CLINICAL PROTOCOL

A 57-WEEK, MULTICENTER, ACTIVE-TREATMENT, OPEN-LABEL EXTENSION TRIAL OF CVL-865 AS ADJUNCTIVE THERAPY IN ADULTS WITH DRUG-RESISTANT FOCAL ONSET SEIZURES

Protocol: CVL-865-SZ-002

Compound Number: CVL-865

Trial Phase: 2

Short Title: An Extension Trial of CVL-865 as Adjunctive Therapy in the Treatment of Focal Onset Seizures

Sponsor Name: Cerevel Therapeutics, LLC

Legal Registered Address: 131 Dartmouth Street, Suite 502, Boston MA 02116 United States

Regulatory Agency Identifier Number

Regulatory Agency File	Identifying #
IND:	126,900
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CONFIDENTIAL – PROPRIETARY INFORMATION

Version 3.0: 14 Jul 2020

Version 2.0: 26 Nov 2019

Original Version 1.0: 30 Oct 2019

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

Sponsor Signatories:

PPD

PPD Cerevel Therapeutics, LLC

PPD

Date

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PPD Inflexion Pharma Solutions Ltd

PPD

Date

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Date

PPD

PPD erapeutics, LLC

PPD

Date

PROTOCOL VERSION 3.0 SUMMARY OF CHANGES TABLE

Document History	
Document:	**Date (Day-Month-Year)**
Version 3.0	14 Jul 2020
Version 2.0	26 Nov 2019
Original Protocol Version 1.0	30 Oct 2019

Amendment: Protocol Version 3.0 (dd Jul 2020)

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

Overall Rationale for the Amendment: The overall rationale for this amendment is to incorporate measures into the protocol to ensure the safety of the trial subjects and the validity of the trial data in the environment of the COVID-19 pandemic and to clarify other aspects of trial conduct unrelated to the COVID-19 pandemic.

Section # and Name	**Description of Change**	**Brief Rationale**
1.2 Schema 1.3 Schedule of Assessments	Changed Week 4 visit to contact only rather than site visit, remove laboratory assessments at this visit	Allow flexibility and reduce burden on subjects
1.3 Schedule of Assessments	Added a footnote to Table 2 and Table 3 to provide an option for specific visits to be completed remotely; remove previous text regarding option for remote pregnancy test as no longer applicable Added option for COVID-19 testing	To reflect risk assessment measures by sponsor to prioritize trial participant safety
1.3 Schedule of Assessments	Remove PGI-C and CGI-S assessments at the end of the Taper Phase	Reduce number of assessments and burden on subject
2.3 Benefit/Risk Assessment	Added a statement regarding sponsor risk assessment related to COVID-19	To reflect measures implemented by the sponsor to prioritize trial participant safety and data validity
4.1 Overall Design	Added text stating subjects who terminate trial during Titration Phase will be provided 3 weeks of IMP for Taper Phase	Additional clarification regarding early discontinuation

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 7.3 Individual Subject Discontinuation 8.4.6.2 Hematologic Abnormalities	Changed decimal places for WBC and neutrophil counts	Correct typographical errors
5.2 Exclusion Criteria	Modified the wording related to current use of prohibited medications	Simplify language by referring to the respective tables that specify prohibited medications during the trial
5.3.1 Meals and Dietary Restrictions	Increased restriction on consuming grapefruit and grapefruit-related citrus fruits until end of trial	Maintain consistency with Trial CVL-865-SZ-001
5.4 Screen Failures	Added language clarifying the definition of screen failures	Clarification of prior language
6.4 Trial Treatment Compliance	Removed information that IMP given once daily in the morning with or without food	Correction of erroneous information
6.6 Dose Modification 7.3 Individual Subject Discontinuation	Removed information regarding discontinuation of IMP from Section 6.6 and added to Section 7.3	Restrict Section 6.6 to information regarding dose interruption and Section 7.3 for information regarding subject discontinuation
7.3 Individual Subject Discontinuation	Added wording to specify that subjects should begin Taper Phase at time decision made to discontinue trial. Added caveat for an alternate taper scheme for subjects who early terminate prior to Day 15.	Further clarification on trial procedures
8.3.1 Physical and Neurological Examinations	Added clarification that prior record of genitourinary examination was within 12 months of enrolling in CVL-865-SZ-001	Further clarification on trial procedures
8.3.2 Vital Sign Measurements	Deleted redundant text in paragraphs 1 and 2	Correction of error in original protocol
8.3.3 Electrocardiograms	Removed information regarding requirement for subjects to be supine prior to ECG; removed specification that ECG is 12-lead	Allow flexibility in case of remote trial visits
8.3.4 Clinical Safety Laboratory Assessments	Removal of language regarding clinically significant laboratory finding	Update to be consistent with company processes and avoid redundant text
8.6 Pharmacokinetics	Simplified wording about sample collection (Sections 8.6.1 and 8.6.2)	Remove duplication of details provided in other materials

Section # and Name	Description of Change	Brief Rationale
10.1.3 Informed Consent Process	Removed references to legally authorized representative	Correct inconsistency with inclusion criteria
10.2 Appendix 2: Clinical Laboratory Tests	Added section on additional required tests, which includes urine pregnancy tests	Correct inconsistency with Schedule of Assessments
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Revised section to remove redundant language and to clarify AE and SAE/AESI reporting procedures	Align wording with actual processes that will be followed in trial and for consistency across Cerevel clinical development programs
10.5 Appendix 5: Inducers and Inhibitors of Cytochrome P450 3A	Added eslicarbazepine as CYP 3A inducer	Add to prohibited medications, due to potential for reduction of CVL-865 concentrations
Signature Page	Changes to signatories	Reflect changes in sponsor personnel
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Reflect changes to visit numbers, visit timing, and visit types (ie, contact visits changed to in-clinic visits), due to changes to schedule of activities Correct errors in original protocol

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CGI-S = Clinical Global Impression-Severity; CYP = cytochrome P450; ECG = electrocardiogram; IMP = investigational medicinal product; PGI-C = Patient Global Impression of Change; SAE = serious adverse event; WBC = white blood cell.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Sponsor Name: Cerevel Therapeutics, LLC

Name of Investigational Medicinal Product: CVL-865

Protocol Title: A 57-Week, Multicenter, Active-treatment, Open-label Extension Trial of CVL-865 as Adjunctive Therapy in Adults with Drug-Resistant Focal Onset Seizures

Short Title: An Extension Trial of CVL-865 as Adjunctive Therapy in the Treatment of Focal Onset Seizures

IND Number: 126,900

EudraCT Number: 2019-004057-83

Trial Phase: 2

Treatment/Indication: Focal Onset Seizures

Rationale: The broad therapeutic use of nonselective benzodiazepines (BZDs) in multiple indications clearly supports the therapeutic potential of γ-aminobutyric acid type A ($GABA_A$) positive allosteric modulators (PAMs) with the potential to offer efficacy with fewer side effects.

This 57-week, active-treatment, open-label extension trial is designed to assess the safety and tolerability of CVL-865 as adjunctive treatment in subjects with drug-resistant focal onset seizures. This trial is open to subjects who completed treatment with the investigational medicinal product (IMP) in the double-blind Phase 2 Trial CVL-865-SZ-001 and who, in the opinion of the investigator, could potentially benefit from treatment with CVL-865.

Objectives and Endpoints

The objectives and endpoints of the trial are summarized in Table 1.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary: To assess the long-term safety and tolerability of CVL-865 as adjunctive therapy in subjects with focal onset seizures	• Nature, frequency, and temporality of treatment-emergent AEs (nonserious and serious), including abuse-related AEs and AEs related to medication handling irregularities • Clinically significant changes in ECGs, vital sign measurements, clinical laboratory assessments, and physical and neurological examination results • Suicidality assessed using the C-SSRS • Withdrawal symptoms assessed using the mCIWA-B
Exploratory: To assess the long-term efficacy of CVL-865 as adjunctive therapy in subjects with focal onset seizures	• Focal onset seizure frequency per week over the Maintenance Phase • Seizure freedom • Seizure rate over time • PGI-C score at each trial visit • Change from Baseline in CGI-S score at each trial visit
Exploratory: To evaluate the plasma exposure of CVL-865	• Summary listing of CVL-865 concentrations by dose and visit

Abbreviations: AE = adverse event; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; mCIWA-B = Modified Clinical Institute Withdrawal Assessment – Benzodiazepines; PGI-C = Patient Global Impression of Change.

Overall Design:

This is a 57-week, active-treatment, open-label extension trial designed to assess the long-term safety and tolerability of CVL-865 as adjunctive therapy in subjects with focal onset seizures. Enrollment into the trial will consist of eligible subjects who completed the Maintenance Phase of Trial CVL-865-SZ-001.

Eligible subjects will enter this trial directly after completing Visit 4 (end of Maintenance Phase) of Trial CVL-865-SZ-001. The efficacy and safety assessments from Visit 4 of Trial CVL-865-SZ-001 will serve as the baseline assessments for the open-label trial for any assessments that are not unique to the open-label trial. All subjects must provide informed consent to participate in the open-label trial before any baseline assessments that are unique to the open-label trial are performed.

This trial is designed with a maximum duration of approximately 61 weeks during which the subjects will receive CVL-865. The trial consists of the following:

- Up to 57-week Treatment Period consisting of the following:

- 2-week double-blind Titration Phase
- 52-week Maintenance Phase
- 3-week Taper Phase

- 4-week Follow-up Period

Disclosure Statement: This is an open-label trial of the safety and tolerability of CVL-865 in subjects with focal onset seizures. To ensure that the treatment assignments in the Phase 2 double-blind Trial CVL-865-SZ-001 remain blinded for the subjects who rollover into this open-label trial, all subjects will be dispensed blinded CVL-865 tablets during the Titration Phase of this trial.

Number of Subjects:

The trial population will be derived from eligible subjects from the double-blind, proof-of-concept Trial CVL-865-SZ-001. Of the approximately150 subjects to be enrolled in Trial CVL-865-SZ-001, approximately 120 are expected to complete the trial and be eligible for enrollment in Trial CVL-865-SZ-002.

Key Entry criteria:

Men and women with a diagnosis of epilepsy with focal onset seizures who have completed the Maintenance Phase of Trial CVL-865-SZ-001 may be eligible for enrollment into this trial.

Intervention Groups, Trial Treatment, and Duration: All subjects will receive CVL-865, administered orally BID during a 57-week Treatment Period.

Statistical Methods

Sample Size Estimation: The sample size is not based on statistical power considerations. The trial population will be derived from eligible subjects from the double-blind, proof-of-concept Trial CVL-865-SZ-001. - Approximately 120 subjects are expected to complete Trial CVL-865-SZ-001 and be eligible for enrollment in CVL-865-SZ-002.

Safety Analyses: The safety analysis will be conducted on the Safety Set. The primary safety analysis is the frequency and severity of adverse events (AEs) during the Treatment Period. All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of treatment-emergent AEs (TEAEs) will include the following summaries:

- TEAEs by severity
- Drug-related TEAEs

- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs
- TEAEs potentially related to abuse as assessed through the active monitoring of adverse events related to potential abuse and AEs involving medication handling irregularities

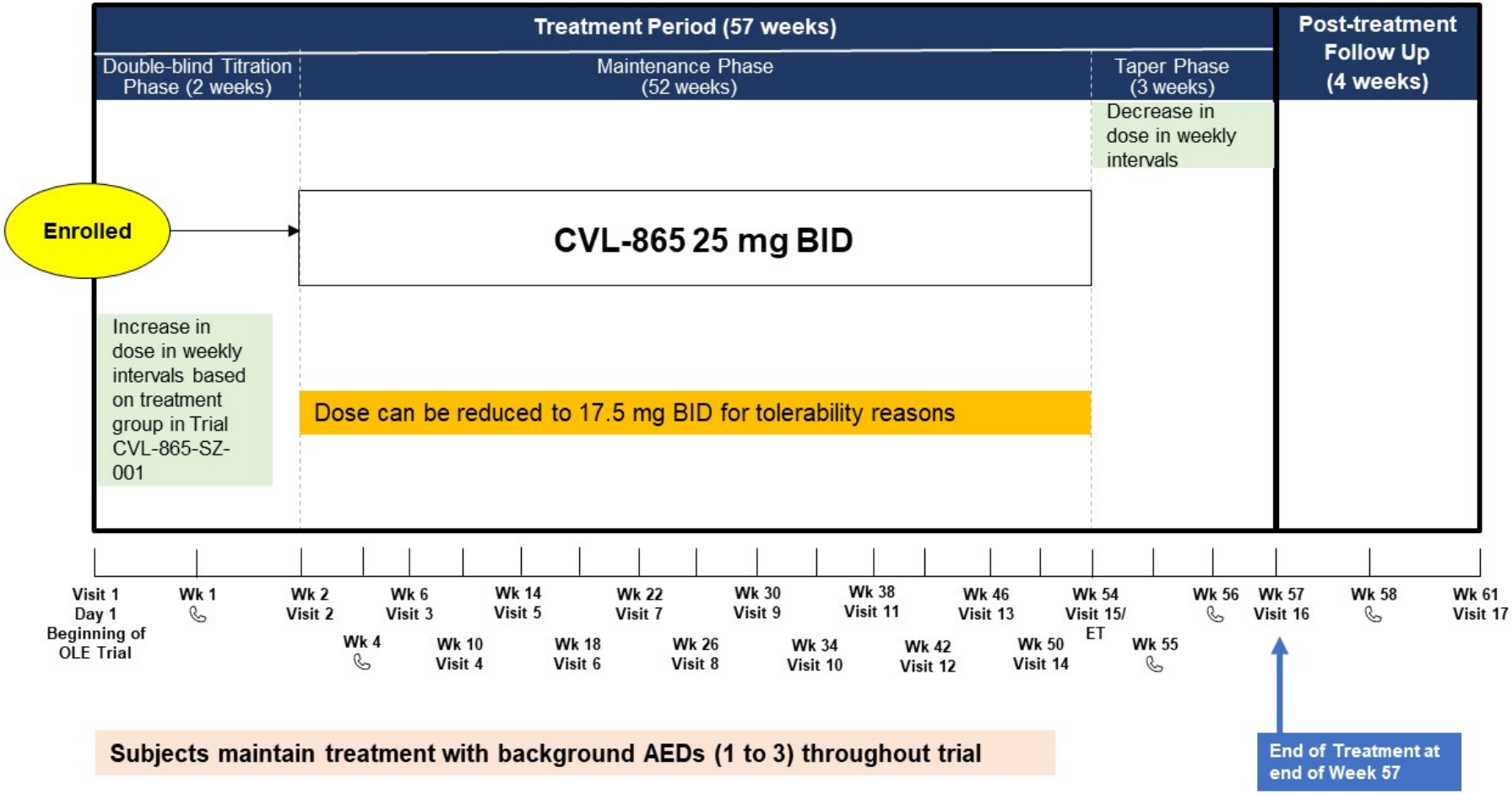
A TEAE for this study is defined as an AE that started after the first dose of IMP in the open-label trial or a previously reported AE that increased in intensity, became serious, trial drug-related, or resulted in death, discontinuation, interruption, of reduction of IMP after the first dose of IMP in the open-label trial.

Other safety endpoints, including clinical laboratory assessments, vital sign measurements, ECGs, medication withdrawal symptoms assessed by the Modified Clinical Institute Withdrawal Assessment – Benzodiazepines total scores at the scheduled visits, and suicidality monitored during the trial using the Columbia-Suicide Severity Rating Scale, will be summarized with descriptive statistics. Baseline is defined as the last assessment prior to the initiation of IMP in CVL-865-SZ-002. Additional presentations may be conducted evaluating changes from the original trial baseline. These analyses will be detailed in the statistical analysis plan.

Exploratory Analyses: Descriptive statistics will be provided for each efficacy endpoint and will be summarized at each trial visit using available data. Baseline is defined as the last assessment prior to the initiation of IMP in CVL-865-SZ-002. Additional presentations may be conducted evaluating changes from the original trial baseline. These analyses will be detailed in the statistical analysis plan.

1.2 Schema

Figure 1 Trial Schematic



1.3 Schedule of Activities

Two schedules are included in this section. The Schedule of Assessments for the Double-blind Titration Phase and for the Maintenance Phase (through Visit 12) is provided in Table 2. The Schedule of Assessments for the subsequent visits during the Maintenance Phase (Visit 13 through Visit 15/Early Termination), for the Taper Phase, and for the Post-treatment Follow-up Phase is provided in Table 3.

Table 2 Schedule of Assessments - Double-blind Titration Phase and Maintenance Phase (Through Visit 12)

Trial Period/ Phases	Double-blind Titration Phase (2 weeks)		Maintenance Phase (52 weeks) Visits 2 through 12											
Visit/Contact[a]	**Visit 1/BL[b,c]**	**Contact**	**Visit 2**	**Contact**	**Visit 3[d]**	**Visit 4[d]**	**Visit 5[d]**	**Visit 6[d]**	**Visit 7[d]**	**Visit 8[d]**	**Visit 9[d]**	**Visit 10[d]**	**Visit 11[d]**	**Visit 12[d]**
Day	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**
Week	**0**	**1**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**
Window	**± 3 days**													
Entrance and History														
Informed consent	X													
Medical history	X													
Assign subject identification	X													
Review inclusion/ exclusion criteria	X													
Review of birth control methods	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
Review eDiary including compliance with use of eDiary	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGI-C	X		X		X		X			X			X	
CGI-S	X		X		X		X			X			X	

Trial Period/ Phases	**Double-blind Titration Phase (2 weeks)**		**Maintenance Phase (52 weeks) Visits 2 through 12**											
Visit/Contact[a]	**Visit 1/BL[b,c]**	**Contact**	**Visit 2**	**Contact**	**Visit 3[d]**	**Visit 4[d]**	**Visit 5[d]**	**Visit 6[d]**	**Visit 7[d]**	**Visit 8[d]**	**Visit 9[d]**	**Visit 10[d]**	**Visit 11[d]**	**Visit 12[d]**
Day	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**
Week	**0**	**1**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**
Window	**± 3 days**													
Safety Assessments														
Physical/ neurological examination[e]	X													
ECG	X				X		X			X			X	
Vital sign measurements	X				X		X			X			X	
C-SSRS[f]	X		X		X		X			X			X	
Prior/concomitant treatments including BZD use[g]	←----------													----------→
Adverse event monitoring[g]	←----------													----------→
Laboratory														
Safety laboratory blood sample	X		X		X	X	X	X	X	X	X	X	X	X
Safety laboratory urine sample	X		X		X		X			X			X	
Urine pregnancy test[h]	X		X		X	X	X	X	X	X	X	X	X	X

Trial Period/ Phases	Double-blind Titration Phase (2 weeks)		Maintenance Phase (52 weeks) Visits 2 through 12											
Visit/Contact[a]	**Visit 1/BL[b,c]**	**Contact**	**Visit 2**	**Contact**	**Visit 3[d]**	**Visit 4[d]**	**Visit 5[d]**	**Visit 6[d]**	**Visit 7[d]**	**Visit 8[d]**	**Visit 9[d]**	**Visit 10[d]**	**Visit 11[d]**	**Visit 12[d]**
Day	**1**	**8**	**15**	**29**	**43**	**71**	**99**	**127**	**155**	**183**	**211**	**239**	**267**	**295**
Week	**0**	**1**	**2**	**4**	**6**	**10**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**
Window	**± 3 days**													
Urine drug screening[i]	X													
Blood sample for PK of CVL-865[j]	X						X			X			X	
Blood sample for PK of AEDs[k]	X						X			X			X	
Other														
IMP dispensing	X		X		X		X			X			X	
IMP compliance assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AED compliance assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AED = antiepileptic drug; BL = baseline; BZD = benzodiazepine; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ICF = informed consent form; IMP = investigational medicinal product; PGI-C = Patient Global Impression of Change; PK = pharmacokinetics.

a. Contact with subject via phone call, internet/web, or other acceptable means of communication to check on their status.

b. Screening/Baseline for Trial CVL-865-SZ-002 occurs at Visit 1, which is the same day as Visit 4 in Trial CVL-865-SZ-001. Any assessments conducted for Visit 4 of Trial CVL-865-SZ-001 will be considered the baseline assessments for Visit 1 of Trial CVL-865-SZ-002.

c. Individual sites may require subjects to have COVID-19 testing done prior to enrollment. COVID-19 testing may be performed after enrollment per the investigator's discretion.

d. In the event that a subject is unable to attend a clinic visit in person due to restrictions related to COVID-19, this visit may be completed remotely. Please refer to the Trial Operations Manual for further instructions related to remote visits.

e. The physical examination should include weight at all time points. Physical and/or neurological examinations can be done at any time point during the trial at the investigator's discretion.

f. The "Since Last Visit" C-SSRS form will be completed at all visits.

g. Adverse events (serious and non-serious) and concomitant medications should be recorded from the time of signing the ICF through the subject's last visit.

h. For women of childbearing potential only. All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Monthly pregnancy tests will be required for all women of childbearing potential.

i. The urine drug screen can be conducted at any time during the trial at the discretion of the investigator.

j. With subjects maintaining their normal BID dosing routine, a single daytime blood sample for determination of plasma CVL-865 concentration will be collected at Visits 5, 8, and 11. The date and time of the PK sample, as well as the time of ingestion of the morning dose of IMP (on the same day), will be recorded in the source documentation.

k. One 5-mL sample for each adjunctive AED collected at Visits 5, 8, and 11.

Table 3 Schedule of Assessments - Maintenance Phase (Visits 13 Through 15/ET Only), Taper Phase, and Post-treatment Follow-up Phase

Trial Period/ Phases	Maintenance Phase (52 weeks) Visits 13 through 15/ET			Taper Phase (3 weeks)			Post-treatment Follow-up	
Visit/Contact[a]	**Visit 13[b]**	**Visit 14[b]**	**Visit 15/ET[c]**	**Contact**	**Contact**	**Visit 16[b]**	**Contact**	**Visit 17**
Day	**323**	**351**	**379**	**386**	**393**	**400**	**407**	**428**
Week	**46**	**50**	**54**	**55**	**56**	**57**	**58**	**~61**
Window	**± 3 days**							
Entrance and History								
Review of birth control methods	X	X	X	X	X	X	X	X
Efficacy Assessments								
Review eDiary including compliance with use of eDiary	X	X	X	X	X	X	X	X
PGI-C			X					
CGI-S			X					
Safety Assessments								
Physical/ neurological examination[d]			X			X		
ECG			X			X		
Vital sign measurements			X			X		
C-SSRS[e]			X			X		X
mCIWA-B			X	X	X	X	X	X
Prior/concomitant treatments including BZD use[f]	←----------→							
Adverse event monitoring[f]	←----------→							
Laboratory								
Safety laboratory blood sample	X	X	X			X		X
Safety laboratory urine sample			X			X		
Urine pregnancy test[g]	X	X	X			X		

Trial Period/ Phases	Maintenance Phase (52 weeks) Visits 13 through 15/ET			Taper Phase (3 weeks)			Post-treatment Follow-up	
Visit/Contact[a]	**Visit 13[b]**	**Visit 14[b]**	**Visit 15/ET[c]**	**Contact**	**Contact**	**Visit 16[b]**	**Contact**	**Visit 17**
Day	**323**	**351**	**379**	**386**	**393**	**400**	**407**	**428**
Week	**46**	**50**	**54**	**55**	**56**	**57**	**58**	**~61**
Window	**± 3 days**							
Other								
IMP dispensing			X					
Collect final eDiary device								X
IMP compliance assessment	X	X	X	X	X	X		
AED compliance assessment	X	X	X	X	X	X	X	X

Abbreviations: AED = antiepileptic drug; BZD = benzodiazepine; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = Early Termination; IMP = investigational medicinal product; mCIWA-B = Modified Clinical Institute Withdrawal Assessment – Benzodiazepines; PGI-C = Patient Global Impression of Change.

a. Contact with subject via phone call, internet/web, or other acceptable means of communication to check on their status.

b. In the event that a subject is unable to attend a clinic visit in person due to restrictions related to COVID-19, this visit may be completed remotely. Please refer to the Trial Operations Manual for further instructions related to remote visits.

c. Subjects should begin the Taper Phase after they have completed treatment in the Maintenance Phase or at the time the decision is made to discontinue. All Taper Phase and Post-treatment Follow-up procedures should be performed as indicated. If a subject discontinues early and it is inadvisable for them to taper IMP (after agreement from medical monitor), the subject should complete the Visit 17 assessments approximately 30 days following the last dose of IMP.

d. The physical examination should include weight at all time points. Physical and/or neurological examinations can be done at any time point during the trial at the investigator's discretion.

e. The "Since Last Visit" C-SSRS form will be completed at all visits.

f. Adverse events (serious and non-serious) and concomitant medications should be recorded from the time of signing the ICF through the subject's last visit.

g. For women of childbearing potential only. All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Monthly pregnancy tests will be required for all women of childbearing potential.

2 INTRODUCTION

2.1 Trial Rationale

CVL-865 (formerly known as PF-06372865) is a potent ligand of the allosteric benzodiazepine (BZD) site of the γ-aminobutyric acid type A ($GABA_A$) receptor, which is being developed for the treatment of epilepsy. The aim of this trial is to evaluate the long-term safety and tolerability of CVL-865 as adjunctive treatment of adult patients with drug-resistant focal onset seizures who completed the Maintenance Phase of Trial CVL-865-SZ-001.

2.2 Background

Epilepsy is the most common serious neurological condition in the world affecting approximately 60 million people worldwide. In the United States (US), more than 3 million people have been diagnosed with epilepsy or have experienced an unprovoked seizure. Approximately 20% to 30% of patients with focal onset seizures have seizures that are refractory to currently available anti-epileptic drugs (AEDs). Drug-resistant seizures have been defined by the International League Against Epilepsy as "failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules to achieve sustained seizure freedom" (Kwan et al, 2010). Furthermore, current AEDs possess undesirable toxicity for many patients; therefore, there remains a clear medical need for the development of improved anti-epileptic therapies that are more efficacious, easy to use, and better tolerated than those already on the market.

Benzodiazepines are nonselective positive allosteric modulators (PAMs) of $GABA_A$ receptors with widespread utility in neurology and psychiatry, but their use is limited by sedation, psychomotor impairment, and other adverse effects. In the treatment of epilepsy, chronic use of BZDs can result in loss of efficacy, which precludes its use in many epilepsy populations.

CVL-865 is a novel, brain-penetrable, partial PAM of α2, α3, and α5 subunit containing $GABA_A$ receptors, with minimal functional activity at α1 subunit-containing receptors, which are believed to mediate many adverse effects observed with BZDs. By reducing the α1 activity, CVL-865 has the potential to retain highly effective anticonvulsant activity, without the BZD-associated adverse effects.

Clinically, the first investigation of the anticonvulsant potential of CVL-865 was demonstrated in a Phase 2 photosensitive epilepsy model trial (Gurrell et al, 2019). In this trial, photosensitive subjects were exposed to intermittent photic stimulation and the reduction in sensitivity was measured. CVL-865 showed robust suppression of the generalized photoparoxysmal electroencephalogram response, following single doses of 17.5 and 52.5 mg, raising the possibility that CVL-865 may have potential efficacy in other epilepsy populations.

Currently, approximately 290 subjects have been administered CVL-865 in single doses ranging from 0.04 to 100 mg, and in multiple doses ranging from 2.5 mg to 42.5 mg twice daily (BID) administered for a total duration of up to 4 weeks. CVL-865 has been safe and well tolerated.

CVL-865-SZ-001 is a 13-week, placebo-controlled, double-blind trial designed to assess the efficacy, safety, and tolerability profile of CVL-865 as adjunctive treatment in subjects with drug-resistant focal onset seizures. This 57-week, active-treatment, open-label extension trial is designed to assess the safety and tolerability of CVL-865 as adjunctive treatment in subjects with drug-resistant focal onset seizures. This trial is open to subjects who completed the Maintenance Phase in the double-blind Trial CVL-865-SZ-001 and who, in the opinion of the investigator, could potentially benefit from treatment with CVL-865.

2.3 Benefit/Risk Assessment

There are no important identified risks for CVL-865. Fetal toxicity, bone marrow suppression, and decrease in peripheral hematologic parameters are important potential risks; however, these risks will be minimized during the trial by monitoring of hematologic parameters and requiring the use of appropriate contraception and regular pregnancy testing.

In a Phase 2 trial using a photosensitivity model, CVL-865 demonstrated highly robust efficacy. This was shown by a marked and statistically significant mean reduction in standardized photosensitivity ranges to intermittent photic stimulations for single doses of 17.5 mg and 52.5 mg CVL-865 compared with placebo, which was similar to the lorazepam 2 mg active control.

Based on available safety and efficacy data for CVL-865, the benefit-risk profile is favorable.

More detailed information about the known and expected benefits and risks and expected adverse events (AEs) of CVL-865 are found in the Investigator's Brochure.

In response to the COVID-19 pandemic, Cerevel has performed a risk assessment of this trial and the investigator of each individual trial site and has implemented measures throughout the protocol, which prioritizes trial participant safety and data validity.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary: To assess the long-term safety and tolerability of CVL-865 as adjunctive therapy in subjects with focal onset seizures	• Nature, frequency, and temporality of treatment-emergent AEs (nonserious and serious), including abuse-related AEs and AEs related to medication handling irregularities • Clinically significant changes in ECGs, vital sign measurements, clinical laboratory assessments, and physical and neurological examination results • Suicidality assessed using the C-SSRS • Withdrawal symptoms assessed using the mCIWA-B
Exploratory: To assess the long-term efficacy of CVL-865 as adjunctive therapy in subjects with focal onset seizures	• Focal onset seizure frequency per week over the Maintenance Phase • Seizure freedom • Seizure rate over time • PGI-C score at each trial visit • Change from Baseline in CGI-S score at each trial visit
Exploratory: To evaluate the plasma exposure of CVL-865	• Summary listing of CVL-865 concentrations by dose and visit

Abbreviations: AE = adverse event; CGI-S = Clinical Global Impression – Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; mCIWA-B = Modified Clinical Institute Withdrawal Assessment – Benzodiazepines; PGI-C = Patient Global Impression of Change.

4 TRIAL DESIGN

4.1 Overall Design

This is a 57-week, active-treatment, open-label extension trial designed to assess the long-term safety and tolerability of CVL-865 as adjunctive therapy in subjects with focal onset seizures. Enrollment into the trial will consist of eligible subjects who completed the Maintenance Phase of Trial CVL-865-SZ-001.

Eligible subjects will enter this trial directly after completing Visit 4 (end of Maintenance Phase) of Trial CVL-865-SZ-001. The efficacy and safety assessments from Visit 4 of Trial CVL-865-SZ-001 will serve as the baseline assessments for the open-label trial for any assessments that are not unique to the open-label trial. All subjects must provide informed consent to participate in the open-label trial before any baseline assessments that are unique to the open-label trial are performed.

This trial is designed with a maximum duration of approximately 61 weeks during which the subjects will receive CVL-865. The trial consists of the following:

- Up to 57-week Treatment Period consisting of the following:

- 2-week double-blind Titration Phase
- 52-week Maintenance Phase
- 3-week Taper Phase

- 4-week Follow-up Period

Following enrollment in Trial CVL-865-SZ-002, subjects will enter a 2-week double-blind Titration Phase. Based on the blinded treatment group subjects were assigned to in Trial CVL-865-SZ-001, the dose will be adjusted during the double-blind Titration Phase to a final dose of 25 mg BID as shown in Table 4. Subjects who completed the Maintenance Phase of Trial CVL-865-SZ-001 on a dose of 25 mg BID will remain on this dose (blinded) for the Titration Phase of Trial CVL-865-SZ-002.

Subjects who terminate during the double-blind Titration Phase (before Day 15) should receive 3 weeks of IMP to complete the Taper Phase. Please refer to Section 7.3.

Subjects will continue to receive treatment with CVL-865 25 mg BID throughout a 52-week Maintenance Phase. However, this daily dose of CVL-865 can be reduced to 17.5 mg BID to address tolerability issues upon investigator discretion. Following the Maintenance Phase, subjects will be tapered off investigational medicinal product (IMP) over 3 weeks. A summary of the dosing schedule is provided in Table 4.

Table 4 Dosing Schedule

	Double-blind Titration Phase[a]		**Maintenance Phase[a]**	**Taper Phase[a]**		
Day of Dose Initiation	**Day 1**	**Day 8**	**Day 15**	**Day 380**	**Day 387**	**Day 394**
Duration	2 weeks		52 weeks	3 weeks		
Dose in Trial CVL-865-SZ-001						
Placebo	5 mg BID	12.5 mg BID	25 mg BID	17.5 mg BID	10 mg BID	5 mg BID
CVL-865 7.5 mg BID	12.5 mg BID	17.5 mg BID	25 mg BID	17.5 mg BID	10 mg BID	5 mg BID
CVL-865 25 mg BID	25 mg BID	25 mg BID	25 mg BID	17.5 mg BID	10 mg BID	5 mg BID
Not applicable[b]			17.5 mg BID[b]	10 mg BID	5 mg BID	2.5 mg BID

Abbreviations: BID = twice daily; IMP = investigational medicinal product.

a Quantity of IMP dispensed at each visit will accommodate ±3-day visit windows so subjects can remain on existing dose until next in-clinic visit.

b Subjects who had their dose reduced to 17.5 mg BID due to tolerability reasons during the Maintenance Phase.

Subjects are to continue treatment with at least 1 and up to a maximum of 3 concurrent AEDs (as permitted; see Table 6 for prohibited medications). The type and dosage of the concurrent AEDs may be adjusted per investigator discretion to optimize seizure control and/or tolerability during the Treatment Period and/or Follow-up Period.

Subjects will continue to record all seizures and the presence or absence of all seizure types experienced, in addition to recording the dosing with CVL-865 and AEDs and the use of seizure rescue medication in the electronic diary (eDiary) each day during the trial.

Follow-up Period:

Follow-up telephone contact will be performed 7±3 days after the last dose of IMP. A Post-treatment Follow-up Visit will be made approximately 4 weeks after last dose of IMP.

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 a trial treatment over an extended trial period.

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

4.3 Dosing Rationale

The 25 mg BID dose of CVL-865 has been selected based on the first-in-human safety and tolerability data, the pharmacodynamic profile, and the efficacious doses used in the clinical photosensitive epilepsy Trial B7431005. Single doses up to 100 mg have been safe and well tolerated and associated with mild adverse effects. No changes in ECGs or vital sign measurements have been observed at doses up to 100 mg. Multiple doses of CVL-865 up to 42.5 mg BID have been found to be safe and well tolerated in healthy adult subjects.

The 25 mg BID dose is the top dose used in Trial CVL-865-SZ-001 and projected to fully test the therapeutic potential of CVL-865 as adjunctive therapy in the treatment of focal onset seizures. This provides the opportunity for all the subjects in Trial CVL-865-SZ-001 to be administered with the top dose in the trial, in an open-label fashion. At the 25 mg BID dose, the steady-state exposure levels of CVL-865 are expected to be comparable with those at which the peak effects in saccadic peak velocity, a reliable biomarker of α2/3 activity, were observed following single dose (65 mg) administration (Trial B7431001). Likewise, the exposure levels are expected to be comparable with those at which efficacy was observed in a single-dose (52.5 mg) photosensitive epilepsy trial (Trial B7431005).

The relationship between $GABA_A$ receptor occupancy in the whole brain and plasma exposure levels of CVL-865 was characterized in an open-label, single-dose (10 and 65 mg) trial in healthy volunteers (Trial B7431004). Pharmacodynamic analysis of the $GABA_A$ receptor occupancy data indicated that nearly complete (ie, >80%) receptor occupancy was achieved at the peak exposure level of the 65 mg dose. More specifically, with respect to α2 receptor occupancy within the brain, the 25 mg BID dosing regimen is projected to achieve steady-state exposure levels of CVL-865 within the range anticipated to produce approximately 80% receptor occupancy.

4.4 Definition of Completed Subject

A subject is considered to have completed the trial if he/she has completed all phases of the trial including the last scheduled procedure (ie, Visit 17 assessments) as shown in the Schedules of Activities (Table 2 and Table 3).

4.5 End of Trial Definition

The end of the trial is defined as the date of the last visit (including phone contact) of the last subject in the trial.

5 TRIAL POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

1.	Subjects who completed treatment in Trial CVL-865-SZ-001 (ie, subjects who completed Visit 4 of Trial CVL-865-SZ-001).
2.	A female subject of childbearing potential (see Section 10.4, Appendix 4) who is sexually active with a nonsterilized male partner must agree to use a highly effective method of contraception (see Section 10.4, Appendix 4) from signing of informed consent through 30 days post last dose. A male subject with a pregnant or a nonpregnant partner of childbearing potential must agree to use a condom during treatment and until the end of relevant systemic exposure in the male subject for 94 days following the last dose with IMP.
3.	Subjects who are capable of giving signed informed consent as described in Section 10.1.3 (Appendix 1)
4.	Subjects who are able, in the opinion of the investigator, to understand the nature of the trial and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, and other trial procedures.

Abbreviations: BID = twice daily; ICF = informed consent form

5.2 Exclusion Criteria

Subjects are excluded from participation in the trial if any of the following criteria apply:

1.	Subjects who, in the opinion of the investigator, medical monitor, or sponsor, should not participate in the trial.
2.	Subjects who, in the judgment of the investigator, experienced poor tolerability to the IMP during the double-blind trial or whose safety assessments resulted in new concerns that would suggest that the subject may not be appropriate for 57 weeks of treatment with CVL-865 in an extension trial.
3.	Subjects who experienced status epilepticus during Trial CVL-865-SZ-001.
4.	Subjects who have demonstrated substantial noncompliance to trial procedures in Trial CVL-865-SZ-001, based on the investigator's judgement, would not be eligible for this trial. The medical monitor should be contacted if the investigator is unsure of a subject's eligibility.
5.	Subjects who answer "yes" on the C-SSRS Suicidal Ideation Item 4 or Item 5 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan, or Active Suicidal Ideation with Specific Plan and Intent), **OR** Subjects who answer "yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior), **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide.
6.	Subjects with any of the following abnormalities in clinical laboratory tests at Visit 1, as assessed by the central laboratory and confirmed by a single repeat measurement, if deemed necessary: • Females: Hemoglobin <10 g/dL; Males: hemoglobin <11 g/dL • White blood cell (WBC) count $<3.0 \times 10^9$/L • Neutrophil count $<2.0 \times 10^9$/L • Platelet count $<150 \times 10^9$/L
7.	Subjects who would be likely to require the use of prohibited concomitant medications during the trial (as listed in Table 6).
8.	Female subjects who have a positive pregnancy test result.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects should adhere to their normal or prescribed dietary regimen during the trial, although subjects must refrain from ingesting preparations containing St. John's Wort. Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of IMP until completion of Visit 17.

5.3.2 Alcohol, Caffeine, and Tobacco Restrictions

Subjects should adhere to their usual regimen of caffeine and tobacco, if applicable. As the potential for interactions between IMP and alcohol have not yet been evaluated, subjects are strongly discouraged from consuming alcohol for the duration of the trial.

5.3.3 Effects on Ability to Drive and Use Machinery

The effect of CVL-865 on the ability to drive and use machines has not been systematically evaluated.

5.4 Screen Failures

Screen failures are subjects who consent to participate in this clinical trial but are deemed not eligible or withdraw consent prior to receiving IMP in Trial CVL-865-SZ-002, defined as any IMP taken after the ICF has been signed by the subject.

Please refer to Section 7.3 for further guidance regarding subjects who sign the ICF but are deemed not eligible for Trial CVL-865-SZ-002.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) should not be rescreened.

6 TRIAL TREATMENTS

Trial treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial subject according to the trial protocol. Investigational medicinal product refers to a pharmaceutical form of any active substance or placebo being tested in this clinical trial and will be used to refer to the trial treatment in this protocol.

6.1 Investigational Medicinal Product Administered

A summary of the IMP administered during this trial is presented in Table 5.

Table 5 Investigational Medicinal Product Administered

Treatment	**CVL-865 25 mg BID**	**CVL-865 17.5 mg BID**
Dose Formulation	Tablet	Tablet
Unit Dose Strengths	2.5 mg, 5 mg, and 7.5 mg	2.5 mg, 5 mg, and 7.5 mg
Route of Administration	Oral	Oral

Treatment	CVL-865 25 mg BID	CVL-865 17.5 mg BID
Sourcing	Provided to the site by Cerevel	
Packaging and Labeling	IMP will be provided in blister packs and should be stored in its original pack in accordance with the drug label. Blister packs will be labeled according to local regulatory requirements.	

Abbreviations: BID = twice daily; IMP = investigational medicinal product

Subjects will receive blister packs with the appropriate combination of tablets necessary in order to achieve the required dose level.

6.2 Preparation/Handling/Storage/Accountability/Disposition

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

Only subjects enrolled in the trial may receive IMP and only authorized 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 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 IMP are provided in appropriate protocol-specific manuals.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label trial with all subjects assigned to treatment with CVL-865. To ensure that the treatment assignments in the Phase 2 double-blind trial CVL-865-SZ-001 remain blinded for the subjects who rollover into the open-label trial, all subjects will be dispensed blinded CVL-865 tablets during the Titration Phase of this trial.

6.4 Trial Treatment Compliance

All IMP will be dispensed by responsible trial personnel. Subjects will be counseled on the importance of taking the IMP as directed at each clinic visit and will be instructed to bring all used and unused blister cards to each clinic visit. Accountability and compliance (as assessed through self-reporting by the subject and by tablet count at each clinic visit) will be documented in the subject's trial records. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

If poor compliance is encountered (eg, multiple missed doses resulting in <80% overall compliance at any point in the trial), discontinuation of the subject from the trial should be considered. Subjects 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 medical monitor should be contacted if the investigator is uncertain whether a subject's lack of compliance merits discontinuation from the trial.

6.5 Prior and Concomitant Therapy

6.5.1 Prior and Concomitant Medications

The investigator will record all medications and therapies (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken by the subject from the time of signing the informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) on the eCRF. The investigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) on the eCRF.

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.

All subjects should be counselled on the importance of taking background medications as prescribed.

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

Table 6 lists all medications prohibited during the trial, including exceptions where appropriate.

Use of BZDs during trial is permitted except in cases specifically defined below.

Table 6 Prohibited Concomitant Medications

	Prohibited Concomitant Medications
1.	Vigabatrin, unless administered to subject in Trial CVL-865-SZ-001
2.	Felbamate unless administered to subject in Trial CVL-865-SZ-001, with a stable dose for ≥49 days
3.	Moderate to strong inducers and inhibitors of CYP3A4 metabolism (see Section 10.5, Appendix 5).
4.	P-gp substrates with a narrow therapeutic index (eg, digoxin, dabigatran)
5.	BCRP substrate rosuvastatin
6.	Psychotropic agents including, but not limited to, the following: a) Antipsychotics b) Non-benzodiazepine anxiolytics, unless medically prescribed and used in a stable, consistent manner c) Non-benzodiazepine sleep medications 1) Non-benzodiazepine sleep medications (ie, zolpidem, zaleplon, and eszopiclone) are permitted if medically prescribed and used no more than twice per week
7.	Drugs that can lower the seizure threshold: a) Tricyclic antidepressants and bupropion 1) Other antidepressants may be included if medically prescribed and used in a stable, consistent manner b) Stimulants, eg, amphetamine, dextroamphetamine, and methylphenidate c) Other – baclofen, dalfampridine, tramadol, buspirone, lithium

Abbreviations: BCRP = breast cancer resistance protein; CYP = cytochrome P450; P-gp = P-glycoprotein

6.5.2 Rescue Medicine

All subjects who normally take BZDs for seizure rescue had an individualized Rescue Protocol approved by TESC in use during Trial CVL-865-SZ-001. This Rescue Protocol describes what rescue treatment can be administered in the event the subject requires a BZD. It also includes different scenarios that would prompt immediate medical attention. The rescue protocol will remain in place for this extension protocol.

6.6 Dose Modification

The dose of CVL-865 will be titrated in a blinded manner for all subjects, as shown in Table 4.

The daily dose of CVL-865 (25 mg BID) can be reduced to 17.5 mg BID to address tolerability issues upon investigator discretion, as described in Section 4.1. An associated AE must be recorded in the eCRF.

A subject may temporarily interrupt IMP for the following reasons:

- Adverse events

6.7 Intervention after the End of the Trial

At the end of the trial, all subjects will resume treatment with available AEDs at the discretion of and as determined by their physician.

7 DISCONTINUATION OF TRIAL TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and regulatory authorities in accordance with regulatory requirements.

7.2 Discontinuation of Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

7.3 Individual Subject Discontinuation

After treatment assignment, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator.

Subjects should begin the Taper Phase at the time the decision is made to discontinue. All Taper Phase and Post-treatment Follow-up procedures should be performed as indicated in the Schedules of Assessments (Table 2 and Table 3). Under certain circumstances, when subjects leave the trial early, dosing with the taper medication or continuing with the taper phase medication may be inadvisable. The decision not to taper the subject is upon agreement from the medical monitor. If the taper will not be utilized, then all assessments required at Visit 17 should be conducted approximately 30 days following the last dose.

For subjects who early terminate prior to Day 15 (prior to the Maintenance Phase), an alternate taper scheme may be used. This includes subjects who sign consent for CVL-865-SZ-002 but who are then determined to not meet eligibility criteria.

A subject will discontinue IMP for the reasons listed below:

- Any of the following AESIs

- Hemoglobin <8 g/dL
- WBC count <2.5 × 10^9/L
- Neutrophil count <1.5 × 10^9/L
- Platelet count <100 × 10^9/L

- Female subjects who have a positive pregnancy test result during the trial
- Withdrawal of consent
- Investigator's discretion (eg, including failure to comply with trial procedures or dosing)

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to interrupt or modify or discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation. A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.5 Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site personnel.

The following actions must be taken if a subject fails to return to the site for a required trial visit:

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

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

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the trial

8 TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the Schedule of Assessments (Table 2 and Table 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 subject should continue or discontinue IMP.

Adherence to the trial design requirements, including those specified in the Schedule of Assessments (Table 2 and Table 3), is essential and required for trial conduct.

8.1 Screening/Baseline Assessments

The timing for all screening/baseline assessments is provided in the Schedule of Assessments (Table 2 and Table 3).

A review of all inclusion and exclusion criteria will occur at Visit 1 (screening/baseline visit) to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable. As there may be a delay in obtaining all relevant assessments (eg, laboratory results) prior to subject enrollment in Trial CVL-865-SZ-002, if any data from assessments are obtained after enrollment and indicate the subject would not be eligible to continue in the extension trial, the medical monitor should be contacted.

Subjects will continue to record the presence or absence of all seizure types experienced daily in the eDiary from Visit 1 through Visit 17 (end of follow-up period). Site personnel should classify the seizure type based upon the description provided by the subject in the eDiary and, if needed, via further discussion with the subject. If a new seizure type occurs during the trial, the seizure category will be evaluated by the investigator and, if confirmed to be new, and not reported previously, it will be submitted to TESC for review. If seizures do not occur on any given day, lack of seizures is also recorded. Subjects will also record any use of benzodiazepines and dosing with CVL-865 in the eDiary.

8.2 Efficacy Assessments

8.2.1 Seizure Frequency and Type (eDiary)

Subjects will record details regarding their seizures (frequency and type) in an eDiary. Any benzodiazepine use will also be recorded in the diary.

Seizure frequency and type will be assessed based on information recorded by the subject in the eDiary (see Section 8.1).

8.2.2 Patient Global Impression of Change

The self-report measure Patient Global Impression of Change (PGI-C) reflects a patient's belief about the efficacy of treatment. It is a 7-point scale depicting a patient's rating of overall improvement. Patients rate their change as ''very much improved,'' ''much

improved,'' ''minimally improved,'' ''no change,'' ''minimally worse,'' ''much worse,'' or ''very much worse.''

8.2.3 Clinical Global Impression-Severity Scale

The Clinical Global Impression – Severity (CGI-S) is an observer-rated scale that will be used to measure symptom severity. It is important to note that the observer or rater will provide their assessment of the subject's symptoms at the time of the current visit.

To perform this assessment, the investigator (or designee) will answer the following question: "Considering your total clinical experience with this particular population, how ill is the subject at this time?" Response choices are 0 = not assessed; 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Table 2 and Table 3).

For the assessments described below, when multiple procedures are scheduled on the same visit, the following chronology of events should be adhered to, where possible:

- ECGs, obtain prior to vital sign measurements
- Blood pressure/heart rate, obtain prior to procurement of blood specimens
- Blood specimen collection
- Other procedures: all other procedures may be obtained before or after blood specimen collection

8.3.1 Physical and Neurological Examinations

A complete physical examination will consist of measurement of weight and a review of the following body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, genitourinary, and musculoskeletal systems. If the investigator/designee is unable to perform a genitourinary examination, special attention will be given to the genitourinary medical history. A prior record (within 12 months of enrolling into CVL-865-SZ-001) of a recent genitourinary examination from a gynecologist or family doctor can substitute for a genitourinary examination.

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

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

- The same scale should be used to weigh a given subject each time, if possible
- Scales should be calibrated and reliable; scales should be at zero just prior to each subject's weigh-in session
- A subject should void prior to being weighed and be minimally clothed (ie, no shoes or heavy overgarments)
- To the best of the subject's and site personnel's ability, weight should be recorded before a subject's meal and at approximately the same time at each visit

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

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

8.3.2 Vital Sign Measurements

Vital sign measurements will include body temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and heart rate.

Vital signs will be measured with the subject in a sitting/semi-recumbent position after 5 minutes rest.

A properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring blood pressure and heart rate is acceptable, although, when done manually, heart rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and heart rate should be obtained prior to the nominal time of the blood collection.

Body temperature will be measured with either an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (ie, oral or tympanic) must be used for all measurements for each individual subject and should be the same for all subjects.

Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF.

8.3.3 Electrocardiograms

Electrocardiogram recordings will be obtained after the subject has been at rest for at least 5 minutes. Additional ECGs may be obtained at the investigator's discretion and should always be obtained in the event of early termination. The ECG results will be evaluated at the investigational site to determine the subject's eligibility and to monitor safety during the trial. The investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF. The ECG will be repeated if any results are considered to be clinically significant. A central ECG service will be used for reading all ECGs in order to standardize interpretations for the safety analysis.

8.3.4 Clinical Safety Laboratory Assessments

See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the Schedule of Assessments (Table 2 and Table 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 in the AE section of the eCRF. 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 such 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 assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the Schedule of Assessments (Table 2 and Table 3).

8.3.5 Modified Clinical Institute Withdrawal Assessment Scale – Benzodiazepines

The modified Clinical Institute Withdrawal Assessment Scale – Benzodiazepines (mCIWA-B) is a sensitive instrument to measure withdrawal under conditions where there is a taper of medication (rather than abrupt discontinuation). It consists of 17 items that monitor the type and severity of benzodiazepine withdrawal symptoms such as irritability, fatigue, appetite, and sleeplessness (Busto et al, 1989). The clinician-observed assessments of sweating, restlessness (pacing), and tremor that are included in the overall version have been removed from this modified version. The total score ranges from 1 to 68 with higher scores indicating more severe withdrawal.

8.3.6 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. Training on the scale will be provided via the sponsor or designee.

The "Since Last Visit" C-SSRS form will be completed at all visits. The investigator will review the results of the "Since Last Visit" C-SSRS during the trial to determine whether it is safe for the subject to continue in the trial. If a subject demonstrates potential suicidal ideation associated with actual intent or method or plan as indicated by "YES" answers on item 4 or 5 of the C-SSRS, the investigator will need to evaluate whether a risk assessment by a qualified mental health professional (MHP, or the investigator alone if the investigator is a qualified MHP) is needed and whether the subject should continue in the trial or be discontinued.

8.4 Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject'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 or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or trial procedures, or that caused the subject to discontinue IMP (see Section 7)

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit (Visit 17 at Day 428) at the time points specified in the Schedule of Assessments (Table 2 and Table 3).

All SAEs will be recorded and reported to the medical monitor immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the medical monitor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the trial, and he/she considers the event to

be reasonably related to the IMP or trial participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

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

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.5). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the medical monitor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) 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.

8.4.5 Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of IMP and until the final contact at Visit 17. At a minimum, monthly pregnancy tests will be completed throughout the trial for all women of

childbearing potential. During periods where monthly visits are not scheduled, female subjects can choose to visit the site for the test or complete the test via a remote option.

If a pregnancy is reported, the investigator should inform the medical monitor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

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

8.4.6 Adverse Events of Special Interest

8.4.6.1 Adverse Events Potentially Related to Abuse or Dependence

A key objective of the Abuse Potential Monitoring Plan (APMP) is to monitor for instances of abuse or diversion of the trial medication and other psychoactive substances.

In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue will also receive special attention. As part of the APMP, medication handling irregularities (MHIs) must be reported, and AEs related to abuse potential and AEs involving MHIs must be reported as AEs of special interest (AESIs) with 24 hours to the sponsor with detailed narratives.

Investigators and site staff at each trial site will be trained on reporting potentially abuse related AEs (eg, recording a description of the event in the subject's own words in the source documents as well as the eCRF, in addition to the clinical term, and to be aware that a subject's report may encompass more than one event and that these should be recorded separately). The investigators will be provided with examples of potentially abuse-related AEs and trained on how to handle such events (eg, additional monitoring).

While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs by the sponsor will be based on a search of all relevant Medical Dictionary for Regulatory Activities (MedDRA) terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, in line with the 2017 Food and Drug Administration guidance (Guidance for Industry, 2017). Refer to the separate APMP documentation for complete details on MHIs and events subject to additional monitoring (ESAMs), including documenting and reporting procedures, examples of potentially abuse-related AE terms that meet the criteria for ESAM reporting, and guidance for the training of investigators and trial site staff.

The following AEs are considered indicative of potential abuse for the CVL-865 mechanism of action:

- Abnormal behavior
- Abnormal dreams
- Amnesia
- Any reports of altered perception or hallucinations

- Apathy
- Balance disorder
- Cognitive disorder
- Depressed level of consciousness
- Depressed mood
- Dizziness
- Euphoric mood
- Feeling drunk
- Feeling of relaxation
- Sedation
- Somnolence

Narratives will be completed for the above terms; information included in the narratives will consist of time to onset/offset, time course of severity, all concurrent events, concurrent medications, and time of onset of events relative to ingestion of IMP.

8.4.6.2 Hematologic Abnormalities

The occurrence of any of the following hematologic abnormalities must be reported as AESI to the sponsor with 24 hours and the clinical course must be discussed with the medical monitor. Management of AESIs should follow instructions described in Table 7.

- Hemoglobin: females <10 g/dL; males <11 g/dL
- WBC count $<3.0 \times 10^9$/L
- Neutrophil count $<2.0 \times 10^9$/L
- Platelet count $<150 \times 10^9$/L

Treatment with study drug must be discontinued if a subject develops any of the following hematologic abnormalities and should be managed as described in Table 7:

- Hemoglobin <8 g/dL
- WBC count $<2.5 \times 10^9$/L
- Neutrophil count $<1.5 \times 10^9$/L
- Platelet count $<100 \times 10^9$/L

Table 7 Management of Hematologic Abnormalities

Hematologic Abnormalities	Management
Hemoglobin: females <10 g/dL; males <11 g/dL WBC count <3.0 × 10^9/L Neutrophils <2.0 × 10^9/L Platelet count <150 × 10^9/L	Concomitant therapies and medical history should be reviewed CBC should be rechecked regularly until CBC returns to near baseline value The finding must be reported as an AESI and must be discussed with the medical monitor
Hemoglobin <8 g/dL WBC count <2.5 × 10^9/L Neutrophils <1.5 × 10^9/L Platelet count <100 × 10^9/L	Treatment with study drug should be permanently discontinued Concomitant therapies and medical history should be reviewed CBC should be rechecked regularly until CBC returns to near baseline value The finding must be reported as an AESI and must be discussed with the medical monitor

Abbreviations: AESI = adverse event of special interest; CBC = complete blood count; WBC = white blood cell

8.4.6.3 Abnormal Liver Function Tests

The finding of an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal range (ULN) in combination with either an elevated total bilirubin >2 × ULN or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report the occurrence of either of the following as an AESI to the sponsor with 24 hours:

- Treatment-emergent ALT or AST >3 × ULN and total bilirubin >2 × ULN
- Treatment-emergent ALT or AST >3 × ULN in combination with clinical jaundice

8.5 Treatment of Overdose

For this trial, any dose of CVL-865 greater than 80 mg within a 24-hour time period (+2 hours) will be considered an overdose.

There is no specific antidote for overdose with CVL-865. Treatment of overdose should consist of general supportive measures. In the event of an overdose, the investigator should complete the following:

1. Contact the medical monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until CVL-865 can no longer be detected systemically (at least 3 days).
3. Document the quantity of the excess dose as well as the duration of the overdose 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 subject.

8.6 Pharmacokinetics

8.6.1 Blood Samples for CVL-865 Concentrations

Samples for determination of CVL-865 concentrations will be collected in appropriately labeled tubes as specified in the Schedule of Assessments (Table 2 and Table 3). Additional instructions are provided in the Laboratory Flow Chart.

8.6.2 Blood Samples for Anti-epileptic Drug Concentrations

Samples for determination of concentrations of adjunctive AEDs will be collected in appropriately labelled tubes as specified in the Schedule of Assessments (Table 2 and Table 3). Additional instructions are provided in the Laboratory Flow Chart.

8.6.3 Methods and Analysis

Additional details regarding the collection, processing, storage, and shipping of all pharmacokinetic (PK) plasma samples will be provided in a laboratory manual. All plasma samples will be analyzed for analyte using a validated bioanalytical method. CVL-865 plasma samples collected in this trial may be used for other exploratory purposes, eg, method development, identification of metabolites and metabolite scouting. Results of such analyses will not be reported in the Clinical Study Report (CSR).

8.7 Pharmacodynamics

Not applicable.

8.8 Pharmacogenomics

Not applicable.

8.9 Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There is no statistical hypothesis for this open-label trial.

9.2 Sample Size Determination

The sample size is not based on statistical power considerations. The trial population will be derived from eligible subjects from the double-blind, proof-of-concept

Trial CVL-865-SZ001. Approximately 120 subjects are expected to complete Trial CVL-865-SZ-001 and be eligible for enrollment in Trial CVL-865-SZ-002.

9.3 Populations for Analyses

The following data sets are defined for analysis:

- Enrolled Set: comprises all subjects who consent to participate in the clinical trial (ie, sign the ICF for Trial CVL-865-SZ-002)
- Safety Set: comprises all subjects that receive at least 1 dose of IMP in Trial CVL-865-SZ-002
- Efficacy Set: comprises all subjects in the Safety Set who have at least 1 post-baseline efficacy evaluation

9.4 Statistical Analyses

Descriptive statistical methods will be used to summarize the data from this trial. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. All available data for enrolled subjects will be listed by subject. Unless otherwise noted, the data will be sorted first by subject number and then by date within each subject number. All statistical analyses will be conducted with the SAS® System, version 9.4 or higher.

A statistical analysis plan (SAP) will be developed and finalized before database lock and will provide descriptions of the subject populations to be used in the analysis and procedures for addressing missing, unused, and spurious data. This section is a summary of the planned statistical analyses.

9.4.1 Safety Analyses

The safety analysis will be conducted on the Safety Set. The primary safety analysis is the frequency and severity of AEs during the Treatment Period. All AEs will be coded according to MedDRA preferred term. The incidence of treatment-emergent AEs (TEAEs) will include the following summaries:

- TEAEs by severity
- Drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs

- TEAEs potentially related to abuse as assessed through the active monitoring of adverse events related to potential abuse and adverse events involving MHI

A TEAE is defined as an AE that started after the first dose of IMP in the open-label trial or a previously reported AE that increased in intensity, became serious, trial drug-related, or resulted in death, discontinuation, interruption, of reduction of IMP after the first dose of IMP in the open-label trial.

Other safety endpoints, including laboratory assessments, vital sign measurements, ECGs, medication withdrawal symptoms assessed by the mCIWA-B total scores at the scheduled visits and suicidality monitored during the trial using C-SSRS, will be summarized with descriptive statistics. Baseline is defined as the last assessment prior to the initiation of IMP in CVL-865-SZ-002. Additional presentations may be conducted evaluating changes from the original trial baseline. These analyses will be detailed in the statistical analysis plan.

9.4.2 Exploratory Analyses

Descriptive statistics will be provided for each efficacy endpoint and will be summarized at each trial visit using available data. Baseline is defined as the last assessment prior to the initiation of IMP in CVL-865-SZ-002. Additional presentations may be conducted evaluating changes from the original trial baseline. These analyses will be detailed in the statistical analysis plan.

9.4.3 Other Analyses

The CVL-865 concentration data will be used to determine the extent to which subjects attain exposure levels within the range predicted at each dosing regimen. Likewise, the AED concentration data will be used to review the exposure levels of AED taken with or without CVL-865. Appropriate tabular and/or graphical summaries of all PK concentration data will be generated as detailed in the SAP.

Concentration data from this trial may be used to update the previously established population PK model for CVL-865. Any population PK analysis (if completed) will be presented separately from the main CSR.

9.5 Interim Analyses

No interim analyses are planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 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 International Council for Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

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, European 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 regulatory 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 subject and answer all questions regarding the trial.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 requirements, where applicable, and the IRB/IEC or trial center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the trial.

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

A separate and similar consent process will be followed for the optional future biospecimen research samples. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data Protection

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

The subject 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 subject and outlined in the ICF.

The subject 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 regulatory authorities.

10.1.5 Dissemination of Clinical Trial Data

Cerevel fulfills its commitment to publicly disclose clinical trial results through posting trial results on ClinicalTrials.gov, the European Clinical Trials Database (EudraCT), 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 subjects 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 4.5 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

Cerevel posts European Union (EU) Basic Results on EudraCT for all Cerevel-sponsored interventional trials that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.5 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 subject 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.

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

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency 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 on-site 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, Contract Research Organizations).

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 subjects 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.

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 developments is discontinued, the date regulatory authorities were notified of discontinuation
- At least 3 years after the sponsor notified the investigator that the final reports has been filed with regulatory authorities
- A longer period if required by local regulations or institutional policies

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

10.1.7 Source Documents

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

Data 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.

10.1.8 Trial and Site Closure

The sponsor or designee reserves the right to close the 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 the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- 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 subjects by the investigator
- Discontinuation of further trial treatment development

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 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 8 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects 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.

Urine (serum tests to confirm any positive urine test) pregnancy tests are required for women of childbearing potential (WOCBP) at the time points indicated in the Schedule of Assessments; however, a serum pregnancy test can be done anytime during the trial at the investigator's discretion.

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	Red Blood Cell Indices:	White blood cell Count with Differential:	
	Red blood cell Count	Mean Corpuscular Hemoglobin	Neutrophils	
	Hemoglobin	Mean Corpuscular Volume	Lymphocytes	
	Hematocrit	%Reticulocytes	Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry	Blood urea nitrogen	Potassium	Aspartate Aminotransferase	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Chloride
	Bicarbonate			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)			
Additional Required Tests	Urine drug screen for illicit drugs Urine dipstick pregnancy test (at time points indicated in Schedules of Assessments and as needed for women of childbearing potential), followed by serum pregnancy test if urine dipstick test is positive.			

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

Laboratory results that could unblind the trial will not be reported to investigative sites or other blinded personnel until the trial has been unblinded.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

Table 9 Definition of AE

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

Table 10 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 treatment 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 treatment or a concomitant medication. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. 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 11 Definition of SAE

A 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 subject 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 subject 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 subject 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. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

Table 12 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

• When an AE/SAE 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.
• The investigator will then record all relevant AE/SAE information in the eCRF.
  ○ Nonserious AEs that are identified at any time during the trial 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 on the eCRF. For any AE having been identified throughout the trial, 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 status becomes available after a subject'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 until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject'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 subject is lost to follow-up, or has died.
  ○ Any new SAEs 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 that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs 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 subject is lost to follow-up or has died.
• It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the AE/SAE 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 subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- 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 treatment 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, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE 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 data to the sponsor or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Table 13 Follow-Up of AEs and SAEs

Follow-Up of AEs and SAEs
• 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 as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject 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 data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs and AESIs

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

SAE/AESI Reporting to the Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE or 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 SAE or AESI form (see next section). • After the trial is completed, the electronic data collection tool will be set to read-only to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE or AESI from a trial subject or receives updated data on a previously reported SAE or AESI after the electronic data collection tool has been taken off-line, then the site can report this information on the paper SAE or AESI form (see next section) or to the sponsor or designee by telephone. •

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

SAE Reporting to the Sponsor or Designee via Paper Form
• If the electronic data collection tool is unavailable, then the site will use the paper SAE/AESI form. The SAE or AESI paper form should be used to electronically transmit this information to the sponsor or designee. • Contacts for electronic transmission of the paper SAE/AESI 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 SAE or AESI 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 SAE or AESI form within the designated reporting time frames. •

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

10.4.1.1 Highly Effective Form of Contraception

A highly effective form of contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion

- Vasectomized partner

10.4.1.2 Contraception and Pregnancy Avoidance Procedures

The following definitions apply for contraception and pregnancy avoidance procedures:

A woman is considered a WOCBP following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Sterilized male subjects should be at least 1 year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

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

- 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 6 to 8 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.

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject 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 subject's pregnancy.

- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 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 treatment by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former trial subjects, he or she may learn of an SAE through spontaneous reporting.

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

10.5 Appendix 5: Inducers and Inhibitors of Cytochrome P450 3A

CYP 3A Inhibitors	CYP 3A Inducers
HIV antivirals	**HIV antivirals**
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Etravirine
Saquinavir	**Miscellaneous**
Boceprevir	Barbiturates
Lopinavir/ritonavir	Carbamazepine
Amprenavir	Eslicarbazepine
Atazanavir	Glucocorticoids (systemic)
Telaprevir	Modafinil
Darunavir/ritonavir	Oxcarbazepine[d]
Fosamprenavir	Phenobarbital
Antibiotics	Phenytoin
Clarithromycin	Pioglitazone
Erythromycin	Rifabutin
Telithromycin	Rifampin
Ciprofloxacin	St. John's wort
Anti-infectives	Troglitazone
Itraconazole	Bosentan
Ketoconazole	Nafcillin
Fluconazole	Avasimibe
Posaconazole	
Voriconazole	
Anti-anginal therapy	
Diltiazem	
Verapamil	
Anti-cancer therapy	
Crizotinib	
Imatinib	
Miscellaneous	
Nefazodone	
Aprepitant	
Grapefruit juice[a,b]	
Conivaptan	
Mibefradil[c]	

a The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

b A 2-week washout prior to dosing is required if grapefruit juice was being consumed continually.

c Withdrawn from the United States market.

d Doses >900 mg/day.

10.6 Appendix 6: Abbreviations

Abbreviation	Definition
AE	Adverse event
AED	Anti-epileptic drug
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AST	Aspartate aminotransferase
BID	Twice daily
BZD	Benzodiazepine
CBC	Complete blood count
CGI-S	Clinical Global Impression-Severity
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ESAM	Events Subject to Additional Monitoring
EudraCT	European Clinical Trials Database
$GABA_A$	γ-aminobutyric acid type A
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
mCIWA-B	Modified Clinical Institute Withdrawal Assessment–Benzodiazepines
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication handling irregularity
MHP	Mental Health Professional
PAM	Positive allosteric modulator

Abbreviation	Definition
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetic
SAE	Serious adverse events
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TESC	The Epilepsy Study Consortium
ULN	Upper limit of normal range
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

10.7 Appendix 7: Protocol Amendment History

Document History	
Document:	**Date (Day-Month-Year)**
Version 3.0	14 Jul 2020
Version 2.0	26 Nov 2019
Original Protocol Version 1.0	30 Oct 2019

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment: Protocol Version 2.0 (26 Nov 2019)

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

Overall Rationale for the Amendment: To revise relevant sections of the protocol to minimize potential risk to subjects.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema 1.3 Schedule of Activities	Changed Contact Only visits during Maintenance Phase to in-clinic visits Scheduled additional safety laboratory blood samples during Maintenance Phase (ie, for visits that been Contact Only in original protocol) and at Post-Treatment Follow-up in-clinic visit Reduced intervals between some Maintenance Phase visits such that interval between visits was not more than 4 weeks	Monitoring of new potential risk of bone marrow suppression and decrease in peripheral hematologic parameters
2.3 Benefit/Risk Assessment 5.2 Exclusion Criteria 7.3 Individual Subject Discontinuation 8.4.6.2 Hematologic Abnormalities	Added potential risk of bone marrow suppression and decrease in peripheral hematologic parameters Updated relevant risk minimization measures, exclusion criterion, criteria for discontinuation of IMP, and added new AESI subsection	Update relevant protocol section with new potential risk of bone marrow suppression and decrease in peripheral hematologic parameters
8.3.2 Vital Sign Measurements	Reworded paragraph about blood pressure measurement	Simplification of vital signs collection procedure
Table 9 Protocol-Required Safety Laboratory Assessments	Added chloride and bicarbonate	Additional biochemistry labs for safety monitoring
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Revision of definitions and language for pregnancy avoidance procedure	Consistency with preceding double-blind protocol
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Reflect changes to visit numbers, visit timing, and visit types (ie, contact visits changed to in-clinic visits), due to changes to schedule of activities Correct errors in original protocol

Abbreviations: AESI = adverse event of special interest; IMP = investigational medicinal product; WBC = white blood cell.

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CLINICAL PROTOCOL PRINCIPAL INVESTIGATOR SIGNATURE PAGE

A 57-WEEK, MULTICENTER, ACTIVE-TREATMENT, OPEN-LABEL EXTENSION TRIAL OF CVL-865 AS ADJUNCTIVE THERAPY IN ADULTS WITH DRUG-RESISTANT FOCAL ONSET SEIZURES

Protocol Number: CVL-865-SZ-002

Compound Number: CVL-865

Trial Phase: 2

Sponsor Name: Cerevel Therapeutics, LLC

Legal Registered Address: 131 Dartmouth Street, Suite 502, Boston MA 02116 United States

Version 3.0: 14 Jul 2020

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)