CLINICAL PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTICENTER TRIAL OF CVL-865 AS ADJUNCTIVE THERAPY IN ADULTS WITH DRUG-RESISTANT FOCAL ONSET SEIZURES (REALIZE TRIAL)

Protocol Number: CVL-865-SZ-001

Compound Number: CVL-865

Trial Phase: 2

Short Title: A Trial of the Efficacy and Safety 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
EudraCT	2019-002576-14

CONFIDENTIAL – PROPRIETARY INFORMATION

Version 4.0: 30 Jun 2020

Version 3.0: 15 Nov 2019

Version 2.0: 03 Oct 2019

Original Version 1.0: 24 Jul 2019

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

Sponsor Signatories:

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30JUN2020
Date

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PROTOCOL VERSION 4.0 SUMMARY OF CHANGES TABLE

Document History	
Document:	**Date (Day-Month-Year)**
Version 4.0	30 Jun 2020
Version 3.0	15 Nov 2019
Version 2.0	03 Oct 2019
Original Protocol Version 1.0	24 Jul 2019

Amendment: Protocol Version 4.0 (30 Jun 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**
1.1 Synopsis 3 Objectives and Endpoints 9.4.1 Efficacy Analyses	Changed the order of the 2 key secondary endpoints	To reflect the sponsor's decision to allow a hierarchical testing sequence
1.1 Synopsis 9.2 Sample Size Determination	Added provision to extend enrollment to maintain the planned statistical power in the event of higher than expected early terminations due to COVID-19 or other reasons	Unknown effect of COVID-19 pandemic on trial enrollment
1.3 Schedule of Assessments	Added a footnote to Table 2 to provide an option for specific visits to be completed remotely Added option for COVID-19 testing Deleted portion of footnote in Table 2 about obtaining PK sample at Visit 6	To reflect risk assessment measures by sponsor to prioritize trial participant safety Correct typographical error
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

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 and prior use of prohibited medications	Simplify language by referring to the respective tables that specify prohibited medications before and during the trial
5.2 Exclusion Criteria 8.3.3 Electrocardiograms	Specify that QTcF interpretation at screening is according to central ECG service reading Align ECG exclusion criterion with methods for obtaining ECGs	Address inconsistency in previous version of the protocol and provide clarification regarding results interpretation
6.7 Intervention after the End of the Trial	Deleted sentence about subjects who require withdrawal from the trial being potentially eligible for entry into the open-label extension trial	Correct error (subjects who do not complete the trial are not eligible for the open-label extension)
8.6 Pharmacokinetics	Simplified wording about sample collection (Sections 8.6.1 and 8.6.2) Revised sample analysis wording (Section 8.6.3)	Remove duplication of details provided in other materials Clarify that only treatment samples will be analyzed
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 serum and 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
10.6 Appendix 6: 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 Reflect consistency of roles across protocols

Section # and Name	Description of Change	Brief Rationale
Overall	Minor grammatical and wording corrections or clarifications throughout protocol	Correct errors in the previous version of the protocol

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CYP = cytochrome P450; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event; WBC = white blood cell

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1 PROTOCOL SUMMARY

1.1 Synopsis

Sponsor Name: Cerevel Therapeutics, LLC

Name of Investigational Medicinal Product: CVL-865

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Parallel group, Multicenter Trial of CVL-865 as Adjunctive Therapy in Adults with D**R**ug-R**E**sist**A**nt Foca**L** Onset Se**IZ**ur**E**s (REALIZE Trial)

Short Title: A Trial of the Efficacy and Safety of CVL-865 as Adjunctive Therapy in the Treatment of Focal Onset Seizures

IND Number: 126,900

EudraCT Number: 2019-002576-14

Trial Phase: 2

Treatment/Indication: Focal Onset Seizures

Rationale: This placebo-controlled, double-blind trial is designed to assess the efficacy, safety, and tolerability profile of CVL-865 as adjunctive treatment in subjects with drug-resistant focal onset seizures.

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.

A double-blind, placebo-controlled trial is an appropriate design in which to assess initial efficacy with CVL-865. This proof-of-concept trial will assess whether CVL-865 demonstrates efficacy compared with placebo, as measured by a decrease in seizure frequency in subjects with a diagnosis of epilepsy with drug-resistant focal onset seizures.

Objectives and Endpoints

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary: To evaluate the efficacy of CVL-865 as adjunctive therapy compared with placebo in subjects with focal onset seizures	Primary Efficacy: RRatio, defined as RRatio=(T−B)/(T+B) ×100, where T represents the focal onset seizure frequency rate per week in the Maintenance Phase and B represents the focal onset seizure frequency rate per week in the Baseline Period Key Secondary Efficacy: • Change from baseline in focal onset seizure frequency per week over the Maintenance Phase • The 50% responder rate, defined as the percent of subjects with at least a 50% reduction in the Maintenance Phase focal onset seizure frequency rate relative to the Baseline Period Other Secondary Efficacy: • Seizure freedom • Seizure rate over time • PGIC score at Visits 2, 3, and 4 • Change from Baseline to Visits 2, 3, and 4 in CGI-S score • CGI-I score at Visit 2, 3, and 4 • Change from Baseline to Visit 4 in QOLIE-31 Overall score • Change from Baseline to Visit 4 in HUI Utility score
Secondary (safety): To evaluate the safety and tolerability of CVL-865 in subjects with focal onset seizures	• Treatment-emergent adverse events, clinically significant changes in ECGs, vital sign measurements, and physical and neurological examination results • Suicidality assessed using the C-SSRS • Withdrawal symptoms assessed using the mCIWA-B • Nature, frequency, and temporality of TEAEs (nonserious and serious), including abuse-related AEs and AEs related to Medication Handling Irregularities (MHI)
Secondary (PK): To evaluate the plasma exposure of CVL-865	• Summary listing of CVL-865 concentrations by dose and visit

Abbreviations: AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity of Symptoms; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG =

electrocardiogram; HUI = Health Utilities Index; mCIWA-B = Modified Clinical Institute Withdrawal Assessment – Benzodiazepines; MHI = Medication Handling Irregularities; PGIC = Patient's Global Impression of Change; QOLIE-31 = Quality of Life in Epilepsy-31; RRatio = Response Ratio; TEAE = treatment-emergent adverse event.

Overall Design:

This is a double-blind, parallel-group, placebo-controlled trial with subjects randomized to 1 of the following 3 arms in a 1:1:1 ratio:

- CVL-865 25 mg twice daily (BID) maintenance
- CVL-865 7.5 mg BID maintenance
- Placebo

Subjects who satisfy all inclusion/exclusion criteria and thus are eligible for the trial will be randomly assigned to 1 of the 3 treatment arms at Visit 1, the start of the 13-week Treatment Period (10 weeks for subjects enrolling into the open-label extension trial, see below).

At the completion of the Maintenance Phase in this trial, the investigator will evaluate the subject's eligibility to continue treatment with CVL-865 in the open-label extension trial CVL-865-SZ-002.

Disclosure Statement: This is a parallel group treatment trial with 3 arms that are blinded to the subjects and the investigator.

Number of Subjects: Approximately 214 subjects will be screened to achieve 150 subjects randomly assigned to treatment (50 per group) and 120 evaluable subjects for an estimated total of 40 evaluable subjects per treatment group.

In the event of higher than anticipated early terminations due to COVID-19 or other reasons, Cerevel may extend enrollment in order to maintain the planned statistical power.

Key Entry Criteria: Men and women 18 to 75 years of age, inclusive, with a diagnosis of epilepsy with focal onset (as defined in the 2017 ILAE Classification of Seizures), focal aware (except subjects with only focal aware seizures without a motor component), focal impaired awareness, and focal to bilateral tonic-clonic seizures for at least 2 years prior to signing the ICF will be enrolled into this trial. A history of an average of 4 or more spontaneous and observable focal onset, focal aware, focal impaired awareness, and focal to bilateral tonic-clonic seizures (as defined in previous sentence) per 28-day period for at least 3 months (84 days) prior to signing the ICF along with a minimum of 8 of these seizure types during the 8-week Baseline Period with no 21-day period free of any of these seizure types is also required for entry into the trial.

Intervention Groups, Trial Treatment, and Duration: This trial is designed with a maximum duration of approximately 25 weeks. The trial consists of the following:

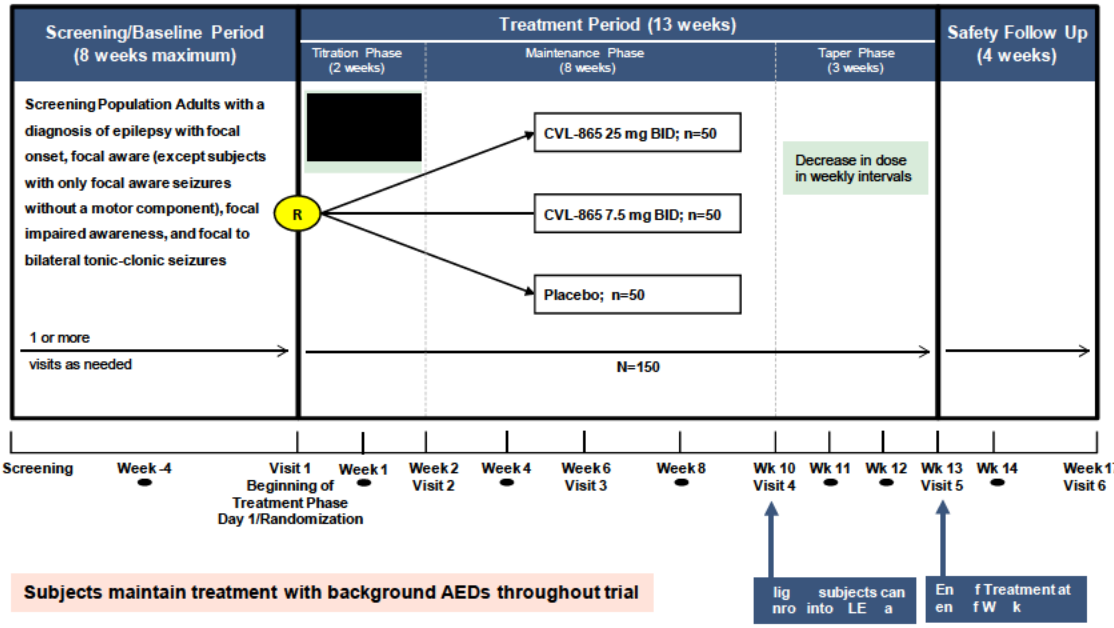
- 8-week Screening/Baseline Period
- 10- or 13-week Treatment Period, including an initial 2-week Titration Phase, an 8-week Maintenance Phase, and a 3-week Taper Phase (only for subjects not continuing treatment in the open-label extension trial). The tablets (including the number of tablets given) will be the same between the placebo and both CVL-865 dose arms during the Titration, Maintenance, and Taper Phases to maintain the blind. All tablets will be administered orally.
- 4-week Follow-up Period
- The daily dosing schedule will start at Day 1 with a 2-week Titration Phase during which time the subject's dose will be increased in a blinded fashion up to the randomized dose level (CVL-865 25 mg BID, CVL-865 7.5 mg BID, or placebo). In the high-dose group, CVL-865 will be administered as [redacted] during the Titration Phase, and then 25 mg BID during the 8-week Maintenance Phase. In the low-dose group, CVL-865 will be administered as [redacted] during the Titration Phase, and then 7.5 mg BID during the 8-week Maintenance Phase. For subjects not enrolling into the open-label extension trial, following the Maintenance Phase, dose will be gradually decreased over a 3-week Taper Phase.

Statistical Methods:

A sample size of 50 subjects per group (total of 150 subjects) will provide at least 80% power to detect a difference in the means of the primary outcome measure (RRatio) of -20 (PASS 2008 Tests of Two Means, Two Sample T-Test, 2-sided alpha level = 0.1, Standard Deviation=34, and a 20% dropout rate).

The primary efficacy endpoint is the Rratio over the Maintenance Phase. This is calculated as Rratio=$(T-B)/(T+B)$ ×100, where T represents the seizure frequency rate per week in the Maintenance Phase and B represents the seizure frequency rate per week in the Baseline Period. The Rratio is between -100 and 100. Negative values will indicate reduction in seizure rate and positive values indicate increase in seizure rate during treatment. Values of Rratio will be analyzed for the modified intent-to-treat population using an analysis of covariance model, including treatment and the baseline seizure frequency per week as a covariate.

1.2 Schema



Abbreviations: AED = anti-epileptic drug; BID = twice daily; OLE = open-label extension; Wk = week.

Figure 1 Trial Schematic

1.3 Schedule of Assessments

Table 2 Schedule of Assessments

Trial Periods/ Phases	Screening/ Baseline Period[a] (8 weeks)		Treatment Period										Post-treatment Follow-up		
			Titration Phase (2 weeks)		Maintenance Phase (8 weeks)					Taper Phase (3 weeks)					
Visit/Contact[b]	**Screen-ing**	**Contact**	**Visit 1[a]**	**Contact**	**Visit 2[c]**	**Contact**	**Visit 3[c]**	**Contact**	**Visit 4[d]**	**Contact**	**Contact**	**Visit 5[c]**	**ET[e]**	**Contact**	**Visit 6**
Day	**-56**	**-28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**78**	**85**	**92**	**NA**	**~99**	**120**
Window	**± 3 days**			**± 3 days**											
Entrance and History															
Informed consent[f]	X														
Assign subject identification	X														
Review inclusion/ exclusion criteria	X	X	X												
Record medical history	X														
Record seizure history	X														
Head MRI/CT[g]	X														
Demography	X														
History of drug and alcohol use	X														
Review of birth control methods	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Trial Periods/ Phases	Screening/ Baseline Period[a] (8 weeks)		Treatment Period										Post-treatment Follow-up		
			Titration Phase (2 weeks)		Maintenance Phase (8 weeks)					Taper Phase (3 weeks)					
Visit/Contact[b]	**Screen-ing**	**Contact**	**Visit 1[a]**	**Contact**	**Visit 2[c]**	**Contact**	**Visit 3[c]**	**Contact**	**Visit 4[d]**	**Contact**	**Contact**	**Visit 5[c]**	**ET[e]**	**Contact**	**Visit 6**
Day	**-56**	**-28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**78**	**85**	**92**	**NA**	**~99**	**120**
Window	**± 3 days**			**± 3 days**											
Complete and send SIF/DRF paperwork to TESC[h]	X														
Complete Rescue Protocol for subjects who normally receive BZD[i]	X														
Confirm eligibility based on TESC[j]			X												
Randomization			X												
Dispense eDiary and train on use	X														
Dispense medical bracelet			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
PGIC					X		X		X				X		
CGI-S			X		X		X		X				X		

Trial Periods/ Phases	Screening/ Baseline Period[a] (8 weeks)		Treatment Period										Post-treatment Follow-up		
			Titration Phase (2 weeks)		Maintenance Phase (8 weeks)					Taper Phase (3 weeks)					
Visit/Contact[b]	Screen-ing	Contact	Visit 1[a]	Contact	Visit 2[c]	Contact	Visit 3[c]	Contact	Visit 4[d]	Contact	Contact	Visit 5[c]	ET[e]	Contact	Visit 6
Day	-56	-28	1	8	15	29	43	57	71	78	85	92	NA	~99	120
Window	± 3 days			± 3 days											
CGI-I[k]					X		X		X				X		
QOLIE-31			X						X				X		
Health Utilities Index			X						X				X		
Safety Assessments															
Physical/ neurological examination[l]	X								X			X	X		
ECG	X		X				X		X			X	X		
Vital sign measurements	X		X				X		X			X	X		
C-SSRS[m]	X		X		X		X		X			X	X		X
mCIWA-B									X	X	X	X	X	X	X
Prior/concomitant treatments including BZD use[n]	←----------														----------→
Adverse event monitoring[n]	←----------														----------→
Laboratory															
Safety laboratory blood sample	X		X		X		X		X			X	X		X

Trial Periods/ Phases	Screening/ Baseline Period[a] (8 weeks)		Treatment Period										Post-treatment Follow-up		
			Titration Phase (2 weeks)		Maintenance Phase (8 weeks)					Taper Phase (3 weeks)					
Visit/Contact[b]	**Screen-ing**	**Contact**	**Visit 1[a]**	**Contact**	**Visit 2[c]**	**Contact**	**Visit 3[c]**	**Contact**	**Visit 4[d]**	**Contact**	**Contact**	**Visit 5[c]**	**ET[e]**	**Contact**	**Visit 6**
Day	**-56**	**-28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**78**	**85**	**92**	**NA**	**~99**	**120**
Window	**± 3 days**			**± 3 days**											
Safety laboratory urine sample	X		X		X				X				X		
Serum pregnancy test[o]	X	<-------->	X	<---------->									X	<-------->	X
Serology (HIV, HBV, HCV)	X														
Urine pregnancy test[o]					X		X		X			X			
Urine drug screening[p]	X														
Blood sample for PK of CVL-865					X[q]		X[q]		X[q]			X[q]	X[q]		
Blood sample(s) for PK of AED[r]	X		X		X		X		X			X	X		X
Future biospecimen research blood sample[s]			X												
Other															
IMP dispensing			X		X		X		X						
Collect final eDiary device															X

Trial Periods/ Phases	Screening/ Baseline Period[a] (8 weeks)		Treatment Period										Post-treatment Follow-up		
			Titration Phase (2 weeks)		Maintenance Phase (8 weeks)					Taper Phase (3 weeks)					
Visit/Contact[b]	**Screen-ing**	**Contact**	**Visit 1[a]**	**Contact**	**Visit 2[c]**	**Contact**	**Visit 3[c]**	**Contact**	**Visit 4[d]**	**Contact**	**Contact**	**Visit 5[c]**	**ET[e]**	**Contact**	**Visit 6**
Day	**-56**	**-28**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**78**	**85**	**92**	**NA**	**~99**	**120**
Window	**± 3 days**			**± 3 days**											
Provide individualized rescue protocol and train subject[i]			X												
IMP compliance assessment					X	X	X	X	X	X	X	X	X		
Adjunctive AED compliance assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X

AED = anti-epileptic drug; BID = twice daily; BZD = benzodiazepine; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression – Severity of Symptoms; C-SSRS = Columbia-Suicide Severity Rating Scale; CT = computed tomography; ECG = electrocardiogram; ET = Early Termination; HBV = hepatitis B virus; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IMP = investigational medicinal product; mCIWA-B = Modified Clinical Institute Withdrawal Assessment – Benzodiazepines; MRI = magnetic resonance imaging; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; QOLIE-31 = Quality of Life in Epilepsy-31; SIF/DRF = Seizure Identification and Diagnostic Review Form; TESC = The Epilepsy Study Consortium.

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

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

c. 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.

d. At Visit 4, the investigator will evaluate the subject's eligibility to continue treatment with CVL-865 in the open-label extension trial CVL-865-SZ-002. If the investigator determines the subject is eligible for the trial, he/she will discuss with the subject if they would like to continue into Trial CVL-865-SZ-002. If the investigator determines the subject is eligible and the subject agrees to continue participation in Trial CVL-865-SZ-002, consent will be obtained and unique procedures for Visit 1 of Trial CVL-865-SZ-002 will be completed. Subjects who do not continue into Trial CVL-865-SZ-002 will begin the Taper Phase.

e. Subjects who require early termination should begin the Taper Period at the time the decision is made to discontinue. All indicated procedures should be performed per protocol. If a subject discontinues early and it is inadvisable for them to taper IMP (after agreement from medical monitor), the subject should complete Visit 6 assessments approximately 30 days following the last dose of IMP.

f. Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened after consultation with the medical monitor. Rescreened subjects should receive a unique subject number for each screening.

g. Unless procedure has been performed within 10 years prior to signing the ICF. This procedure, if necessary, should be conducted as soon as possible during the Screening/Baseline Period (per local guidelines) with the report available prior to randomization.

h. A SIF/DRF will need to be completed by site personnel for every subject. This information will be faxed or emailed to TESC after the Screening Visit for review and approval. The SIF/DRF will be used by TESC to ensure that the seizures are classified accurately, the subject is appropriate for the trial, and will help to confirm the diagnosis.

i. All subjects who normally take BZDs for seizure rescue will be required to have an individualized Rescue Protocol approved by TESC. The Rescue Protocol will be submitted along with the SIF/DRF and will describe what rescue treatment can be administered in the event the subject requires a BZD. It will also include different scenarios that will prompt immediate medical attention.

j. Subjects cannot be enrolled until site personnel have received the TESC approval notification.

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

l. Full physical and neurological examinations should be completed at Screening Visit 4, and Visit 5/ET. The physical examination should include weight at all time points and height at the Screening Visit only. Physical and/or neurological examinations can be done at any time point during the trial at the investigator's discretion.

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

n. Adverse events (serious and non-serious) and concomitant medications should be recorded from screening through the subject's last visit.

o. 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.

p. A urine drug screen is required at screening; see the exclusion criteria for exclusions based on the urine drug screen. The urine drug screen can be conducted at any time during the trial at the discretion of the investigator.

q. 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 2, 3, 4, and 5. 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.

r. One 5-mL sample for each individual adjunctive AED.

s. Future biospecimen research sample is optional and is to only be collected if signed consent is obtained from the subject.

2 INTRODUCTION

2.1 Trial Rationale

This placebo-controlled, double-blind trial is designed to assess the efficacy, safety, and tolerability profile of CVL-865 as adjunctive treatment in subjects with drug-resistant focal onset seizures.

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.

A double-blind, placebo-controlled trial is an appropriate design in which to assess initial efficacy with CVL-865. This proof-of-concept trial will assess whether CVL-865 demonstrates efficacy compared with placebo, as measured by a decrease in seizure frequency in subjects with a diagnosis of epilepsy with drug-resistant focal onset seizures.

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 (ILAE) 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 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, small molecule 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.

CVL-865 has been shown to be anticonvulsant in several nonclinical models of epilepsy including the pentylenetrazol model in mice, the amygdala kindling model of temporal

lobe epilepsy in rats, and in the genetic absence epilepsy rat from Strasbourg. The strong efficacy across a broad spectrum of models is suggestive of potential clinical utility of CVL-865 in epilepsy.

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 proof-of-principle 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 (EEG) 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 doses ranging from 0.04 to 100 mg single dose, and 2.5 mg to 42.5 mg twice daily (BID) multiple dose. CVL-865 has been safe and well tolerated.

Please refer to the Investigator's Brochure for a summary of available nonclinical and clinical safety data for 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 study by monitoring of hematologic parameters and requiring the use of appropriate contraception and regular pregnancy testing.

Results from a recently completed Phase 2a trial using a photosensitivity model as a proof-of-concept for 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 lorazepam 2 mg active control.

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

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

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary: To evaluate the efficacy of CVL-865 as adjunctive therapy compared with placebo in subjects with focal onset seizures	Primary Efficacy: RRatio, defined as RRatio=(T−B)/(T+B) ×100, where T represents the focal onset seizure frequency rate per week in the Maintenance Phase and B represents the focal onset seizure frequency rate per week in the Baseline Period Key Secondary Efficacy: • Change from baseline in focal onset seizure frequency per week over the Maintenance Phase • The 50% responder rate, defined as the percent of subjects with at least a 50% reduction in the Maintenance Phase focal onset seizure frequency rate relative to the Baseline Period Other Secondary Efficacy: • Seizure freedom • Seizure rate over time • PGIC score at visits 2, 3, and 4 • Change from Baseline to Visits 2, 3, and 4 in CGI-S score • CGI-I score at Visit 2, 3, and 4 • Change from Baseline to Visit 4 in QOLIE-31 Overall score • Change from Baseline to Visit 4 in HUI Utility score
Secondary (safety): To evaluate the safety and tolerability of CVL-865 in subjects with focal onset seizures	• Treatment-emergent adverse events, clinically significant changes in ECGs, vital sign measurements, and physical and neurological examination results • Suicidality assessed using the C-SSRS • Withdrawal symptoms assessed using the mCIWA-B • Nature, frequency, and temporality of TEAEs (nonserious and serious), including abuse-related AEs and AEs related to Medication Handling Irregularities (MHI)
Secondary (PK): To evaluate the plasma exposure of CVL-865	• Summary listing of CVL-865 concentrations by dose and visit

Abbreviations: AE = adverse event; CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity of Symptoms; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HUI = Health Utilities Index; mCIWA-B = Modified Clinical Institute Withdrawal Assessment – Benzodiazepines; MHI = Medication Handling Irregularities; PGIC = Patient's Global

Impression of Change; QOLIE-31 = Quality of Life in Epilepsy-31; RRatio = Response Ratio; TEAE = treatment-emergent adverse event.

4 TRIAL DESIGN

4.1 Overall Design

This is a double-blind, parallel-group, placebo-controlled trial with subjects randomized to 1 of the following 3 arms in a 1:1:1 ratio:

- CVL-865 25 mg BID maintenance
- CVL-865 7.5 mg BID maintenance
- Placebo

This trial is designed with a maximum duration of approximately 25 weeks. The trial consists of the following:

- 8-week Screening/Baseline Period
- 10- or 13-week Treatment Period, including an initial 2-week Titration Phase, an 8-week Maintenance Phase, and a 3-week Taper Phase (only for subjects not continuing treatment in the open-label extension trial). The tablets (including the number of tablets given) will be the same between the placebo and both CVL-865 dose arms during the Titration, Maintenance, and Taper Phases to maintain the blind
- 4-week Follow-up Period

Screening/Baseline Period:

Only subjects who have signed an informed consent form (ICF) and are expected to fulfill the inclusion/exclusion criteria enter into the Screening/Baseline Period for evaluation at the Screening Visit. Subjects are to continue on their current AEDs at the same dosages throughout the Screening/Baseline Period. If a subject has a vagus nerve stimulator (VNS), a deep brain stimulator (DBS), or a responsive neurostimulator (RNS), the settings must remain stable throughout the Screening/Baseline Period.

During this Screening/Baseline Period, subjects will be required to complete electronic seizure diaries (eDiary) and record all seizures in the eDiary for each day. The presence or absence of all seizure types experienced by each subject will be recorded daily in the eDiary.

Treatment Period:

Subjects who satisfy all inclusion/exclusion criteria and thus are eligible for the trial will be randomized to 1 of 3 treatment arms at Visit 1.

The daily dosing schedule will start at Day 1 with a 2-week Titration Phase during which time the subject's dose will be increased in a blinded fashion up the randomized dose level (CVL-865 25 mg BID, CVL-865 7.5 mg BID, or placebo). In the high-dose group, CVL-865 will be administered as [redacted] during the Titration Phase, and then 25 mg BID during the 8-week Maintenance Phase. In the low-dose group, CVL-865 will be administered as [redacted] during the Titration Phase, and then 7.5 mg BID during the 8-week Maintenance Phase.

At the completion of the Maintenance Phase, the investigator will evaluate the subject's eligibility to continue treatment with CVL-865 in the open-label extension trial CVL-865-SZ-002. If the investigator determines the subject is eligible for the trial, he/she will discuss with the subject if they would like to continue into Trial CVL-865-SZ-002. If the investigator determines the subject is eligible and the subject agrees to continue participation in Trial CVL-865-SZ-002, consent will be obtained and unique procedures for Visit 1 of Trial CVL-865-SZ-002 will be completed.

For subjects who do not continue into Trial CVL-865-SZ-002, following the Maintenance Phase, the dose will be gradually decreased over a 3-week Taper Phase.

A summary of the dosing schedule is provided below.

Table 4 Dosing Schedule

	Titration Phase		Maintenance Phase	Taper Phase[a]		
Dose Initiation	[redacted]	[redacted]	**Day 15**	**Day 78**	**Day 85**	**Day 92**
Duration	2 weeks		8 weeks	3 weeks		
CVL-865 7.5 mg BID	[redacted]		7.5 mg BID	5 mg BID	5 mg BID	2.5 mg BID
CVL-865 25 mg BID			25 mg BID	17.5 mg BID	10 mg BID	5 mg BID
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Abbreviations: BID = twice daily.
a Only for subjects who do not continue treatment with CVL-865 in Trial CVL-865-SZ-002.

Subjects are to continue the same concurrent AEDs at the same dosages administered during the Treatment Period. If a subject has a VNS, DBS, or RNS, the settings must remain stable throughout the Treatment Period.

Subjects will continue to record all seizures and the presence or absence of all seizure types experienced in the eDiary for each day during the Treatment Period.

Follow-up Period:

See Figure 1 for a schematic of the trial design and Table 2 for the schedule of assessments.

4.2 Scientific Rationale for Trial Design

CVL-865 is a novel small molecule with a first-in-class mechanism of action, which, based on the nonclinical and clinical data, has the potential to be highly efficacious in a broad spectrum of patients with epilepsy via modulation of $GABA_A$ receptors. As an α2/α3/α5 subtype selective partial PAM with minimal effect at the α1 subunit, CVL-865 would be expected to maintain efficacy whilst overcoming many of the adverse events (AEs) that limit the use of BZDs, such as cognitive impairment, sedation, withdrawal symptoms, abuse potential, and tolerance.

The clinical development of anti-epileptic agents in focal onset epilepsy in the adjunctive setting is well established. Usually, focal seizures in adults represent the first patient population, since they are the most frequent seizure type, and a substantial percentage of patients have seizures that are not well controlled using current medications. The initial evaluation process for a new AED involves determination of its efficacy in reducing the frequency of seizures in patients who continue to have seizures despite therapy with an adequate dosage of appropriate drug(s) and thus represent a drug-resistant population.

This trial includes a randomized, double-blind, placebo-controlled parallel group design, which are the key features recommended by the European Medicines Agency draft guidelines 2018 on the clinical investigation of medicinal products in the treatment of epileptic disorders (EMA 2018).

4.3 Dosing Rationale

The 2 arms of CVL-865 have been selected based on the first-in-human safety and tolerability data, the pharmacodynamic (PD) 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 electrocardiograms (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 top maintenance dose of 25 mg BID is designed to fully test the therapeutic potential of CVL-865 as adjunctive therapy in the treatment of focal onset seizures. At that dose level 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 anticipated to achieve steady-state exposure levels of CVL-865 within the range anticipated to produce approximately 80% receptor occupancy. In addition, pharmacokinetic (PK)/PD modeling of saccadic peak velocity and α2 receptor occupancy data also suggests that no additional benefit would come from increasing the dose above 25 mg BID.

The lower dose of 7.5 mg of CVL-865 administered BID is anticipated to result in exposures with limited overlap with the high dose and a submaximal effect based on the same neurofunctional endpoints described above. The 7.5 mg BID and 25 mg BID doses will facilitate evaluation of a wide exposure and target occupancy range in this trial to facilitate appropriate dose selection for future clinical trials. Exposures from both dosing regimens are not expected to exceed the no observed adverse effect level (NOAEL) established based on the pivotal 13-week toxicological studies in rats and dogs.

4.4 Definition of Completed Subject

Subjects continuing treatment with CVL-865-SZ-001 in the open-label extension trial are considered to have completed this trial if he/she has completed the Maintenance Phase of the trial (ie, completed Visit 4) as shown in the Schedule of Assessments.

Subjects not continuing in the open-label extension trial, are considered to have completed this trial if he/she has completed all phases of the trial including the last scheduled procedure (Day 120 phone contact) shown in the Schedule of Assessments.

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 globally.

5 TRIAL POPULATION

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

A Seizure Identification and Diagnostic Review Form (SIF/DRF) will need to be completed by site personnel for every subject. This information will be faxed or emailed to The Epilepsy Study Consortium (TESC) after the Screening Visit for review and approval. The SIF/DRF will be used to ensure that the seizures are classified accurately, the subject is appropriate for the trial, and will help to confirm the diagnosis. Subjects cannot be enrolled until the TESC review and feedback of the SIF/DRF has been completed and the site personnel have received final notification.

5.1 Inclusion Criteria

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

1.	Male and female subjects, ages 18 to 75 years, inclusive, at the time of signing the ICF.
2.	A diagnosis of epilepsy with focal onset (as defined in the 2017 ILAE Classification of Seizures [Fisher et al, 2017]), focal aware (except subjects with only focal aware seizures without a motor component), focal impaired awareness, and focal to bilateral tonic-clonic seizures for at least 2 years prior to signing the ICF. Diagnosis will be based on the investigator's assessment of available clinical, radiographic, and EEG data and the review by TESC.
3.	A history of an average of 4 or more spontaneous and observable focal onset (as defined in the 2017 ILAE Classification of Seizures [Fisher et al, 2017]), focal aware (except subjects with only focal aware seizures without a motor component), focal impaired awareness, and focal to bilateral tonic-clonic seizures per 28-day period for at least 3 months (84 days) prior to signing the ICF.
4.	A minimum of 8 focal onset (as defined in the 2017 ILAE Classification of Seizures [Fisher et al, 2017]), focal aware (except subjects with only focal aware seizures without a motor component), focal impaired awareness, or focal to bilateral tonic-clonic seizures during the 8-week Baseline Period with no 21-day period free of any of these seizure types.
5.	Subjects who have tried and failed at least 2 appropriate AEDs in the past.
6.	Subjects currently taking 1 to 3 permitted AEDs (see concomitant medication exclusions) at a stable dose for 4 weeks prior to the Screening Visit. VNS, DBS, and RNS is permitted and is not considered an AED. The VNS, DBS, and RNS settings should remain stable for 4 weeks prior to the Screening Visit. Note: Should a subject require a change of AED therapy/dose or VNS, DBS, or RNS settings between the Screening Visit and Visit 1, that subject should not continue in the trial at that time but must remain on the new regime for at least 4 weeks and then may repeat the screening process.
7.	An MRI or CT scan of the head within 10 years prior to Screening Visit to demonstrate no progressive structural abnormality. If a scan is not available, one should be conducted during the Baseline Period with a report that demonstrated no progressive structural abnormality available prior to randomization.
8.	BMI of 17.5 to 40.0 kg/m^2 and a total body weight >50 kg (110 lbs).
9.	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 throughout the duration of the study and for 30 days post last dose. A male subject with a pregnant or a nonpregnant partner of childbearing potential must agree to use condom during treatment and until the end of relevant systemic exposure in the male subject for 94 days following the last dose with IMP.
10.	Capable of giving signed informed consent as described in Section 10.1.3 (Appendix 1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
11.	Ability, 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: AED = anti-epileptic drug; BMI = body mass index; CT = computed tomography; DBS = deep brain stimulator; EEG = electroencephalogram; ICF = informed consent form; ILAE = International League Against Epilepsy; IMP = investigational medicinal product; MRI = magnetic resonance imaging; RNS = responsive neurostimulator; TESC = The Epilepsy Study Consortium; VNS = vagus nerve stimulator

5.2 Exclusion Criteria

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

Target Disease	
1.	Subjects with (genetic) idiopathic generalized epilepsies or combined generalized and focal epilepsies, including a history of Lennox-Gastaut Syndrome.
2.	Subjects with only focal aware seizures without a motor component.
3.	Subjects with a history of seizures over the past 12 months that occur at such a high frequency they cannot be counted (eg, repetitive seizures, cluster seizures).
4.	Subjects with a history of psychogenic non-epileptic seizures within the year prior to signing the ICF.
5.	Subjects with a history of status epilepticus within 5 years prior to signing the ICF.
6.	Subjects with a history of neurosurgery for seizures less than 1 year prior to signing the ICF, or radiosurgery less than 2 years prior to signing the ICF.
Medical History and Concurrent Diseases	
7.	Subjects with a current history of significant cardiovascular, pulmonary, gastrointestinal, renal, hepatic, metabolic, hematological, immunological, or neurological (excluding focal onset epilepsy) disease that, in the opinion of the investigator or medical monitor, could compromise either subject safety or the results of the trial. In addition, subjects with a psychiatric illness of sufficient severity as to make them inappropriate for the trial are excluded. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the subject to an undue risk of a significant AE or interfere with the assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a subject's medical conditions(s) and the potential impact of the condition(s) on trial participation.
8.	Subjects with an active CNS infection, demyelinating disease, degenerative neurological disease or any CNS disease deemed to be progressive during the course of the trial that may confound the interpretation of the trial results.
9.	Subjects with a history of substance or alcohol-use disorder (excluding nicotine; DSM-5 criteria) within 2 years prior to signing the ICF.
10.	Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) and whose most recent episode meeting criteria for this C-SSRS Item 4 occurred within the last 6 months, **OR** Subjects who answer "Yes" on the C-SSRS Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) and whose most recent episode meeting criteria for this C-SSRS Item 5 occurred within the last 6 months **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) and whose most recent episode meeting criteria for any of these 5 C-SSRS Suicidal Behavior Items occurred within the last 2 years, **OR** Subjects who, in the opinion of the investigator, present a serious risk of suicide.
Physical Examination and Clinical Laboratory Results	
11.	Subjects who test positive for human immunodeficiency virus (HIV), hepatitis B and/or or hepatitis C infection.
12.	Subject with a positive drug screen for illicit drugs are excluded and may not be retested or rescreened. Subjects with a positive urine drug screen resulting from use of marijuana (any cannabinoids), prescription, or over the counter medications or products that, in the investigator's documented opinion do not signal a clinical condition that would impact the safety of the subject or interpretation of the trial results may continue evaluation for the trial following consultation and approval by the medical monitor.
13.	Subjects with a 12-lead ECG demonstrating either of the following: • QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec (average of 3 ECGs obtained at the Screening Visit assessed by central reader) • QRS interval >120 msec at the Screening Visit
14.	Subjects with any of the following abnormalities in clinical laboratory tests at the Screening Visit, as assessed by the central laboratory and confirmed by a single repeat measurement, if deemed necessary: • AST or ALT ≥2 × ULN • Total bilirubin ≥1.5 × ULN. Subjects with a history of Gilbert's syndrome may be eligible provided the direct (conjugated) bilirubin is <ULN • Females: Hemoglobin <11 g/dL; Males: hemoglobin <12 g/dL • White blood cell (WBC) count <3.0 × 10^9/L • Neutrophil count <2.0 × 10^9/L • Platelet count <150 × 10^9/L
15.	Subjects with other abnormal laboratory test results, vital sign results, or ECG findings unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the subjects or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a subject based on criteria provided in this protocol. For ECGs, 3 consecutive recordings are required and if 2 of the 3 remain exclusionary, then the subject is not eligible for the trial.
Disallowed Prior and Concomitant Medications	
16.	Subjects receiving more than 3 background AEDs for their epilepsy.
17.	Subjects taking BZD medication chronically or who require a BZD (oral, intramuscular, or suppository) as rescue medication for epilepsy for more than 4 days on average over a 28-day period. (Note: a rescue BZD will be permitted if used ≤4 days on average over a 28-day period). During the Screening/Baseline Period, subjects requiring a BZD (oral, intramuscular, or suppository) as rescue medication for epilepsy more than 4 days on average over a 28-day period will be excluded.

18.	Subjects taking other prohibited medications prior to randomization (as listed in Table 6) or who would be likely to require the use of prohibited concomitant medications during the trial (as listed in Table 7).
19.	Subjects taking any drug that is strong or moderate inducer/inhibitor CYP3A4 metabolism, which has the potential to alter CVL-865 exposure levels (see Section 6.5).
20.	Subjects taking any drug that is a sensitive P-gp and BCRP substrate (see Section 6.5).
21.	Vigabatrin is excluded as a concomitant AED, unless subject has been taking it for at least 2 years prior to signing the ICF and have no evidence of visual field defects on at least 2 visual field tests within 6 months of signing the ICF.
22.	Felbamate is excluded as a concomitant AED, unless subject has been taking it for at least 2 years prior to signing the ICF, with a stable dose for ≥49 days, and have acceptable hematology and liver function test values (or discontinued felbamate no less than 49 days prior to signing the ICF).
Other	
23.	Female subjects who are breastfeeding and/or who have a positive pregnancy test result prior to receiving IMP.
24.	Any condition possibly affecting drug absorption, including bowel resections, bariatric weight loss surgery, or gastrectomy (this does not include gastric banding).
25.	Subjects with difficulty swallowing.
26.	Subjects who are known to be allergic or hypersensitive to the IMP or any of its components.
27.	Subjects who have participated in any clinical trial within 60 days prior to signing the ICF or who have participated in more than 2 clinical trials within the year prior to signing the ICF.
28.	Any subject who, in the opinion of the sponsor, investigator, or medical monitor, should not participate in the trial.

Abbreviations: AE = adverse event; AED = anti-epileptic drug; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCRP = breast cancer resistance protein; BZD = benzodiazepine; CNS = central nervous system; C-SSRS = Columbia – Suicide Severity Rating Scale; CYP = cytochrome P450; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ECG = electrocardiogram; ICF = informed consent form; IMP = investigational medicinal product; P-gp = P-glycoprotein; ULN = upper limit of normal range.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects should adhere to their normal or prescribed dietary regime 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 6.

5.3.2 Alcohol, Caffeine, and Tobacco Restrictions

Subjects should adhere to their usual regime 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 Machines

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 defined as subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to treatment in the trial. 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 (CONSORT) 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) may be rescreened after consultation with the medical monitor. Rescreened subjects should receive a unique subject number for each screening.

If the subject fails screening due only to safety laboratory results, the Investigator may, at their discretion, decide to repeat the safety laboratory tests and perform additional tests as appropriate. In this case, no other screening procedures need to be repeated, as long as the procedures stay within the protocol-specified timelines.

If a subject requires a change in AED dose, type or number of AEDs, or a change in the settings on their VNS, DBS, or RNS, the subject may be rescreened with medical monitor approval at a time when they have been a stable dose and/or setting for a period of a least 4 weeks.

6 TRIAL TREATMENT

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 (IMP) refers to a pharmaceutical form of any active substance or placebo being tested in this clinical trial.

6.1 Trial Treatments Administered

Table 5 Trial Treatments Administered

Treatment Group	CVL-865 25 mg BID	CVL-865 7.5 mg BID	Placebo
Dose Formulation	Tablet	Tablet	Matching tablet
Unit Dose Strengths	2.5, 5 mg, and 7.5 mg	2.5, 5 mg, and 7.5 mg	2.5, 5 mg, and 7.5 mg (matching)
Dosage Levels	25 mg BID	7.5 mg BID	Placebo
Route of Administration	Oral	Oral	Oral
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 the appropriate combination of tablets necessary in order to achieve the required dose level. In order to maintain the blind, subjects assigned to the placebo treatment group will receive the same number of tablets as subjects in the CVL-865 groups.

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

6.3.1 Subject Assignment to Treatment

During the entire trial, treatment will be double-blind, ie, neither the investigator nor the subject will have knowledge of the treatment assignment at any visit.

Treatment assignments will be based on a computer-generated randomization code provided by Cerevel or designee. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment codes during the trial. Access to the treatment codes will be restricted to personnel charged with generating and maintaining randomization files, packaging IMP, operating the interactive response technology (IRT), and reporting SAEs to regulatory agencies.

Once a randomization number has been assigned, it must not be reassigned.

6.3.2 Blinding

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

Documentation of breaking the blind should be recorded on the subject's medical record and in the electronic case report form (eCRF) with reason for breaking the blind, the date and time the blind was broken, and the names of the personnel involved. Once the blind is broken for a subject, reinitiation of treatment with IMP cannot occur for that subject.

6.4 Trial Treatment Compliance

Responsible trial personnel will dispense the IMP. The time and dose of each IMP administration, along with information on any missed or inappropriately administered dose, will be recorded in source documents and the eCRF.

Subjects must be counseled on the importance of taking the IMP as directed. If poor compliance is encountered (eg, multiple missed doses resulting in less than 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 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 30 days prior to signing of 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.

6.5.2 Prohibited Medications

All subjects must agree to discontinue all prohibited medications per defined washout times in table below.

Table 6 Prohibited Prior Medications

	Prohibited Prior Medications	Washout (if applicable)
1.	AEDs including, but not limited to, the following: 1. BZD taken chronically or as rescue medication for epilepsy for more than 4 days on average over a 28-day period (prior to signing ICF and/or during the Screening/Baseline Period) 2. Vigabatrin, unless subject has been taking it for at least 2 years prior to signing the ICF and have no evidence of visual field defects on at least 2 visual field testing within 6 months of signing the ICF 3. Felbamate unless subject has been taking it for at least 2 years prior to signing the ICF, with a stable dose for ≥49 days, and has acceptable hematology and liver function test values	
2.	Inducers of CYP3A4 metabolism (see Section 10.6, Appendix 6). Oxcarbazepine will be permitted up to a maximum dose of 900 mg/day.	5 weeks
3	Moderate or strong inhibitors of CYP3A4 (see Section 10.6, Appendix 6)	2 weeks or 5 half-lives
4.	P-gp substrates with a narrow therapeutic index (eg, digoxin, dabigatran)	
5.	BCRP substrate rosuvastatin	
6.	Any investigational agent	60 days

Abbreviations: AED = anti-epileptic drug; BCRP = breast cancer resistance protein; BZD = benzodiazepine; CYP = cytochrome P450; ICF = informed consent form; P-gp = P-glycoprotein

The table below 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 7 Prohibited Concomitant Medications

	Prohibited Concomitant Medications
1.	Vigabatrin, unless subject had been taking it for at least 2 years prior to signing the ICF
2.	Felbamate unless subject had been taking it for at least 2 years prior to signing the ICF, with a stable dose for ≥49 days
3.	Moderate to strong inducers and inhibitors of CYP3A4 metabolism (see Section 10.6, Appendix 6)
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 a. 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 a. 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; ICF = informed consent form; P-gp = P-glycoprotein

6.5.3 Rescue Medicine

All subjects who normally take BZDs for seizure rescue will be required to have an individualized Rescue Protocol approved by TESC. The Rescue Protocol will be submitted along with the SIF/DRF and will describe what rescue treatment can be administered in the event the subject requires a BZD. It will also include different scenarios that will prompt immediate medical attention.

6.6 Dose Modification

No dose modifications are permitted in this trial.

6.7 Intervention after the End of the Trial

All subjects who complete all visits through Visit 4 (all visits through the Maintenance Phase) of this trial will be eligible to screen to confirm eligibility to participate in the extension trial.

7 DISCONTINUATION OF TRIAL INTERVENTION 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.

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 6 should be conducted 30 days following the last dose.

A subject will discontinue IMP for the reasons listed below:

- Any of the following AESIs
  - 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
- Failure to comply with trial procedures or dosing
- Withdrawal of consent

- Investigator's discretion

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

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.

Details on the withdrawal of consent from the optional pharmacogenomic (PGx) assessment and/or optional future biospecimen research sample are provided in the ICF.

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, if necessary, 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). 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), is essential and required for trial conduct.

8.1 Screening and Baseline Assessments

All screening evaluations must be completed and reviewed 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.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Assessments (Table 2).

As part of the screening procedures, a head magnetic resonance imaging or computed tomography scan will be completed to demonstrate no progressive structural abnormality, unless the procedure has been performed within 10 years prior to signing the ICF. This procedure, if necessary, should be conducted as soon as possible during the Screening/Baseline Period (per local guidelines) with the report available prior to randomization.

Subjects will be dispensed an electronic diary (eDiary) and be trained on its use at the screening visit. The presence or absence of all seizure types experienced by each subject will be recorded daily in the diary from the Screening Visit through Visit 6 (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 BZDs.

As described in Section 5.1, a minimum of 8 focal onset (as defined in the 2017 ILAE Classification of Seizures [Fisher et al, 2017]), focal aware (except subjects with only focal aware seizures without a motor component), focal impaired awareness, or focal to bilateral tonic-clonic seizures during the 8-week Baseline Period with no 21-day period free of any of these seizure types should be confirmed by site personnel in order for the subject to be eligible for the trial.

A medical bracelet with subject and trial information will be dispensed at Visit 1.

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 BZD 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's Global Impression of Change

The self-report measure Patient's Global Impression of Change (PGIC) 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 of Symptoms Scale

The 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.

8.2.4 Clinical Global Impression-Improvement Scale

The CGI-I is an observer-rated scale that will be used to measure the subject's symptom severity compared with before initiation of treatment with IMP. It is important to note that the observer or rater will provide their assessment of the subject's current level of symptoms compared with their symptoms at baseline (Visit 1).

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

8.2.5 Quality of Life in Epilepsy – 31

The Quality of Life in Epilepsy – 31 (QOLIE-31) was developed in cooperation with professional postgraduate services, a division of Physicians World Communications Group and the QOLIE Development Group. The 31-item QOLIE-31 (Version 1.0) has been derived from the longer QOLIE-89 (Rausch & Crandall, 1982; Cramer et al, 1998).

The QOLIE-31 contains 7 multi-item scales that tap the following health concepts: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. A QOLIE-31 overall score is obtained using a weighted average of the multi-item scale scores. The QOLIE-31 also includes a single item that assessed overall health.

8.2.6 Health Utilities Index

The Health Utilities Index (HUI) is a rating scale used to measure general health status and health-related quality of life. The HUI questionnaires are designed to map onto 2 classification systems, HUI-2 and HUI-3, capable of measuring 24,000 and 972,000 unique health states, respectively. The HUI classifications measure a range of health domains with examples including sensation, mobility, pain, cognition, ambulation, and emotion (Horsman et al, 2003).

8.3 Safety Assessments

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

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
- Vital sign measurements, 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 height (screening only) and 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 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.

Height will be measured at screening only.

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)

- 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 and will include temperature, systolic and diastolic blood pressure, and heart rate.

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 at each investigational site.

8.3.3 Electrocardiograms

Electrocardiogram recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. Additional 12-lead 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.

If, during screening, an abnormal ECG finding is deemed medically significant according to the investigator's judgment (impacting the safety of the subject or the interpretation of the trial results) or meets an exclusion criterion (see Section 5.2), the subject should be excluded from the trial. At screening, triplicate ECG recordings should be taken approximately 1 minute apart. The central ECG service will provide the QT interval corrections based on Fridericia's formula (QTcF) for the 3 screening ECGs. A mean QTcF >450 msec as assessed by the central reader from the screening triplicate ECGs will be exclusionary.

Exclusion criteria for screening do not apply as mandatory discontinuation criteria for subjects who are already randomized. A repeat ECG should be performed to confirm any clinically significant abnormality that is identified in a randomized subject during the treatment period (which will be confirmed by central service read) and, in these cases, the medical monitor should be consulted on the appropriateness of the subject continuing in the trial.

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) 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

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).

8.3.5 Modified Clinical Institute Withdrawal Assessment – Benzodiazepines

The modified Clinical Institute Withdrawal Assessment – 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 BZD 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 Columbia – Suicide Severity Rating Scale (C-SSRS). This semi-structured interview was originally developed to evaluate the link between antidepressants and suicidal behavior and ideation in youth and AEs 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.

This trial will use the "Baseline/Screening" and "Since Last Visit" versions of the scale. The "Baseline/Screening" version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the trial, will be completed for all subjects at screening to determine eligibility and confirmed at baseline. Any subject with active suicidal ideation or suicidal behaviors within the last 6 months, suicidal behaviors within the last 2 years, or who in the clinical judgment of the investigator presents a serious risk of suicide should be excluded from the trial (see Section 5.2).

The "Since Last Visit" C-SSRS form will be completed at all visits after screening and Visit 1. 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 through the subject's last visit at the time points specified in the Schedule of Assessments (Table 2).

Adverse events that begin before the start of IMP but after obtaining informed consent will be recorded and categorized as pretreatment AEs. Any AE occurring after initiation of IMP are defined as treatment-emergent AEs (TEAEs).

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 (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a 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 on Day 120.

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 FDA 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 8.

- Hemoglobin: females <10 g/dL; males <11 g/dL

- WBC count <3.0 × 10^9/L
- Neutrophil count <2.0 × 10^9/L
- Platelet count <150 × 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 8:

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

Table 8 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).

4. 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). 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). 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 PK plasma samples will be provided in a laboratory manual. Plasma samples from treatment groups 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

Pharmacodynamic parameters are not evaluated in this trial.

8.8 Future Biospecimen Research

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

Future biospecimen research samples will be collected from subjects who provide additional consent specifically for this sample collection. Research performed on these samples may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects.

8.9 Health Economics

Health economics will be assessed using the QOLIE-31 and the HUI, which are described in Section 8.2.5 and Section 8.2.6, respectively.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint is the Response ratio (Rratio), defined as Rratio=(T−B)/(T+B) ×100, where T represents the focal onset seizure frequency rate per week in the Maintenance Phase and B represents the focal onset seizure frequency rate per week in the Baseline Period.

The hypotheses of interest are 2-sided tests of superiority comparing each active CVL-865 dose (CVL1, CVL2) to placebo.

H_{01}: $\mu_{placebo} = r_{CVL1}$ vs H_{11}: $\mu_{placebo} \neq r_{CVL1}$

H_{02}: $\mu_{placebo} = r_{CVL2}$ vs H_{12}: $\mu_{placebo} \neq r_{CVL2}$

9.2 Sample Size Determination

A sample size of 50 subjects per group (total of 150 subjects) will provide at least 80% power to detect a difference in the means of the primary outcome measure (Rratio) of -20 (PASS 2008 Tests of Two Means, Two Sample T-Test, 2-sided alpha level = 0.1, Standard Deviation=34, and a 20% dropout rate).

Therefore, approximately 214 subjects will be screened to achieve 150 subjects randomly assigned to treatment and 120 evaluable subjects for an estimated total of 40 evaluable subjects per treatment group.

In the event of higher than anticipated early terminations due to COVID-19 or other reasons, Cerevel may extend enrollment in order to maintain the planned statistical power.

9.3 Populations for Analyses

The following data sets are defined for analysis:

Screen Failures (SFs): comprises all subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to treatment in the trial.

Intent-to-Treat (ITT): comprises all randomized subjects

Full Analysis Set (FAS): comprises all randomized subjects who receive at least 1 dose of IMP

Modified ITT (mITT) Set: comprises all randomized subjects who receive at least 1 dose of IMP and have at least 1 entry in the seizure diary.

9.4 Statistical Analyses

Descriptive statistical methods will be used to summarize the data from this study, with statistical testing performed for the efficacy endpoints. 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. Statistical testing, if performed, will be 2-sided and will be performed using a significance (alpha) level of 0.1. 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.

The remainder of this section is a summary of the planned statistical analyses of the primary and secondary endpoints as well as a description of planned safety analyses. Full details of these analyses will be included in the statistical analysis plan (SAP). The SAP will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

9.4.1 Efficacy Analyses

Seizure frequency is defined as the total number of focal onset seizures over the treatment period of interest divided by the total number of days with no missing seizure counts in the corresponding period multiplied by 7.

The primary efficacy endpoint is the Rratio over the Maintenance Phase. This is calculated as Rratio=$(T-B)/(T+B) \times 100$, where T represents the seizure frequency rate per week in the Maintenance Phase and B represents the seizure frequency rate per week in the Baseline Period. The Rratio is between -100 and 100. Negative values will indicate reduction in seizure rate and positive values indicate increase in seizure rate during treatment.

Values of Rratio will be analyzed for the mITT population using an analysis of covariance model, including treatment and the baseline seizure frequency per week as a covariate. This estimand will include response data that occur before discontinuation of treatment. The differences between the treatment groups will be based on the least square mean (LSMean) difference between each CVL-865 group and placebo. A separate comparison of the combined CVL-865 groups and placebo may be conducted. The corresponding 95% confidence interval (CI) will be presented. Sensitivity analyses will be conducted by including all available data (de facto estimand).

A key secondary efficacy endpoint is the change from baseline in focal onset seizure frequency per week over the Maintenance Phase. These data will be log-transformed using the convention ln(X+1), where X represents the focal onset seizure frequency. The log-transformed values will be analyzed using an analysis of covariance model, including treatment as a factor and the log-transformed baseline focal onset seizure frequency per week as a covariate. The differences between the treatment groups will be based on the LSMean difference between each CVL-865 group and placebo. The percent reduction relative to placebo will be constructed by exponentiating the LSMean difference between each CVL-865 treatment group and placebo using the following formula:

$$\%\text{Reduction/Placebo} = 100\frac{\exp\left(LSMean_{placebo}\right) - \exp(LSMean_{CVL-865})}{\exp\left(LSMean_{placebo}\right) - 1}$$

The corresponding 95% CI will be calculated. A secondary analysis of this endpoint will be conducted using a Poisson Regression model on the untransformed data.

An additional key secondary endpoint is the 50% responder rate, defined as the percentage of subjects with at least a 50% reduction in the Maintenance Phase focal onset seizure frequency relative to the Baseline Period. This key secondary endpoint will be analyzed for the mITT population using a logistic regression model with effects for treatment. Odds ratios representing the odds of being a responder compared with placebo will be constructed for each CVL-865 treatment group. Subjects with missing or incomplete seizure information will be treated as non-responders for this analysis.

Continuous endpoints with repeated post-baseline assessments (CGI-S, CGI-I, PGIC) will be analyzed for the mITT population using a Mixed Model for Repeated Measures (MMRM). This estimand will include available post-baseline response data that occur before discontinuation of treatment. The baseline score (if applicable) will be included as the covariate, and treatment group (CVL-865 7.5 mg, CVL-865 25 mg, or placebo), visit, and the interaction between treatment group and visit will be included as fixed factors in the MMRM. The difference between each CVL-865 level versus placebo at each visit will be estimated based on the LSMeans from the MMRM. Changes from baseline in QOLIE-31 Domain and Overall Scores and HUI Utility Function scores will be analyzed using an analysis of covariance model (ANCOVA) with the baseline score and treatment group included in the model as fixed effects. The difference between each CVL-865 level versus placebo will be estimated based on the LSMeans from the ANCOVA model.

9.4.2 Safety Analyses

The safety analysis will be conducted on the FAS. Should there be any subjects that receive a treatment other the randomized treatment, the treatment as received will be used for safety presentations. Treatment-emergent adverse events will be coded according to MedDRA and summarized by treatment group, system organ class, and preferred term. Further summaries will be done by seriousness, severity, relationship to IMP, and dose at the time of onset.

The number of subjects withdrawing from IMP due to AEs, as well as the number of subjects with treatment-emergent AEs potentially related to abuse will be summarized by treatment group. Abuse potential will be assessed through the active monitoring of AEs related to potential abuse and AEs involving MHI.

Other safety endpoints will be summarized with descriptive statistics by treatment group, 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.

All data collected for subjects in the SF data set will be listed separately.

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. In addition, the relationship between the exposure levels (or dose) of CVL-865 and one or more efficacy/safety endpoints may be evaluated for the purpose of exploratory PK/PD analyses. Any population PK analysis and

exploratory biomarker analyses (if completed) will be presented separately from the main CSR.

9.5 Interim Analysis

The sponsor may perform an interim analysis to obtain preliminary information on safety and efficacy. Interim analysis results may be used for internal business decisions regarding future trial planning or stopping for futility. Before any interim analysis is instigated, the details of the objectives, decision criteria, and method of maintaining the trial blind will be documented and approved in an interim SAP or final SAP (as applicable).

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 (CIOMS) 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, HIPAA 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 subject who is rescreened is not required to sign another ICF if the rescreening occurs within 4 weeks from the previous ICF signature date.

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 report 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.

Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

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 9 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.

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

Serum 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. Female subjects with exclusively same sex partners may not be required to have pregnancy tests per investigator discretion; confirmation with the medical monitor is required.

Table 9 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)			

Laboratory Assessments	Parameters
Additional Required Tests	Serum pregnancy test (at screening and as needed for women of childbearing potential). Urine dipstick pregnancy test (at all other time points as needed for women of childbearing potential), followed by serum pregnancy test if urine dipstick test is positive.
Other Screening Tests	Urine drug screen for illicit drugs Serology (human immunodeficiency virus antibody, hepatitis B virus, hepatitis C virus)

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 10 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 result indicating a common underlying pathology/diagnosis should be reported as a single adverse event.

Table 11 Events Meeting the AE Definition

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after trial 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 12 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 13 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 14 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 15 SAE Reporting to the Sponsor of Designee via an Electronic Data Collection Tool

SAE 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 at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a trial subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on the paper SAE form (see next section) or to the sponsor or designee by telephone.

Table 16 SAE 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 woman of childbearing potential (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.

10.4.2 Collection of Pregnancy Information

10.4.2.1 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.

10.4.2.2 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: Future Biospecimen Research

Use/Analysis of DNA

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

- DNA samples will be used for research related to CVL-865 or epilepsy and related diseases. They may also be used to develop tests/assays including diagnostic tests related to CVL-865 or interventions of this drug class and epilepsy. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

- There are no planned analyses of DNA samples. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

- The samples may be analyzed as part of a multi-trial assessment of genetic factors involved in the response to CVL-865 or IMPs of this class to understand trial disease or related conditions.

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

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

- The samples will be retained while research on CVL-865 or interventions of this class or epilepsy continues but no longer than 15 years or other period as per local requirements.

10.6 Appendix 6: 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.

10.7 Appendix 7: Abbreviations

Abbreviation	Definition
AE	Adverse event
AED	Anti-epileptic drug
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APMP	Abuse Potential Monitoring Plan
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
BZD	Benzodiazepine
CBC	Complete blood count
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity of Symptoms
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standard of Reporting Trials
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
DBS	Deep brain stimulator
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalogram
ESAM	Events Subject to Additional Monitoring
ET	Early Termination
EU	European Union

Abbreviation	Definition
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
$GABA_A$	γ-aminobutyric acid type A
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HUI	Health Utilities Index
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
K_2EDTA	Dipotassium ethylenediamine tetraacetic acid
LSMean	Least square mean
mCIWA-B	Modified Clinical Institute Withdrawal Assessment–Benzodiazepines
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MHI	Medication handling irregularity
MHP	Mental Health Professional
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic resonance imaging
NOAEL	No observed adverse effect level
OLE	Open-label extension
PAM	Positive allosteric modulator
PD	Pharmacodynamic
PGIC	Patient's Global Impression of Change

Abbreviation	Definition
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PK	Pharmacokinetic
QOLIE-31	Quality of Life in Epilepsy-31
QTcF	QT interval as corrected for heart rate by Fridericia's formula
RNA	Ribonucleic acid
RNS	Responsive neurostimulator
RRatio	Response ratio
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SF	Screen Failures
SIF/DRF	Seizure Identification and Diagnostic Review Form
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TESC	The Epilepsy Study Consortium
ULN	Upper limit of normal range
US	United States
VNS	Vagus nerve stimulator
WBC	White blood cell
WOCBP	Women of childbearing potential

10.8 Appendix 8: Protocol Amendment History

Document History	
Document:	**Date (Day-Month-Year)**
Version 4.0	30 Jun 2020
Version 3.0	15 Nov 2019
Version 2.0	03 Oct 2019
Original Protocol Version 1.0	24 Jul 2019

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

Amendment: Protocol Version 3.0 (15 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
Table 1 Objectives and Endpoints Table 3 Objectives and Endpoints	Reworded secondary endpoint for TEAEs	Consistency with open-label extension protocol
Table 2 Schedule of Assessments	Addition of time points for safety laboratory blood samples (Visits 3, 5, and 6)	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 new AESI subsection	Update relevant protocol section with new potential risk of bone marrow suppression and decrease in peripheral hematologic parameters
5.2 Exclusion Criteria	Revised criterion for HIV, hepatitis B, and hepatitis C	Exclude subjects regardless of LFT results
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

Abbreviations: AESI = adverse event of special interest; HIV = human immunodeficiency virus; IMP = investigational medicinal product; WBC = white blood cell; TEAE = treatment-emergent adverse event

Amendment: Protocol Version 2.0 (03 Oct 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.

Section # and Name	Description of Change	Brief Rationale
Title Page Section 1 Protocol Summary	Addition of the EudraCT number	EudraCT number was included based on decision to conduct trials in countries in the European Union
Sponsor signatories	Change from [redacted], MD to [redacted] MD	Change in sponsor personnel
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Assessments Section 4.1 Overall Design	Text added to indicate subjects would enter the open-label extension trial CVL-865-SZ-002 at the end of the Maintenance Phase instead of Taper Phase; modification to duration of Treatment Phase to indicate 10 weeks for subjects who continue treatment in Trial CVL-865-SZ-002; footnote for dosing table added to clarify dosing for subjects who continue treatment in Trial CVL-865-SZ-002; footnote in Schedule of Assessments modified	In order to avoid unnecessary taper and retitration of investigational medicinal product for subjects entering Trial CVL-865-SZ-002, the point of entry into that trial was moved to the end of the Maintenance Phase (Visit 4)
Section 1.3 Schedule of Assessments	Change to row for "blood pressure and pulse rate" to "vital sign measurements"	Change made as measurements also include body temperature and respiratory rate
Section 1.3 Schedule of Assessments	Addition of physical/neurological examination to Visit 4 assessments	Based on decision to have eligible subjects enter the open-label extension trial CVL-865-SZ-002 at the end of the Maintenance Phase, this examination serves as baseline for the extension trial

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments	Footnote regarding rescreening was modified to indicate subjects would not retain their subject number in the event they were rescreened.	Correction of inaccurate information
Section 1.3 Schedule of Assessments	Footnote regarding timing of physical/neurological examinations was modified.	Correction of inaccurate information and addition of examination at Visit 4
Section 1.3 Schedule of Assessments	Removal of language stating female subjects with exclusively same sex partners are not required to have pregnancy tests	Change made to be consistent with sponsor standard practices
Section 4.4 Definition of Completed Subject	Modified text to indicate subjects who continued into Trial CVL-865-SZ-002 were considered to have completed Trial CVL-865-SZ-001 at Visit 4.	In order to avoid unnecessary taper and re-titration of investigational medicinal product for subjects entering Trial CVL-865-SZ-002, the point of entry into that trial was moved to the end of the Maintenance Phase (Visit 4)
Section 5.2 Exclusion Criteria Section 8.3.3 Electrocardiograms	Exclusion criterion 13 modified to exclude subjects with QTcF values >450 msec, regardless of sex	Change made to be consistent with ICH E14
Section 5.4 Screen Failures	Text regarding rescreening was modified to indicate subjects would not retain their subject number in the event they were rescreened	Correction of inaccurate information
Section 6.7 Intervention after the End of the Trial	Modified text to indicate subjects who were eligible would enter Trial CVL-865-SZ-002 after completion of the Maintenance Phase (Visit 4) of Trial CVL-865-SZ-001	In order to avoid unnecessary taper and re-titration of investigational medicinal product for subjects entering Trial CVL-865-SZ-002, the point of entry into that trial was moved to the end of the Maintenance Phase (Visit 4)
Section 8.3.1 Physical and Neurological Examinations	Removed specifications on methods to measure height at screening	No standard method to measure height will be required
Section 8.3.2 Vital Sign Measurements	Added respiratory rate to list of vital signs to be measured; clarified vital signs would be measured with subject in sitting/semi-recumbent position; removed requirement for triplicate blood pressure and heart rate measurements; added specifications for measurement of body temperature	Further clarification on how to assess vital signs

Section # and Name	Description of Change	Brief Rationale
Section 8.3.3 Electrocardiograms	Added language stating clinically relevant changes in ECGs will be recorded in the AE section of eCRF	Inadvertent omission in original protocol
Section 8.6.3 Methods and Analysis	Added language to provide flexibility to use CVL-865 samples for future exploratory analyses for potential metabolites and method development activities	Judicious use of collected human samples for future use towards potential method development activities and understanding metabolic fate of CVL-865
Section 8.6.3 Methods and Analysis	Moved text regarding use of CVL-865 concentration data to Section 9.4.3 Other Analyses	Text was moved to a more appropriate location within protocol
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	Correct errors in original protocol

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CLINICAL PROTOCOL PRINCIPAL INVESTIGATOR SIGNATURE PAGE

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTICENTER TRIAL OF CVL-865 AS ADJUNCTIVE THERAPY IN ADULTS WITH DRUG-RESISTANT FOCAL ONSET SEIZURES (REALIZE TRIAL)

Protocol Number: CVL-865-SZ-001

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 4.0: 30 Jun 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)