STATISTICAL ANALYSIS PLAN

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

Protocol Number: CVL-865-SZ-002

Compound: CVL-865

Trial Phase: 2

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

Sponsor Name: Abbvie

Protocol Version:	**Version 3.0**	**Date: 14 July 2020**
	Version 2.0	**Date: 26 November 2019**
	Original Version 1.0	**Date: 30 October 2019**

Analysis Plan Version: **Final Version 1.0, 23 January 2025**

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol CVL-865-SZ-002. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. Study Overview

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

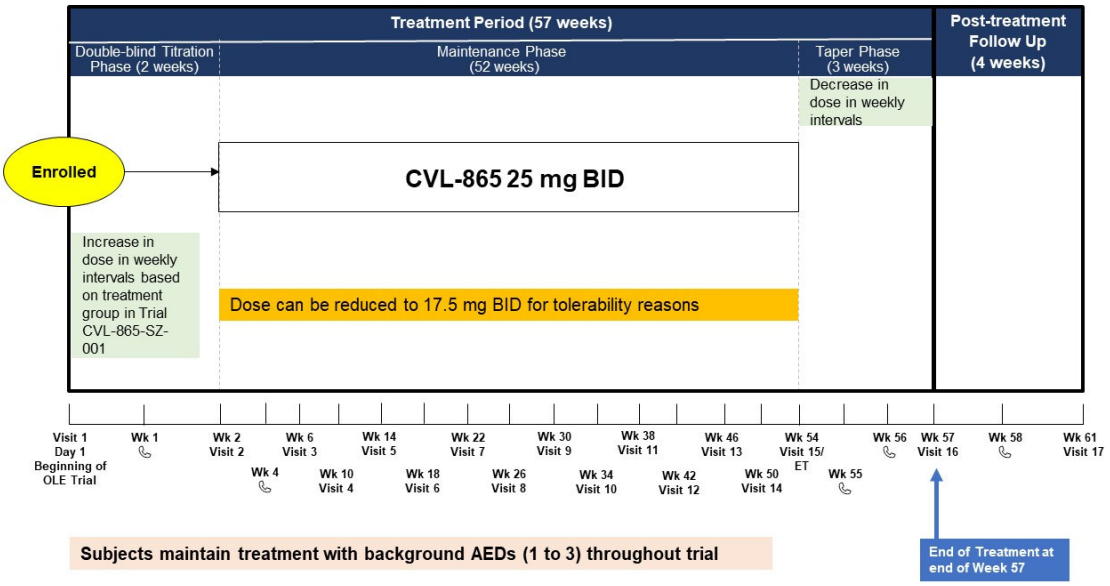
Eligible subjects will enter this trial directly after completing Visit 4 (end of Maintenance Phase) of Trial CVL-865-SZ-001. The efficacy and safety assessments from Visit 4 of Trial CVL-865-SZ-001 will serve as the baseline assessments for the open-label trial for any assessments that are not unique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

1.1.1. Study Design

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

- Up to 57-week Treatment Period consisting of the following:
  - 2-week double-blind Titration Phase
  - 52-week Maintenance Phase
  - 3-week Taper Phase
- 4-week Follow-up Period

Figure 1: Trial Schematic



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

1.2. Sample Size Considerations

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

1.3. Measures to Minimize Bias: Randomization and Blinding

1.3.1. Subject Assignment to Treatment

All patients will receive CVL-865.

1.3.2. Blinding

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

1.4. Treatment Period

Titration Phase:

Following enrollment in Trial CVL-865-SZ-002, subjects will enter a 2-week double-blind Titration Phase. Based on the blinded treatment group subjects were assigned to in Trial CVL-865-SZ-001, the dose will be increased in weekly intervals during the double-blind Titration Phase to a final dose of 25 mg BID as shown in table (Table 1). Subjects who completed the Maintenance Phase of Trial CVL-865-SZ-001 on a dose of 25 mg BID will remain on this dose (blinded) for the Titration Phase of Trial CVL-865-SZ-002.

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

Maintenance Phase:

Subjects will continue to receive treatment with CVL-865 25 mg BID throughout a 52-week Maintenance Phase. However, this daily dose of CVL-865 can be reduced to 17.5 mg BID to address tolerability issues upon investigator discretion. Following the Maintenance Phase, subjects will be tapered off investigational medicinal product (IMP) over 3 weeks in weekly intervals. A summary of the dosing schedule is provided in table below (Table 1).

A summary of the dosing schedule is provided below (Table 1).

Table 1. Summary of the Dosing Schedule

	Blinded Titration Phase		**Maintenance Phase**	**Taper Phase**		
Dose in Trial CVL-865-SZ-001	**Day 1**	**Day 8**	**Day 15-Day 379**	**Day 386**	**Day 393**	**Day 400**
Duration	2 weeks		52 weeks	3 weeks		
Placebo	5 mg BID	12.5 mg BID	25 mg BID	17.5 mg BID	10 mg BID	5 mg BID
CVL-865 7.5 mg BID	12.5 mg BID	17.5 mg BID	25 mg BID	17.5 mg BID	10 mg BID	5 mg BID
CVL-865 25 mg BID	25 mg BID	25 mg BID	25 mg BID	17.5 mg BID	10 mg BID	5 mg BID
Not applicable			17.5 mg BID[a]	10 mg BID	5 mg BID	2.5 mg BID

Abbreviations: BID = twice daily.
[a] Subjects who had their dose reduced to 17.5 mg BID due to tolerability reasons during the Maintenance Phase

Follow-up Phase:

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

2. OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are summarized in Table 2.

Table 2. Objectives and Endpoints

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

3. KEY ASSESSMENTS AND DERIVATIONS

3.1. Efficacy Assessments

3.1.1. Seizure Frequency, Type and Seizure Rate

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

Seizure rate is defined as the total number of focal onset seizures over the analysis period of interest divided by the total number of days with no missing seizure counts in the corresponding period. Seizure frequency will be defined as the seizure rate multiplied by the days within the period of interest. For cluster seizures, which are a group of seizures too numerous to count, the number of cluster episodes will be included as one seizure event. Unless otherwise specified, Seizure rate will only be calculated for focal onset seizures, which include focal aware seizures without motor signs, focal aware seizures with motor signs, focal impaired awareness seizures and focal to bilateral tonic-clonic seizures.

3.1.2. Seizure Freedom

Seizure freedom will be represented as a binary outcome defined as having no seizures during the maintenance period.

3.1.3. 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".

3.1.4. Clinical Global Impression-Severity of Symptoms Scale

The Clinical Global Impression-Severity of Symptoms Scale (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.

3.2. Safety Assessments

3.2.1. Adverse Event (AE)

An adverse event 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.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of trial treatment. All adverse events will be recorded on the ADVERSE EVENTS eCRF.

3.2.1.1. Adverse Event of Special Interest (AESI)

AESIs will be captured and monitored during this study. AESI include AEs potentially related to abuse or dependence, AEs involving medical handling irregularities, hematologic abnormalities and abnormal liver function tests. These events will be noted by the investigator in the ADVERSE EVENTS CRF.

3.2.1.2. Pre-Treatment Adverse Event

Any recorded Adverse Event that occurs after obtaining informed consent but prior to the start of IMP.

3.2.1.3. Treatment-emergent Adverse Event (TEAE)

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

3.2.2. Clinical Safety Laboratory Assessments

The clinical laboratory tests as listed in the protocol will be performed in accordance with the laboratory manual and the Schedule of Assessments. All results, including repeats, will be included in the laboratory reports. 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.

3.2.2.1. Treatment-emergent Laboratory Abnormality

A treatment-emergent laboratory abnormality is defined as value outside the normal range which occurs on or after the start of IMP through the last follow up contact. Where applicable, these abnormalities will be graded.

3.2.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the trial using the C-SSRS. It was designed to quantify the severity of suicidal ideation and behavior.

The “Since Last Visit” C-SSRS form will be completed at all visits. The investigator will review the results of the “Since Last Visit” C-SSRS during the trial to determine whether it is safe for the subject to continue in the trial. If a subject demonstrates potential suicidal ideation associated with actual intent or method or plan as indicated by “YES” answers on item 4 or 5 of the C-SSRS, the investigator will need to evaluate whether a risk assessment by a qualified mental health professional (MHP, or the investigator alone if the investigator is a qualified MHP) is needed and whether the subject should continue in the trial or be discontinued. Baseline values for C-SSRS will come from study CVL-865-SZ-001.

Details of C-SSR categories are provided in Section 9.2.

3.2.4. Modified Clinical Institute Withdrawal Assessment – Benzodiazepines (mCIWA-B)

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

3.2.5. Vital Signs

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.

3.2.6. Electrocardiograms

Electrocardiogram (ECG) recordings will be obtained after the subject has been 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.

3.2.7. Concomitant Medications and Non-Drug Therapy/Procedures

3.2.7.1. Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of IMP. These medications include those medications started before the initiation of IMP and continuing post Day 1 through the last dose of IMP. Medications that start after the last dose of IMP will be classified as taken post last dose and will not be considered as concomitant and will be noted as 'Post' in the data listing. All medications will be recorded in the CONCOMITANT MEDICATIONS CRF.

3.2.7.2. Concomitant Non-Drug Therapy/Procedures

Concomitant non-drug therapy/procedures are defined similarly to concomitant medications and will be recorded in the NON-DRUG THERAPY/PROCEDURES eCRF.

3.2.7.3. Prior Medications

Prior medications are those medications taken prior and ended prior to the initiation of IMP. These medications will be recorded in the CONCOMITANT MEDICATION eCRF.

3.2.7.4. Prior Non-Drug Therapy/Procedures

Prior non-drug therapy/procedures are defined similarly to prior medications and will be recorded in the NON-DRUG THERAPY/PROCEDURES eCRF.

3.2.8. Rescue Medicine

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

3.3. Pharmacokinetics

To evaluate the plasma exposure of CVL-865 (and anti-epileptic drug, if appropriate), a single daytime blood sample will be collected at Visits 1, 5, 8, and 11. The date and time of the pharmacokinetic (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.

4. DATA CONVENTIONS AND VISIT WINDOWS

4.1. Data Conventions

4.1.1. Age

Age is the age at the time of informed consent and is as captured on the DEMOGRAPHY eCRF.

4.1.2. Screen Failures

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

4.1.3. Study Day 1 (Extension)

Day 1 is the day IMP is first initiated in CVL-865-SZ-002. The extension Day 1 will be referred to as 'Day 1' throughout the document.

4.1.4. Study Day 1 (Double-Blind)

Day 1 is the day IMP is first initiated in CVL-865-SZ-001.

4.1.5. Study Day of an Event (Extension)

Study day of an event is defined relative to Day 1 as:

Study Day = event date – date of Extension Day 1 (+ 1, if event date ≥ date of Day 1).

This calculation will result in negative study days for an event occurring prior to the start of IMP and positive study days for an event on or after the start of IMP. There will be no Day 0 value to match the schedule of events.

4.1.6. Days on Study (Extension)

Days on Study is the number of days from Day 1 to the date of completion/discontinuation as recorded on the END OF STUDY CRF.

4.1.7. Days on Study (Double-Blind + Extension)

Days on Study is the number of days from Double-Blind Day 1 to the date of completion/discontinuation as recorded on the END OF STUDY CRF.

4.1.8. Days on IMP (Extension)

Days on IMP is the number of days from Day 1 to the date of last dose of IMP as recorded on the EXPOSURE CRF.

4.1.9. Days on IMP (Double-Blind + Extension)

Days on IMP is the number of days from Double-Blind Day 1 to the date of last dose of IMP as recorded on the EXPOSURE CRF.

4.1.10. Double-Blind (DB) Baseline Value

DB baseline values will be defined as the baseline values from SZ-001 double-blind study.

4.1.11. Extension Baseline Value

For purposes of analysis, the baseline value is defined as the last value obtained prior to initiation of IMP in CVL-865-SZ-002 (e.g. the Study Day 1 value). Should the Day 1 visit value be obtained after the first dose of IMP or if this value is not available at Day 1, then the most recent value obtained prior to earliest initiation of IMP will be used for the baseline value.

4.1.12. Last Dose of IMP

Last Dose of IMP is defined as the last date that the subject received IMP.

4.1.13. Overdose

Overdose is any dose of CVL-865 greater than 80 mg within a 24-hour time period (+2 hours).

4.1.14. Change from Baseline (Extension)

Change from baseline for a given endpoint is defined as the value on a given Study Day (time point) minus the Baseline Value.

4.1.15. Change from Double-Blind Baseline

Change from double-blind baseline for a given endpoint is defined as the value on a given Study Day (time point) minus the double-blind Baseline Value.

4.1.16. Cumulative Dose of IMP (Extension)

The cumulative dose of IMP is calculated in milligrams and is based on the daily dose of IMP as recorded in the EXPOSURE CRF.

4.1.17. Cumulative Dose of IMP (Double-Blind + Extension)

The cumulative dose of IMP is calculated in milligrams and is based on the daily dose of IMP as recorded in the EXPOSURE CRF.

4.1.18. Compliance with Study Drug (Extension)

Dosing compliance based on daily dose of IMP as recorded in the EXPOSURE CRF will be defined by the dosing compliance ratio: the number of doses actually taken by the subject divided by the number of doses that were expected to be taken during the same period multiplied by 100. If poor compliance is encountered (e.g., 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.

4.1.19. Diary Days

Diary days are defined as days with completed ediary assessments.

4.1.20. Diary Compliance

Diary compliance will be calculated as 100 times the number of diary days (i.e., days with completed diary assessments) during the period and dividing this quantity by the expected number of diary days that should have been completed during this period.

4.1.21. Handling of Missing Severity or Relationship for Adverse Events

Adverse events with missing severity will have the severity imputed as 'Severe'. Adverse events with missing relationship to CVL-865 will have the relationship imputed as 'Related' if the AE started after the first CVL-865 dose in CVL-865-SZ-002.

Actual values will be presented in the data listings.

4.1.22. Handling of Incomplete or Missing Dates

An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. The database contains data fields for month, day, and year. A date is incomplete if at least one of these three fields is not known.

For many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (e.g. if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

- Missing start day, but month and year present:

  If the event occurs same month and year as the occurrence of IMP, then the start day of the event will be assigned to the day of first dose of IMP (i.e., Day 1).

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

- Missing start day and month, but year present:

  If event occurs in the same year as IMP, then the start date of the event will be assigned to Day 1.

  Otherwise, the start day and month will be set to 01 January.

- In the unlikely event of a completely missing start date (year not present), the start date will be imputed as Day 1.

- Missing end day, but month and year present:

  The day will be set to the last day of the month.

- Missing end day and month, but year present:

  The end day and month will be set to the date of study completion.

  However, if study completion year is greater than the year of the event, then the day and month will be set to 31 December.

- Missing all components of an end date and the event is not marked as ongoing:

  The event will be considered as 'ongoing' and will be considered treatment-emergent if the start date is on or after Day 1.

If any imputed date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date. If the imputed date is later than the date of study withdrawal, then the date of study withdrawal will be imputed for the date. In subject data listings, start and stop date of events will be displayed as reported on the eCRF (i.e., imputed values will not be listed).

4.1.23. Handling of Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, as for example, "<0.1" or ">10", the data will be imputed for quantitative summaries. The actual values as reported in the database will be presented in data listings.

For incorporation in quantitative summaries (except for concentration data), the following imputation rules will be employed:

- The lower limit of quantification will be replaced with ½ the value of the lower limit. For example, < 0.1 will be replaced with 0.05.
- The upper limit of quantitation will be increased by one level of precision that precedes the value. For example, ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1".

Additionally, the upper limit of normal (ULN)/lower limit of normal (LLN) values may be reported as alphanumeric (e.g., '<5', '≤5', '>5', '≥5'). In these cases, if the ULN or LLN is necessary for determination of the laboratory severity grade, the following conventions will be employed:

If the value is in the form of ≤5, the ULN will be populated with the value after removing the symbol (i.e., the ULN is set to 5). If the value is in the form of <5, the ULN will be decreased by two levels of precision in the direction of the symbol (i.e., the ULN is set to 4.99).

If the value is in the form of ≥5, the LLN will be populated with the value after removing the symbol (i.e., the LLN is set to 5). If the value is in the form of >5, the LLN will be increased by two levels of precision in the direction of the symbol (i.e., the LLN is set to 5.01).

4.2. Analysis Periods

The start and end dates of each analysis period (following the study design) are used for the classification of efficacy data. The exact start and end of each of these periods is described for calculation purposes in Table 3. Seizure frequency for each analysis period will be calculated based on Table 3.

Table 3. Definition of Analysis Periods for Efficacy Data

Analysis Period	Duration	Start Date	End Date
Extension Titration Phase	~2 Weeks	Study Day, 1	The lesser of: Day 15 (Visit 2) minus 1 or **Early termination (minus 1) or End of Treatment
Extension Maintenance Phase	~52 Weeks	Day 15 (Visit 2)	The lesser of: ***Day 379 (Visit 15) minus 1 or **Early termination (minus 1) or End of Treatment
Extension Taper Phase	~3 Weeks	Day 379 (Visit 15) or **Early termination	End of Treatment

** If a subject experiences early termination from the study and continues to Taper Phase, end dates will be bound by early termination minus 1, while the start of Taper Phase will begin on the date of early termination.
*** If a subject continues to Taper Phase from Maintenance Phase

4.3. Visit Windows

When data are collected serially over time, individual data presentations may include by-study visit displays. Visits will be presented according to the nominal study day and visit as obtained from the CRF or laboratory data unless the visit is an early termination or unscheduled visit. Early termination and unscheduled visits will be assigned visit windows based on the study day completed according to Table 4 , Table 5 and Table 6.

If assessments are collected multiple times within a given visit, the scheduled visit, if available, will be used for summary presentations. If no scheduled visit is available, then the result closest to the scheduled visit date will be used for summary presentations. If two unscheduled measurements (discharge or unscheduled visit) have the same distance to the expected date, the earlier value will be used. If a subject has multiple non-missing unscheduled values on the same date, then the last one is used, as determined by the time collected, if available.

Table 4. Visit Windows for Early Termination and Unscheduled Visits – ECGs, Vital Signs, C-SSRS, PGI-C, CGI-S and Safety Laboratory Urine Sample

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
≤ 1 Predose	Baseline	1
>1 to 29 (Except ECG and Vitals)	Day 15 (Visit 2)	15
>1 to 71 (ECG and Vitals only) 30 to 71	Day 43 (Visit 3)	43
72 to 127	Day 99 (Visit 5)	99
128 to 211	Day 183 (Visit 8)	193
212 to 323	Day 267 (Visit 11)	267
>323 (PGI-C, CGI-S only) 324 to 389 (C-SSRS, ECG, Vital Signs and Safety Laboratory urine sample only)	Day 379 (End of Maintenance Phase)	379
>389 (ECG, Vital Signs and Safety Laboratory urine sample only) 390 to 414 (C-SSRS only)	Day 400 (End of Taper Phase)	400
>414 (C-SSRS only)	Day 428 (End of Post-treatment Follow-up	428

Table 5. Visit Windows for Early Termination and Unscheduled Visits – Safety Laboratory Blood Sample Assessments

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target day
≤ 1 Predose	Baseline	1
>1 to 29	Day 15 (Visit 2)	15
30 to 57	Day 43 (Visit 3)	43
58 to 85	Day 71 (Visit 4)	71
86 to 113	Day 99 (Visit 5)	99
114 to 141	Day 127 (Visit 6)	127
142 to 169	Day 155 (Visit 7)	155
170 to 197	Day 183 (Visit 8)	183
198 to 225	Day 211 (Visit 9)	211
226 to 253	Day 239 (Visit 10)	239
254 to 281	Day 267 (Visit 11)	267
282 to 309	Day 295 (Visit 12)	295
310 to 337	Day 323 (Visit 13)	323
338 to 365	Day 351 (Visit 14)	351
366 to 389	Day 379 (End of Maintenance Phase)	379
390 to 414	Day 400 (End of Taper Phase)	400
414 and higher	Day 428 (End of Post-treatment Follow-up)	428

Table 6. Visit Windows for Early Termination and Unscheduled Visits – mCIWA-B

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 to 379 (on treatment, prior to Taper Phase)	Baseline	379
1 to 389 (off treatment)	Day 386 (Contact)	386
390 to 396	Day 393 (Contact)	393
397 to 403	Day 400 (End of Taper Phase)	400
403 to 417	Day 407 (Contact)	407
418 and higher	Day 428 (End of Post-treatment Follow-up)	428

Table 7. Visit Windows for Early Termination and Unscheduled Visits – PK Sampling

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 to 141	Day 99 (Visit 5)	99
142 to 450	Day 183 (Visit 8)	183
451 and higher	Day 267 (Visit 11)	267

5. STATISTICAL ANALYSIS METHODS

5.1. General Considerations

Descriptive statistical methods will be used to summarize the data from this trial. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (N), number of observations (n), arithmetic mean, median, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum, and maximum for continuous data, and frequencies and percentages for categorical data. Certain figure presentations will include the standard error of the mean (SE). The term "treatment group" refers to treatment assignment in Trial CVL-865-SZ-001: Placebo, 7.5 mg BID CVL-865, 25 mg BID CVL-865 and assignment in Trial CVL-865-SZ-002: 25 mg BID CVL-865. All data collected from subjects who sign the informed consent form, including screen failures, will be included in data listings. Unless otherwise noted, the data listings will be sorted first by treatment, subject number and then by date within each subject number.

5.2. Populations for Analyses

The analysis populations are defined (Table 8).

Table 8. Populations for Analysis

Population	Description	Analysis
Enrolled Set	All subjects who signed the informed consent form.	Disposition
Safety Set	All subjects that receive at least 1 dose of IMP.	Demographics, baseline characteristics and safety analysis
Efficacy Set	All subjects in the Safety Set who have at least 1 post-baseline seizure diary entry.	Exploratory analyses
PK analysis set	All subjects who receive at least 1 dose of IMP and have at least 1 measurable CVL-865 concentration	PK analysis

Abbreviations: IMP = investigational medicinal product, PK = pharmacokinetic.

5.3. Statistical Hypotheses

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

5.4. Time of Analysis

A final analysis will be conducted once the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, the pre-analysis meeting has occurred, and the database has been locked.

No interim analyses are planned.

5.5. Multiplicity Adjustment

No adjustments for multiplicity are required as only descriptive statistics will be generated.

5.6. Strata and Covariates

No stratification was implemented in randomization.

5.7. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition will be based on the Enrolled set population with tabulation of the number of subjects who complete the study, the number who discontinued from the study, reasons for discontinuation including the number of discontinues due to COVID-19 will be summarized. Additionally, the number of days on study for extension and double-blind will be summarized.

Number of subjects in each analysis population set will be summarized.

Demographic data and baseline characteristics including age, gender, childbearing potential, race, ethnicity and weight will be summarized using descriptive statistics for the Safety set.

5.8. Exposure to Treatment

The number of subjects who received IMP, treatment compliance, cumulative exposure to IMP (Double-Blind + Extension), days on IMP (Double-Blind and Extension), prematurely discontinued, and reason for IMP discontinuation will be summarized.

5.9. Medical History

Medical history events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 or higher by preferred term and system organ class. Medical history will be summarized by treatment group using preferred terms and system organ classes. All events will be listed.

5.10. eDiary compliance

Exploratory efficacy variables are based on diary-collected seizure frequencies, and as such, diary compliance will be evaluated along with treatment compliance. Subjects are instructed to complete their diary entries at least once a day during the study. A dairy day will be considered missing for compliance if a seizure diary record is missing for that day. Diary compliance will be evaluated during the Maintenance Phase and overall treatment period.

Diary compliance will be calculated as 100 times the number of diary days (i.e., days with completed diary assessments) during the period and dividing this quantity by the expected number of diary days that should have been completed during this period of time. Compliance is only computed for actual time of participation in the study up to the end of the Treatment Period. Only data prior to and on the date of last dose of study medication will be included in the compliance calculation. If a subject did not enter an analysis period, the diary compliance for the analysis period will not be calculated.

Diary compliance data will be listed and sorted by treatment group and subject.

5.11. Exploratory Efficacy Analyses

5.11.1. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Focal onset seizure frequency per week over the Maintenance Phase and change from baseline
- Focal onset seizure frequency per 8 week period over the Maintenance Phase and change from baseline
- Seizure freedom
- Seizure rate over time
- PGI-C score at each trial visit
- Change from Baseline in CGI-S score at each trial visit

5.11.2. Exploratory Efficacy Analysis Approach

All Exploratory Efficacy Analysis endpoints will be summarized on the Efficacy Set.

Descriptive statistics will be provided for each efficacy endpoint and will be summarized at each trial visit using available data. Focal onset seizure frequency per week and 8 week period over the maintenance phase will include change from baseline. Baseline is derived from Trial CVL-865-SZ-001 and will be adjusted to an appropriate frequency for comparison. Any period which does not maintain greater than 20% diary compliance will not be summarized. Seizure rate over time will be displayed as adjusted frequencies over the maintenance phase. CGI-S will be displayed separately as change from baseline and change from Double-Blind Baseline. Baseline (Extension) is defined as the last assessment prior to the initiation of IMP in CVL-865-SZ-002. Double-Blind Baseline will be the baseline value from study CVL-865-SZ-001.

5.12. Safety Analyses

The safety analysis will be conducted on the Safety Set.

Listings will be sorted such that all data collected for screen failed subjects will be grouped separately.

5.12.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 27.1 or higher PT and SOC. If a subject experiences multiple events that map to a single PT, the greatest intensity and strongest investigator assessment of relation to IMP will be assigned to the PT for the appropriate summaries. Events with missing intensity or relationship will be classified as outlined in Section 4.1.21. Summaries of TEAEs will include any AEs reported beginning with the initiation of study drug on Day 1 through last follow up contact. The occurrence of TEAEs will be summarized by PTs, SOCs, and intensity. Separate summaries of treatment-emergent serious adverse events (TESAEs), TEAEs related to IMP, TEAEs leading to death, AESIs (including those potentially related to abuse as assessed through the active monitoring of adverse events related to potential abuse and AEs involving medication handling

irregularities), AESIs not leading to discontinuation of IMP, TEAEs leading to the discontinuation if IMP and events leading to discontinuation of study will be generated respectively. A presentation of AEs by dose at event onset will be prepared. All adverse events reported will be listed for individual subjects showing both verbatim and PTs. All adverse events that occurred prior to the initiation of study will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.1.22 as required to determine TEAEs.

5.12.2. Non-AED Concomitant Medications and Non-Drug Therapy/Procedures

Prior and concomitant medications taken during the study will be coded using the World Health Organization (WHO) dictionary (Version: Global B3, March 2024 or higher). Each concomitant medication will be classified as either an anti-epileptic (AED) or a non-AED medication. Non-AED prior and concomitant medications will be summarized by frequency of drug classification and generic drug name. Prior and concomitant medications will be presented in a data listing. The drug classification will be the anatomic therapeutic chemical (ATC) classification 4. If this classification is not present, the next available classification will be utilized.

Prior and concomitant non-drug therapy/procedures will be coded using MedDRA Version 27.1 or higher. Concomitant non-drug therapy/procedures will be summarized by frequency of SOC and PT. Prior and concomitant non-drug therapy/procedures will be presented in a data listing.

5.12.3. Concomitant AED Medication and Therapy/Procedures

Concomitant AED medications will be summarized by frequency of drug classification and generic drug name.

5.12.4. Clinical Laboratory Assessments

Descriptive summaries of selected (quantitative) clinical laboratory results and change from baseline will be presented by visit. Change from double-blind baseline will be summarized by visit. Additionally, for hematology, blood chemistry, coagulation, and urinalysis parameters, toxicity grade will be determined for laboratory tests with toxicity grade specified in Section 9.4. Shifts from baseline to greatest (worst) treatment-emergent laboratory toxicity will be presented. For parameters not graded by CTCAE, laboratory values outside the normal range for each parameter will be identified using shift tables. Each subject's hematology, blood chemistry, and quantitative urinalysis values will be flagged as "low" (below the lower limit of normal/LLN), "normal" (within the normal range), or "high" (above the upper limit of normal/ULN) relative to the normal ranges of the central laboratory. In addition, the shift from baseline to the maximum post-baseline value and the minimum post-baseline value for each laboratory test.

The number and percentage of subjects who have post-baseline elevations in liver transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or bilirubin abnormalities in relation to fold above the upper limit of normal will be summarized according to the Food and Drug Administration's Premarketing Clinical Evaluation on Drug-Induced Liver Injury Guidance for Industry (FDA 2009).

Abnormal hepatic laboratory values will be categorized and evaluated for any occurrence among all post-baseline assessments (where "and" in the bulleted list below indicates elevations occurring at the same visit). Within each laboratory parameter grouping, a subject may be counted once per elevation criteria using the worst-case result. That is, a subject with a worst case ALT elevation > 5 × the ULN would be counted once in the ALT > 3 × ULN category and once in the ALT > 5 × ULN category, regardless of how many ALT elevations the subject had that met the > 5 × ULN and > 3 × ULN elevation criteria.

- ALT and/or AST > 3 × ULN and total bilirubin > 1.5 or 2 × ULN at the same visit at the same visit
- AST > 3, 5, 10, 20 × ULN
- ALT > 3, 5, 10, 20 × ULN
- Total bilirubin > 1.5, 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN

In addition, an eDISH plot, a shift plot showing liver safety panel tests over time (baseline vs. post-baseline), and distribution plots of ALT, AST, ALP, and bilirubin over time will be produced to aid identification of any potential cases (Merz M. et. al. 2014). The plots to be included are the scatter plot of maximum transaminase versus maximum bilirubin, the liver test safety panel over time, and the distribution of ALT by time. The distribution plots for AST, ALP, and bilirubin will use the same format as used for ALT.

5.12.5. Vital Signs

Vital sign measurements will include body temperature (oral or tympanic), respiratory rate, systolic blood pressure, diastolic blood pressure, and heart rate. Body temperature, blood pressures, and heart rate will be measured with the subject in a sitting/semi-recumbent position after a 5-minute rest. For the body temperature, the same method must be used for all measurements for each individual subject and should be the same for all subjects at each investigational site. Vital signs and corresponding changes from extension baseline will be summarized by visit using descriptive statistics. Change from double-blind baseline will be summarized by visit using descriptive statistics.

Out of range vital signs occurring post-baseline will be summarized.

The following out-of-range criteria will be summarized for post-baseline assessments:

- Systolic Blood Pressure (Supine)
  - < 90 mmHg
  - > 140 mmHg
- Diastolic Blood Pressure (Supine)
  - <50 mmHg
  - > 90 mmHg

- Heart Rate (Supine)
  - < 60 bpm
  - > 100 bpm
- Respiratory Rate
  - < 12 bpm
  - > 20 bpm
- Temperature
  - < 36° C
  - > 38° C

Vital signs results will be listed.

5.12.6. Electrocardiograms (ECGs)

ECGs measurements and corresponding changes from extension baseline will be summarized by visit using descriptive statistics. Change from double-blind baseline will be summarized by visit using descriptive statistics.

The number and percentage of subjects who experience any post-baseline occurrence of potentially clinically significant corrected QT values using Fridericia's method (QTcF) will be summarized. These presentations will include QTcF values > 450 msec to ≤ 480 msec, > 480 msec to ≤ 500 msec, and > 500 msec; or changes of > 30 msec to ≤ 60 msec or > 60 msec. Important abnormalities in ECG waveform that are changes from baseline readings will also be reported in a listing.

5.12.7. Physical and Neurological Examinations

Physical and neurological examination data will be listed.

5.12.8. Modified Clinical Institute Withdrawal Assessment – Benzodiazepines (mCIWA-B)

The clinician-observed assessment section has been removed for the modified version of CIWA-B, and the total scores of mCIWA-B ranges from 1 to 68. The total score will be summarized descriptively at the scheduled visits. Change from on-treatment Day 379 assessment will be included.

5.12.9. Columbia-Suicide Severity Rating Scale (C-SSRS)

The maximum post-baseline results from the C-SSRS will be summarized. The maximum of each subscale (suicidal ideation [Categories 1-5], suicidal behavior [Categories 6-10], suicidal ideation or behavior [Categories 1-10], and self-injurious behavior without suicidal intent) will be presented. The number of patients with suicide-related treatment-emergent events, treatment-emergent suicidal ideation, and suicidal behavior, based on a comparison of the C-SSRS at double-blind baseline and/or previous lifetime experience to maximum C-SSRS scores across all post-baseline assessments will be provided. All C-SSRS elements will be reflected in a listing.

5.12.10. Missed Visits Due to COVID-19

The number and proportion of missing visits and key assessments due to COVID-19 control measures and the frequency of remote assessments performed due to COVID-19 restrictions will be tabulated by visit, and assessment.

5.13. Pharmacokinetics

5.13.1. Pharmacokinetic Sampling

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

5.13.2. Pharmacokinetic Analysis

Plasma concentrations of CVL-865 in unit as reported by the analytical laboratory will be summarized by nominal time point using descriptive statistics. Summaries will include mean, standard deviation and coefficient of variation, median, minimum, maximum, and geometric mean.

Concentration values that are below the level of quantification (BLQ) will be set to zero for summary tables. The geometric mean, however, will be calculated by imputing BLQ values as ½ BLQ. Individual values that are BLQ will be presented as “BLQ” in the concentration data listing.

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/pharmacodynamic analyses. Any population PK analysis and exploratory biomarker analyses (if completed) will be presented separately from the main clinical study report.

5.14. Protocol Deviations

All protocol deviations will be reviewed by the project team prior to database lock to identify subjects with important protocol deviations. Summaries of important deviations will be presented by category of deviation. All deviations from the protocol will be listed by category along with a description and any additional comments.

6. CHANGES IN THE PLANNED ANALYSES

Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

7. REVISION HISTORY

Date	Revision	Rationale

8. REFERENCES

Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. J Clin Psychopharmacol. 1989;9(6):412-6.

Merz M, Lee KR, Kullak-Ublick GA, Brueckner A, Watkins PB. Methodology to Assess Clinical Liver Safety Data. Drug Saf (2014) 37 (Suppl 1):S33–S45

US Food and Drug Administration (FDA). Guidance for Industry: Adaptive Designs for Clinical Trials of Drugs and Biologics; 2019.

US Food and Drug Administration (FDA). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation; 2009.

9. APPENDICES

9.1. Schedule of Assessments

Table 9. Double-blind Titration Phase and Maintenance Phase (Through Visit 12)

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

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

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

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

a. Contact with subject via phone call, internet/web, or other acceptable means of communication to check on their status.
b. Screening/Baseline for Trial CVL-865-SZ-002 occurs at Visit 1, which is the same day as Visit 4 in Trial CVL-865-SZ-001. Any assessments conducted for Visit 4 of Trial CVL-865-SZ-001 will be considered the baseline assessments for Visit 1 of Trial CVL-865-SZ-002.
c. Individual sites may require subjects to have COVID-19 testing done prior to enrollment. COVID-19 testing may be performed after enrollment per the investigator's discretion.
d. In the event that a subject is unable to attend a clinic visit in person due to restrictions related to COVID-19, this visit may be completed remotely. Please refer to the Trial Operations Manual for further instructions related to remote visits.
e. The physical examination should include weight at all time points. Physical and/or neurological examinations can be done at any time point during the trial at the investigator's discretion.
f. The "Since Last Visit" C-SSRS form will be completed at all visits.
g. Adverse events (serious and non-serious) and concomitant medications should be recorded from the time of signing the ICF through the subject's last visit.
h. For women of childbearing potential only. All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Monthly pregnancy tests will be required for all womenof childbearing potential.
i. The urine drug screen can be conducted at any time during the trial at the discretion of the investigator.

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

Table 10. Maintenance Phase (Visits 13 Through 15/ET Only), Taper Phase, and Post-treatment Follow-up Phase

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

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

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

a. Contact with subject via phone call, internet/web, or other acceptable means of communication to check on their status.
b. In the event that a subject is unable to attend a clinic visit in person due to restrictions related to COVID-19, this visit may be completed remotely. Please refer to the Trial Operations Manual for further instruction related to remote visits.
c. Subjects should begin the Taper Phase after they have completed treatment in the Maintenance Phase or at the time the decision is made to discontinue. All Taper Phase and Post-treatment Follow-up procedures should be performed as indicated. If a subject discontinues early and it is inadvisable for them to taper IMP (after agreement from medical monitor), the subject should complete the Visit 17 assessments approximately 30 days following the last dose of IMP.
d. The physical examination should include weight at all time points. Physical and/or neurological examinations can be done at any time point during the trial at the investigator's discretion.
e. The "Since Last Visit" C-SSRS form will be completed at all visits.
f. Adverse events (serious and non-serious) and concomitant medications should be recorded from the time of signing the ICF through the subject's last visit.
g. For women of childbearing potential only. All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests can be performed at any time during the trial at the discretion of the investigator if pregnancy is suspected. Monthly pregnancy tests will be required for all women of childbearing potential.

9.2. Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior Scores

The C-SSRS is comprised of 10 categories with binary responses. The 10 categories include:

Category 1 – Wish to be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Categories 1-5 represent Suicidal Ideation and categories 6-10 represent Suicidal Behavior. Each category is scored as 1 if there is a positive response in the category and a 0 if there are no positive responses in the category.

- Self-Injurious Behavior Without Suicidal Intent During Treatment

A subject will be categorized as having self-injurious behavior without suicidal intent if there is an occurrence of non-suicidal self-injurious behavior on the C-SSRS – Since Last Visit eCRF at any post-baseline visit.

- Baseline C-SSRS Score

Baseline represents the pre-treatment assessment of recent history, with elements of suicidal ideation assessed over the prior 6 months and elements of suicidal behavior assessed over the prior 2 years. It is scaled from 0 (no suicidal ideation or behavior) to 10 (completed suicide)

- Treatment-Emergent Suicide-Related Event

A subject will be categorized as having a treatment-emergent suicide-related event if at least one post-baseline suicidal ideation or suicidal behavior score is greater than 0.

- Treatment-Emergent Suicidal Ideation Compared to Recent History

A subject will be categorized as having treatment-emergent suicidal ideation compared to recent history when there is at least one post-baseline suicidal ideation score > 0 and is an increase from baseline. Lifetime scores are not considered for baseline suicidal ideation responses.

- Treatment-Emergent Serious Suicidal Ideation Compared to Recent History

A subject will be categorized as having treatment-emergent serious suicidal ideation compared to recent history if the baseline score was < 4 and the post-baseline suicidal ideation score increases to 4 or 5. Lifetime scores are not considered for baseline suicidal ideation responses.

- Emergence of Serious Suicidal Ideation Compared to Recent History

A subject will be categorized as having emergence of serious suicidal ideation compared to recent history if baseline score was 0 (no suicidal ideation) and post-baseline C-SSRS suicidal ideation score is either 4 or 5. Lifetime scores are not considered for baseline suicidal ideation responses.

- Emergence of Suicidal Behavior Compared to all Prior History

A subject will be categorized as having emergence of suicidal behavior compared to all prior history if there had been no suicidal behavior in Categories 6-10 reported at any pre-treatment assessment, including responses to lifetime history questions, and there is at least one positive post-baseline C-SSRS assessment in Categories 6-10. 'All Prior History' represents lifetime history.

9.3. Programming Conventions

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a 1.0" boundary on the left and right edges. The top and bottom margins are 1.0" for tables and listings but may vary for figures. Output should be printed in Courier New with a point size of 8.
- Identification of analysis population: Every summary table and figure will clearly specify the analysis population being summarized. Listings will be prepared for all subjects randomized.
- Group headers: In the summary tables, the group headers will identify the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.
  - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations
  - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by subject number and date, if applicable. If a listing is sorted in a different manner, it will be indicated on the listing shells.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.

  - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.
  - Means and quartiles will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
  - Calculated percentages will be reported with one decimal.
  - Coefficient of variation will be reported to the same number of decimal places as the standard deviation.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
- Time will be presented according to the 24-hour clock (HH:MM).
- Verification of Results: All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

9.4. CTCAE Based Laboratory Test Results Grading Specifications

Lab Test = Albumin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death

Albumin will have grades 1-3,

- Grade 1 being any values from the LLN to 3 g/dL,
- Grade 2 from 2 to < 3 g/dL and
- Grade 3 < 2 g/dL

Lab Test = Amylase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-

Amylase will have Grades 1, 2 and 3:

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 5.0 x ULN
- Grade 3 from>5 x ULN

Lab Test = Alkaline Phosphatase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Alkaline Phosphatase will have grades 1-4 and grading is based ULN only.

- Grade 1 being any values from the ULN to 2.5 x ULN
- Grade 2 from >2.5 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Alanine Aminotransferase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

ALT will have grades 1-4 and grading is based ULN only. The baseline abnormality will be ignored.

- Grade 1 being any values from the ULN to 3.0 x ULN
- Grade 2 from >3.0 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Aspartate Aminotransferase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

AST will have grades 1-4 and grading is based ULN only.

- Grade 1 being any values from the ULN to 3.0 x ULN
- Grade 2 from >3.0 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Bilirubin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-

Bilirubin will have grades 1-4 and grading is based ULN only

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 3.0 x ULN
- Grade 3 from >3.0 to 10.0 x ULN
- Grade 4 from>10.0 x ULN

Lab Test = Corrected Serum Calcium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death

Calcium will have to be corrected for albumin using the formula previously discussed (NOTE: It should be confirmed with the lab whether or not the correction has already been applied). The grading is in both directions High and Low. Both directions are graded in 4 categories as
Hypercalcemia

- Grade 1 being any values from the ULN to 11.5 mg/dL,
- Grade 2 from >11.5 to 12.5 mg/dL,
- Grade 3 from >12.5 to 13.5 mg/dL,
- Grade 4 >13.5 mg/dL

Hypocalcemia

- Grade 1 being any values from the LLN to 8.0 mg/dL,
- Grade 2 from 7.0 to <8.0 mg/dL,
- Grade 3 from 6.0 to <7.0 mg/dL,
- Grade 4 <6.0 mg/dL

Lab Test = Cholesterol

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-

Cholesterol will have grades 1-4,

- Grade 1 being any values from the ULN to 300 mg/dL,
- Grade 2 from >300 to 400 mg/dL,
- Grade 3 from >400 to 500 mg/dL,
- Grade 4 >500 mg/dL

Lab Test = Creatine Kinase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-

Creatine Kinase will have grades 1-4,

- Grade 1 being any values from the ULN to 2.5 x ULN,
- Grade 2 from >2.5 to 5 x ULN,
- Grade 3 from >5 to 10 x ULN,
- Grade 4 >10 ULN

Lab Test = Creatinine

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-

Creatinine will have grades 1-4 and will be based on the baseline value in some cases. Grading for pre-baseline values will ignore the baseline requirement.

- Grade 1 being any values from the ULN to 1.5 x ULN,
- Grade 2 from >1.5 to 3.0 x ULN or >1.5 - 3.0 x baseline,
- Grade 3 from >3.0 to 6.0 x ULN or >3.0 x baseline,
- Grade 4 >6.0 x ULN

Lab Test = Fibrinogen

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	-

Fibrinogen will have Grades 1- 4:

- Grade 1 <1.0 - 0.75 x LLN
- Grade 2 <0.75 - 0.5 x LLN
- Grade 3 <0.5 - 0.25 x LLN
- Grade 4 <0.25 x LLN

Lab Test = Gamma-Glutamyl Transpeptidase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

Gamma-Glutamyl Transpeptidase will have grades 1-4 and based on ULN only

- Grade 1 being any values from the ULN to 2.5 x ULN,
- Grade 2 from >2.5 to 5.0 x ULN
- Grade 3 from >5.0 to 20.0 x ULN
- Grade 4 from>20.0 x ULN

Lab Test = Glucose

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death

Glucose is graded in 2 directions.

Hypoglycemia will have grades 1-4,

- Grade 1 being any values from the LLN to 55 mg/dL,
- Grade 2 from 40 to <55 mg/dL,
- Grade 3 from 30 to <40 mg/dL,
- Grade 4 <30 mg/dL

Hyperglycemia will have one grade. We discussed using the WHO criterion as noted below

- Grade 1 >200 mg/dL;

Lab Test = Lipase

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Serum lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-

Lipase will have Grades 1, 2 and 3:

- Grade 1 being any values from the ULN to 1.5 x ULN
- Grade 2 from >1.5 to 5.0 x ULN
- Grade 3 from>5 x ULN

Lab Test = Magnesium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death

Hypermagnesemia will have grades 1, 3, and 4,

- Grade 1 being any values from the ULN to 3.0 mg/dL,
- Grade 3 from >3.0 to 8.0 mg/dL,
- Grade 4 from>8.0 mg/dL

Hypomagnesemia will have grades 1 - 4,

- Grade 1 being any values from the LLN to 1.2 mg/dL,
- Grade 2 from 0.9 to <1.2 mg/dL,
- Grade 3 from 0.7 to <0.9 mg/dL,
- Grade 4 <0.7 mg/dL

Lab Test = Potassium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death

Hyperkalemia will have grades 1-4,

- Grade 1 being any values from the ULN to 5.5 mmol/L,
- Grade 2 from >5.5 to 6.0 mmol/L,
- Grade 3 from >6.0 to 7.0 mmol/L,
- Grade 4 from>7.0 mmol/L

Hypokalemia will have grades 1, 3, and 4,

- Grade 1 being any values from the LLN to 3.0 mmol/L,
- Grade 3 from >2.5 to 3.0 mmol/L,
- Grade 4 <2.5 mmol/L

Lab Test = Sodium

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death

Hypernatremia will have grades 1-4,

- Grade 1 being any values from the ULN to 150 mmol/L,
- Grade 2 from >150 to 155 mmol/L,
- Grade 3 from >155 to 160 mmol/L,
- Grade 4 from>160 mmol/L

Hyponatremia will have grades 1-4,

- Grade 1 being any values from the LLN to 130 mmol/L,
- Grade 2 from 125 to <130 mmol/L,
- Grade 3 from 120 to <125 mmol/L,
- Grade 4 <120 mmol/L

Lab Test = Triglycerides

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death

Triglycerides will have grades 1-4,

- Grade 1 being any values from the 150 to 300 mg/dL,
- Grade 2 from >300 to 500 mg/dL,
- Grade 3 from >500 to 1000 mg/dL,
- Grade 4 from>1000 mmol/L

Lab Test = Uric Acid

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	Death

- Do not grade based on CTCAE

Lab Test = Bicarbonate or CO2

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-

Do not Grade based on CTCAE

Lab Test = Phosphorus or Phosphate

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death

Do not Grade based on CTCAE

Lab Test = Serum pH [This is not urine pH]

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	-
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	-

Serum pH will be graded in both directions with Grades 1 and 3 only.

Acidosis Grade 1.<LLN, but >=7.3 Grade 3, pH < 7.3

Alkaosis Grade 1.>ULN, but <=7.5 Grade 3, pH < 7.5

Lab Test = Activated Partial Thromboplastin Time

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-

APTT will have grades 1-3

- Grade 1 being any values from the >ULN to 1.5 x ULN,
- Grade 2 from >1.5 to 2.5 x ULN,
- Grade 3 from >2.5 x ULN,

Lab Test = International Normalized Ratio

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-

INR will have grades 1-3

- Grade 1 being any values from the >1.2 to 1.5,
- Grade 2 from >1.5 to 2.5,
- Grade 3 from >2.5,

Lab Test = Eosinophils

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-

Do not grade based on CTCAE

Lab Test = Hemoglobin

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hemoglobin Increased	Increase in > 0-2	Increase in >2-4g/dL	Increase > 4 g/DL	-	Death

Decreased Hemoglobin will have grades 1-3, with

- Grade 1 being any values from the LLN to 10 g/dL,
- Grade 2 from 8 to < 10 g/dL and
- Grade 3 < 8 g/dL

Increased Hemoglobin will not be graded.

Lab Test = CD4 Lymphocytes

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-

Decreased CD4 count will have grades 1-4, with

- Grade 1 being any values from the LLN to 500/mm3,
- Grade 2 from <500 to 200/mm3 and
- Grade 3 from <200 to 50/mm3 and
- Grade 4 <50/mm3

Lab Test = Lymphocytes

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	Lymphocyte count decreased
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	Lymphocyte count increased

Lymphocytes will be graded in both directions.

Decreased Lymphocytes will have grades 1-4, with

- Grade 1 being any values from the LLN to 800/mm3,
- Grade 2 from <800 to 500/mm3 and
- Grade 3 from <500 to 200/mm3 and
- Grade 4 <200/mm3

Increase Lymphocytes will have grades 2 and 3 only, with

- Grade 2 from >4000 to 20,000/mm3 and
- Grade 3 >20,000/mm3

Lab Test = Neutrophils

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-

Neutrophils will have grades 1-4, with

- Grade 1 being any values from the LLN to 1500/mm3,
- Grade 2 from 1000 to <1500/mm3 and
- Grade 3 from 500 to <1000/mm3 and
- Grade 4 <500/mm3

Lab Test = Platelets

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

Do not grade with CTCAE.

Lab Test = WBC

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death

Decreased WBC will have grades 1-4, with

- Grade 1 being any values from the LLN to 3000/mm3,
- Grade 2 from 2000 to <3,000/mm3 and
- Grade 3 from 1000 to <2,000/mm3 and
- Grade 4 <1000/mm3

High WBC will have grade 1, with

- Grade 1 >11,000/mm3 (https://www.aafp.org/afp/2000/1101/p2053.html),

Lab Test = Urine Glucose

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Glucosuria	Present	-	-	-	-

Urine Glucose will have grade 1

- Grade 1 if not negative or trace

Lab Test = Urine Protein

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	**Adult:** Urinary protein >=3.5 g/24 hrs; 4+ proteinuria; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9	-	-

Urine Protein will have grades 1-3, with

- Grade 1 =1+,
- Grade 2 = 2+ to 3+
- Grade 3 = 4+

Lab Test: Urine RBCs/Blood

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death

Do not grade urine in blood using CTCAE

Lab Test: eGFR or CrCl

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
eGFR decreased/CrCl decreased	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death

Values will be graded using the CTCAE values noted above with Grade 1 – Grade 4 values.

eGFR/CrCl:

Grade 1: < LLN – 60 ml/min/1.73 m2

Grade 2: 30 - < 60 ml/min/1.73 m2

Grade 3: 15 - < 30 ml/min/1.73 m2

Grade 4: < 15 ml/min/1.73 m2

9.5. Abbreviations

Abbreviation	Definition
AE	Adverse event
AED	Anti-epileptic drug
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BID	Twice daily
BLQ	Below the level of quantification
BMI	Body mass index
BZD	Benzodiazepine
CGI-S	Clinical Global Impression – Severity of Symptoms
CI	Confidence interval
COVID-19	Coronavirus 2019, SARS-CoV-2
CRF	Case Report Form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CVL-865	Study drug
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ET	Early termination
FDA	Food and Drug Administration
ICF	Informed consent form
IMP	Investigational medicinal product
LLN	Under the lower limit of normal
LOQ	Limit of quantification

Abbreviation	Definition
mCIWA-B	Modified Clinical Institute Withdrawal Assessment – Benzodiazepines
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Medical health professional
msec	Milliseconds
N, n	Number of subjects, number of observations
OLE	Open-label Extension
PGI-C	Patient's Global Impression of Change
PK	Pharmacokinetic
PT	Preferred Term
QTc	QT interval value corrected for heart rate
QTcF	QT interval value corrected for heart rate using Fridericia's formula
Q1, Q3	First quartile, third quartile
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse events
TESC	The Epilepsy Study Consortium
ULN	Above the upper limit of normal
WBC	White Blood Cell
WHO	World Health Organization