.

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.

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 for de novo participants to confirm their 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.

[redacted]

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

[redacted]

[redacted]

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 for de novo participants only with a stadiometer, measuring stick, or tape.

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

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

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.

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

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 CTCAE toxicity grades summarized in Section 10.3.3 (Table 13) 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 (12 lead) recordings will be obtained after the participant has been supine and at rest for approximately 3 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an early termination. 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 (de novo participants only), triplicate 12-lead ECGs are required to assess participant eligibility. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period. 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 enrolled. 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 relevant 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 de novo 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 at all specified visits after the Screening visit for de novo participants and at all specified visits for rollover participants. 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.

[redacted]

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 and Aggregate Safety Reports

Prompt (ie, within 24 hours of awareness by site personnel) 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. Adverse events that meet criteria as a suspected unexpected serious adverse reaction (SUSAR) require reporting by the sponsor. These SUSAR reports involve events that are not listed (ie, unexpected) in the reference safety information section of the emraclidine Investigator's Brochure.

The sponsor or their designee is required to report SUSARs to regulatory authorities (including EudraVigilance database, as applicable), IECs/IRBs, and investigators in accordance with Article 42 of Regulation (EU) No 536/2014 and country-specific regulatory requirements.

The sponsor or their designee is responsible for meeting SUSAR reporting timelines, which are no later than 7 days following the sponsor's initial receipt of fatal or life-threatening SUSARs and no later than 15 days following the sponsor's initial receipt of non-fatal or non-life-threatening SUSARs. Any follow-up information received by the sponsor that pertains to a previously submitted SUSAR must be submitted no later than 15 calendar days after receipt by the sponsor. If follow-up information includes the addition of fatal or life-threatening criteria of the existing event(s) or an additional

event(s) meeting fatal of life-threatening criteria, the SUSAR follow-up report will be submitted no later than 7 days after receipt by the sponsor.

Additionally, the sponsor is required to submit an annual safety report in the format of a Development Safety Update Report in accordance with EU CTR Article 43.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SUSAR 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).

[redacted]

[redacted]

8.4 Pharmacokinetics

Pharmacokinetics are not evaluated in this trial.

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. [redacted]

[redacted]

Future biospecimen research samples will be collected from de novo 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.

[redacted]

9 STATISTICAL CONSIDERATIONS

The SAP for this trial will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section.

9.1 Statistical Hypotheses

No formal statistical hypothesis testing is planned for this open-label trial.

9.2 Analysis Sets

The analysis sets that are defined for this trial are described in Table 8.

Table 8 Analysis Set Descriptions

Term	Description	Analysis
ITT	All participants who are enrolled in the trial	Demographic and Baseline Characteristics
Safety Analysis Set	All participants who receive at least 1 dose of emraclidine in Trial CVL-231-2003	Safety analyses

Abbreviations: ITT=intent-to-treat.

9.3 Statistical Analyses

9.3.1 General Considerations

Descriptive statistical methods will be used to summarize the data from this trial. [redacted] Unless stated otherwise, the term "descriptive statistics" includes the number of participants (n), mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. All available data for enrolled participants will be listed by participant. All statistical analyses will be conducted with the SAS® System, version 9.4 or higher.

[redacted]

9.3.3 Safety Analyses

Treatment-emergent AEs will be coded according to MedDRA and summarized by treatment group, system organ class, and preferred term. The frequencies of AEs will be determined for the entire treatment period, as well as by time interval to evaluate the time trend. Further summaries will be done by seriousness, severity, and relationship to IMP.

Other safety endpoints will be summarized with descriptive statistics including clinical laboratory assessments and metabolic parameters, vital sign measurements, and EPS

assessed by AIMS, SAS, and BARS. Clinically significant changes in vital sign measurements, body weight, physical and neurological examination results, ECG assessments, clinical laboratory assessments, metabolic parameters, [redacted] information, and C-SSRS assessments will be tabulated by time interval as well as overall.

9.4 Interim Analyses

No interim analysis is planned.

9.5 Sample Size Determination

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

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, IB, 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. The Declaration of Helsinki does not only require that the information is provided, but also that the investigator needs to make sure that the potential participant has understood the information (Article 26).

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 (including General Data Protection Regulation) 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.

Any secondary use of participant data for additional research outside the scope of the trial (clinical data, biological samples, images, biopsies, etc) requires disclosure of the purpose of the research and additional consent of the participant. As described in Section 10.5, additional consent will be required for participants from whom future biospecimen research samples will be collected.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the trial, unless the changes from the previous version are solely editorial in nature.

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

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.

The contract between the sponsor, investigators, and trial site personnel specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the investigator and the institution will promptly notify the sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, sponsor's personnel, trial participants or their relatives, healthcare professionals), the approximate number of participants concerned, the type and approximate number of data records concerned, and the likely consequences of the breach. The institution and/or investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.

Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

Participants must be informed that their trial-related data will be used for the whole "drug development program," ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Should a serious breach occur, it will be reported to the Member States concerned in order for action to be taken by those Member States, where necessary, and in accordance with local regulation.

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, CTIS, EudraCT (if applicable), 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 CTIS (or EudraCT, if applicable) 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, institutional policies, or Article 58 of EU Regulation 536/2014

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 9 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 for de novo participants only.

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.

Table 9 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	

Laboratory Assessments	Parameters
Additional Required Protocol-specific Tests	Serum/urine pregnancy test (as needed in women of childbearing potential) If CPK >3 × ULN, consider serum troponins as clinically indicated; urine myoglobin collected if CPK >5 × ULN
Other Screening Tests (de novo participants)	A confirmatory FSH is required for post-menopausal women Breathalyzer test for alcohol and urine drug screen Serology (HIV, HBsAg, hepatitis C antibody) 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; 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 10 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 11 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 12 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 13 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 14 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 15 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 16 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 17). • 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 17) or to the sponsor or designee by telephone.

Table 17 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 Acceptable Birth Control Methods (Failure Rate >1% per Year)

Acceptable birth control methods that result in a failure rate of more than 1% per year include the following:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide*
- Cap, diaphragm, or sponge with spermicide*

*A combination of male condom with a cap, diaphragm, or sponge with spermicide (double barrier methods) is also considered acceptable but is not a highly effective birth control method.

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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.8 Abbreviations

Abbreviation	Definition
ABPM	ambulatory blood pressure monitoring
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
BARS	Barnes Akathisia Rating Scale
BID	twice daily
bpm	beats per minute
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum (peak) plasma concentration
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTIS	Clinical Trials Information System
CTR	Clinical Trials Register
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EPS	extrapyramidal symptoms
ET	early termination
EU	European Union
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board

Abbreviation	Definition
mAChR	muscarinic acetylcholine receptor
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
PK	pharmacokinetic(s)
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
SAS	Simpson Angus Scale
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time of maximum plasma concentration
ULN	upper limit of normal
US	United States
[redacted]	[redacted]

10.9 Protocol Amendment History

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

Document History	
Protocol Version	**Date**
4.0	30 Apr 2024
3.0	15 Mar 2023
2.0	23 May 2022
1.0	21 Mar 2022

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 signatory	Change in internal responsibilities
[redacted]		

Section # and Name[a]	Description of Change	Brief Rationale
[redacted]		
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 increases in blood pressure
[redacted]		

Abbreviations: AE=adverse event; AESI=adverse event of special interest; [redacted] CTCAE=Common Terminology Criteria for Adverse Events; SAE=serious adverse event; [redacted]

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

Amendment: Protocol Version 2.0 (23 May 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.

[redacted]

[redacted]

[redacted]

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.

[redacted]

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.

[redacted]

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.

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.

[redacted]

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.

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.

[redacted]

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

[redacted]

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.

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.

[redacted]

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.

[redacted]

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 Department of Health and Human Services (DHHS). Guidance for industry: Assessment of pressor effects of drugs. Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research (CDER); Draft Guidance; May 2018.

US Food and Drug Administration (FDA). Guidance for Industry: E1A the extent of population exposure to assess clinical safety: for drugs intended for long-term treatment of non-life-threatening conditions; March 1995.

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.

[redacted]

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Title:	A 52-week, Phase 2, Open-label Trial to Evaluate the Long-term Safety and Tolerability of CVL-231 in Adult Participants With Schizophrenia
Trial Number:	CVL-231-2003
Trial Phase:	2
Compound:	Emraclidine
Sponsor Name:	Cerevel Therapeutics, LLC
Legal Registered Address:	222 Jacobs Street, Suite 200 Cambridge, MA 02141 US

Version 4.0: 30 Apr 2024

I, the undersigned principal investigator, have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

Principal Investigator Printed Name

Principal Investigator Signature

Date (DD MMM YYYY)