STATISTICAL ANALYSIS PLAN

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: Darigabat (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

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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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1. INTRODUCTION

This document describes the statistical methods and data presentations planned for the analysis of the efficacy and safety data from Protocol CVL-865-SZ-001. Background information is provided for the study designs and objectives. Further details of study conduct, and data collection are provided in the study protocol and electronic case report forms (eCRFs)

1.1. Study Overview

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 maximum duration is to be approximately 25 weeks, consisting 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 (only for subjects not continuing treatment in the open-label extension trial)

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 and days free of seizures. The presence or absence of all seizure types experienced by each subject will be recorded daily in the eDiary.

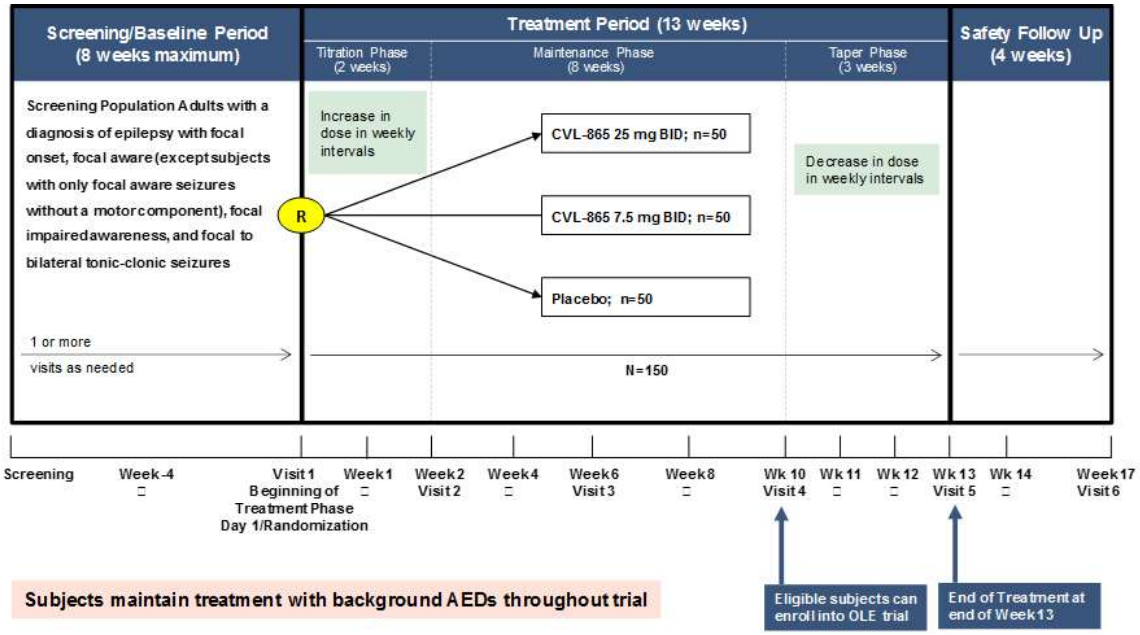
Subjects who satisfy all inclusion/exclusion criteria and thus are eligible for the trial will be randomized to 1 of 3 treatment arms at Visit 1 (Day 1). The daily dosing schedule will start at Day 1 with a 2-week Titration Phase during which time the subject's dose will be increased in a blinded fashion 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.

The trial design is depicted in Figure 1 and details of schedule of assessments are provided in Section 9.1.

Figure 1: Trial Schematic



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

1.2. Sample Size Considerations

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.

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). Approximately 214 subjects will be screened to achieve 150 subjects randomized.

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.

1.3. Measures to Minimize Bias: Randomization and Blinding

1.3.1. Subject Assignment to Treatment

All subjects will be centrally randomized in a 1:1:1 ratio to 3 treatment arms (CVL-865 7.5 mg BID, 25 mg BID, or placebo) at the Visit 1 (Day 1) via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS), according to a computer generated randomization scheme generated by a non-study statistician and be kept strictly confidential. Subjects will be sequentially assigned to the next available randomization number and will receive the IMP that corresponds to that randomization number. Once a randomization number has been assigned, it will not be reassigned.

1.3.2. Blinding

The CVL-865 and placebo tablets will be identical in appearance. 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.

Treatment assignments will be blinded to the investigators and other trial site personnel, the subjects, and all sponsor personnel who are involved in the conduct of the trial (including trial monitoring, data management, and data analysis). Access to the treatment codes will be restricted to personnel who are responsible for generating and maintaining the randomization code, packaging the IMPs, operating the IVRS/IWRS, analyzing the PK blood samples, or reporting serious adverse events (SAEs) or adverse events of special interest (AESI) to regulatory agencies.

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

1.4. Treatment Period

The dose of CVL-865 will be titrated to the assigned dose over the first 2 weeks of the trial during the Dose Titration Phases followed by 8 weeks of Maintenance Phase at the assigned dose level. At the end of Maintenance Phase, eligible subjects have the option to continue treatment with CVL-865 in the open-label extension trial CVL-865-SZ-002. If 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.

The dosing schedule is summarized in Table 1.

Table 1: 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.

2. OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are summarized in Table 2.

Table 2: 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)

Objectives	Endpoints
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.

3. KEY ASSESSMENTS AND DERIVATIONS

3.1. Efficacy Assessments

3.1.1. 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.

Seizure frequency 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 multiplied by 7. 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 frequency 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. 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."

3.1.3. 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.

3.1.4. 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.

3.1.5. 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.

Details of QOLIE-31 categories are provided in Section 9.2.

3.1.6. 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).

Details of HUI categories are provided in Section 9.3.

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.

Adverse events with missing severity will have the severity imputed as ‘Severe’ for the AE tabulations. Adverse events with missing relationship to IMP will have the relationship imputed as ‘Related’ for the AE tabulations if the AE started on or after the first dose of IMP. However, in the data listings these missing severity and/or relationship will be presented as missing.

3.2.1.1. Treatment-emergent Adverse Event (TEAE)

Any event reported on the eCRF 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 Adverse Event which was reported to have started on Day 1 without an associated onset time is assumed to be treatment emergent.

3.2.1.2. Serious Adverse Event (SAE)

Adverse events that meet the definition of SAE in the protocol will be captured in the ADVERSE EVENTS eCRF.

3.2.1.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) will be captured and monitored during this study. AESI include Adverse Events Potentially Related to Abuse or Dependence, Hematologic Abnormalities and Abnormal Liver Function Tests as defined in the protocol. These events will be noted by the investigator in the ADVERSE EVENTS eCRF.

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.

3.2.3. 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.

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.

The “Since Last Visit” C-SSRS form will be completed at all visits after screening and baseline. 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 evaluate whether a risk assessment by a qualified mental health professional (or the investigator alone if the investigator is a qualified mental health professional) is needed and whether the subject should continue in or be discontinued from the trial.

Details of C-SSRS categories as well as definition of treatment emerging events are provided in Section 9.4.

3.2.4. Vital Signs

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

3.2.5. 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.

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.

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.

3.2.6. 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.

3.2.7. Concomitant Medications and Non-Drug Therapy/Procedures

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. Medications that start and stop before the first dose of IMP will be classified as prior medications and will not be considered concomitant. Medications that start after the last dose of IMP will be classified as taken post last dose and will not be considered concomitant. These medications will be recorded in the eCRF. The investigator will record all medications and therapies (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that are used by the subject from 30 days before the informed consent form (ICF) is signed through the end of Post-treatment Safety Follow-up Period. The investigator will also

record all medications and therapies taken or received by a subject for treatment of an AE or that cause an AE through the end of Post-treatment Safety Follow-up Period.

Non-drug therapy/procedures will also be recorded as medications described above.

3.2.8. Rescue Medicine

All subjects who normally take BZDs for seizure rescue will be required to have an individualized Rescue Protocol approved by TESC (The Epilepsy Study Consortium). The Rescue Protocol will be submitted along with the SIF/DRF (Seizure Identification and Diagnostic Review Form) 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.

3.2.9. Physical and Neurological Examinations

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.

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.

3.3. Pharmacokinetics

To evaluate the plasma exposure of CVL-865 (and adjunctive AEDs, if appropriate) over time, a single daytime blood sample will be collected as specified in the Schedule of Assessments (Section 9.1).

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 eCRF (note: date of birth is not captured on the eCRF).

4.1.2. Day 1

Day 1 is the day IMP is first initiated.

4.1.3. Study Day of an Event

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

Study Day = event date – date of 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.

4.1.4. Days on Study

Days on Study is the number of days from Day 1 to the date of study completion or early termination as recorded on the END OF STUDY eCRF.

4.1.5. Days on IMP

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

4.1.6. Baseline Value

For purposes of analysis of safety assessments and efficacy assessments outside of eDiary, the baseline value is defined as the last value obtained prior to initiation of IMP. 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.

4.1.7. Change from Baseline

Change from baseline for a given variable is defined as the value on a given Study Day (Time Point) minus the Baseline Value.

4.1.8. Last Dose of IMP

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

4.1.9. Average Daily Dose by Period

The cumulative dose of IMP, calculated in milligrams and based on the daily dose of IMP as recorded in the EXPOSURE eCRF for each Period defined in Table 3 will be used to derive average daily dose for the period.

4.1.10. Compliance with Study Drug

Dosing compliance, based on daily dose of IMP as recorded in the EXPOSURE eCRF, will be defined by the ratio of 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. Subjects could be considered for discontinuation of the trial for non-compliance if poor study drug compliance is observed.

4.1.11. Handling of Incomplete or Missing Dates Associated with an Event

An incomplete date occurs when the exact date an event (e.g. an adverse 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.

  For completely missing date of epilepsy diagnosis in medical history, the first start date of anti-epilepsy medication(s) will be used to impute the diagnosis date.

If any imputed start date causes the start date to occur after the end date, the end date will be used for the imputation of the start date. If any imputed end 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).

4.1.12. 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 values < LLN will be replaced with ½ the value of the lower limit. For example, "< 0.1" will be replaced with 0.05 if the LLN is 0.1.
- The values > ULN will be replaced by values of increased precision by one level. For example, ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1" if the ULN is 10.

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 Section 4.3. Seizure frequency and average daily dose for each analysis period will be calculated based on Table 3.

Table 3: Definition of Analysis Periods for Seizure Frequency and Average Daily Dose Data

Analysis Period	Duration	Start Date	End Date
Baseline Period	~8 Weeks	The greater of: Study Day, -56 or Informed consent	Study Day, -1
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
Maintenance Phase	~8 Weeks	Day 15 (Visit 2)	The lesser of: **Day 71 (Visit 4) minus 1 or *Early termination (minus 1) or End of Treatment
Taper Phase	~3 Weeks	Day 71 (Visit 4) 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.
** For subjects continues to Taper Phase from Maintenance Phase

4.3. Visit Windows

Data collected longitudinally across visits will be summarized and analyzed by visit. Visits will be presented according to the nominal study day and visit as obtained from the eCRF 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 9.

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 and Vital Signs

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 (pre-dose) or earlier	Baseline	
1* to 15	Day 1 (Visit 1)	1
16 to 57	Day 43 (Visit 3)	43
58 to 82	Day 71 (Visit 4)	71
83 to 106	Day 92 (Visit 5)	92
107 and higher	Day 120 (Visit 6)	120

*Only post-dose values at Day 1 will be windowed to Day 1.

Table 5: Visit Windows for Early Termination and Unscheduled Visits - Safety Labs and C-SSRS

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 or earlier	Baseline	
2 to 8	Day 1 (Visit 1)	1
9 to 29	Day 15 (Visit 2)	15
30 to 57	Day 43 (Visit 3)	43
58 to 82	Day 71 (Visit 4)	71
83 to 106	Day 92 (Visit 5)	92
107 and higher	Day 120 (Visit 6)	120

Table 6: Visit Windows for Early Termination and Unscheduled Visits – CGI-S

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 or earlier	Baseline	
2 to 8	Day 1 (Visit 1)	1
9 to 29	Day 15 (Visit 2)	15
30 to 57	Day 43 (Visit 3)	43
58 or higher	Day 71 (Visit 4)	71

Table 7: Visit Windows for Early Termination and Unscheduled Visits – PGIC and CGI-I

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
29 or earlier	Day 15 (Visit 2)	15
30 to 57	Day 43 (Visit 3)	43
58 or higher	Day 71 (Visit 4)	71

Table 8: Visit Windows for Early Termination and Unscheduled Visits – QOLIE-31 and HUI

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 or earlier	Baseline	
2 or greater	Day 71 (Visit 4)	71

Table 9: Visit Windows for Early Terminations and Unscheduled – mCIWA-B

Study Day of Early Termination or Unscheduled Visit	Analysis Visit	Analysis Visit Target Day
1 to 74 (on treatment, prior to Taper Phase)	Baseline	
1 to 82 (off treatment)	Day 78 (Contact)	78
83 to 89	Day 85 (Contact)	85
90 to 96	Day 92 (Visit 5)	92
97 to 110	Day 99 (Contact)	99
110 and higher	Day 120 (Visit 6)	120

5. STATISTICAL ANALYSIS METHODS

5.1. GENERAL CONSIDERATIONS

Descriptive statistical methods will be used to summarize the data from this trial, with statistical testing performed for the efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (N), number of observations (n), arithmetic mean, median, standard deviation (SD), coefficient of variation (CV%) (for concentration data only), 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: placebo and each active CVL 865 dose (7.5 mg BID, 25 mg BID). 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 group and subject number and

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 treatment, visit, and assessment as well as the overall number and proportion of subjects with any such missing visits, assessments, or remote visits in each treatment group.

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher.

5.2. Populations for Analyses

The analysis populations are defined Table 10.

Table 10: Populations for Analysis

Population	Description	Analysis
All Screened Subjects	All Screened Subjects includes all subjects who signed the informed consent form.	Disposition
ITT	All randomized subjects	Disposition, Demographic and Baseline Characteristics
FAS	All randomized subjects who receive at least 1 dose of IMP. This will be the safety analysis set.	Safety analysis
mITT	All randomized subjects who receive at least 1 dose of IMP and have both baseline seizure frequency recorded in the eDiary with entry compliance ≥ 20% and at least 1 post baseline entry in the seizure diary during maintenance phase.	Primary analysis set for efficacy
PK Analysis Set	All randomized subjects who receive at least 1 dose of IMP and have at least 1 measurable CVL-865 concentration	PK analysis

Abbreviations: FAS = full analysis set, IMP = investigational medicinal product, ITT = intent-to-treat, mITT = modified intent-to-treat, PK = pharmacokinetic.

5.3. Statistical Hypotheses

The primary efficacy hypotheses and the key secondary hypotheses will be tested with 2-sided tests of superiority comparing each active CVL 865 dose (CVL1-25 mg BID, CVL2-7.5 mg BID) to placebo at individual test α level of 0.1.

Primary Endpoint	Active CVL 865 dose vs Placebo
Response ratio (RRatio)	• $H_{01}: \mu_{placebo} = r_{CVL1}$ vs $H_{11}: \mu_{placebo} \neq r_{CVL1}$ • $H_{02}: \mu_{placebo} = r_{CVL2}$ vs $H_{12}: \mu_{placebo} \neq r_{CVL2}$
Key Secondary Endpoints	
Change from baseline in focal onset seizure frequency per week over the Maintenance Phase	
Percent of subjects with at least a 50% reduction in the Maintenance Phase focal onset seizure frequency rate relative to the Baseline Period	

5.4. Multiplicity Adjustment

As the study is of exploratory nature, multiplicity adjustment is not planned.

5.5. Strata and Covariates

No stratification was implemented in randomization. The baseline value of each efficacy variable will be included as a covariate in the efficacy analyses.

5.6. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition will be based on the ITT population. The number of subjects who completed the study, discontinued from the study, reason for early discontinuation of the study at any point, and discontinuation relationship to COVID-19 also will be presented by treatment group. Additionally, the number of days on study will be summarized for all treated subjects.

The number of subjects who are screened, screen failed, reason for screen failures and reason related to COVID-19 will also be summarized.

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

Demographic data including age, sex, race, ethnicity, height (at screening), weight (at screening), and BMI (at screening) will be summarized by treatment group using descriptive statistics within the ITT population.

5.6.1. Medical History

Medical history and ongoing medical conditions will be listed and summarized by MedDRA system organ class (SOC) and preferred term (PT). The start date and end date (or ongoing if applicable) will be included in the listing as collected.

5.6.2. History of Epilepsy

The number and percentage of subjects who received epilepsy surgery and the type of surgeries will be summarized.

Epileptic seizure profile is based on the historical seizure types reported by the subject on the Seizure History form. The number and percentage of subjects experiencing each seizure type at any time in the past will be summarized.

The number and percentage of subjects with each category of focus localization will be summarized. Subjects may be counted in more than one category of focal localization. The average number of seizures for each category of focus localization will be summarized.

The date of diagnosis of epilepsy is collected on Seizure History eCRF. If the date of diagnosis date is missing, the date will be imputed as the earliest start date of any Anti-Epileptic Drug taken. The duration of epilepsy will be derived as the years between informed consent date and diagnosis date as reported on the Seizure History eCRF. The duration of epilepsy and age at epilepsy diagnosis will be summarized descriptively.

The background AEDs and history of RNS/VNS procedures at study entry will also be summarized.

5.7. Exposure to Treatment

The number of days on study drug, reasons for premature discontinuation of IMP, treatment compliance, days in each phase (Titration, Maintenance, and Taper), average dose in each phase, will be summarized by treatment group for the FAS Population.

5.7.1. eDiary compliance

Primary and secondary, and other 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 diary day will be considered missing for compliance if a seizure diary record is missing for that day. Diary compliance will be evaluated during the Baseline Period, during the entire Treatment Period, and during the Maintenance Period.

Diary compliance will be calculated as 100 times the number of diary days (days with diary completed) 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 didn't enter an analysis period, the diary compliance for the analysis period will not be calculated.

Diary compliance data will be listed by treatment then subject.

5.8. Primary Efficacy Analysis

5.8.1. Derivation of Primary Efficacy Endpoint

The primary efficacy endpoint is the response ratio (RRatio) over the Maintenance Phase:

$$RRatio = \frac{T-B}{T+B} \times 100$$

where T = focal onset seizure frequency rate per week in the Maintenance Phase and

B = focal onset seizure frequency rate per week in the Baseline Period

It ranges between -100 and 100 where negative values will indicate reduction in seizure rate and positive values indicate increase in seizure rate during treatment.

5.8.2. Primary Estimand

The key research question for the primary endpoint will be addressed with an estimand based on the following attributes:

1. Treatments: treatments as randomized regardless of the actual treatment received.
2. Target study population of interest: subjects in the modified intent-to-treat (mITT) population.
3. Endpoint (variable) of interest: RRatio over the Maintenance Phase.
4. Population level summary of interest: difference between CVL-865 treated and placebo subjects in RRatio over the Maintenance Phase.
5. Strategy for Intercurrent events (ICEs): a hypothetical strategy will be used to address intercurrent events (ICEs) of potential death, and treatment discontinuations. The data after treatment discontinuations will typically be missing or be treated as missing even if collected. Under the hypothetical strategy, these missing values as the result of ICEs of discontinuation will be assumed to follow the observed trajectory of the subject and thus the endpoint will include only eDiary based response data that occur before discontinuation of treatment. It should be noted that the use of protocol defined rescue medication will not be considered as an ICE.

5.8.3. Main Analytical Approach

Primary efficacy endpoint will be summarized using descriptive statistics by treatment group and visit, if appropriate. Statistical comparisons for each endpoint will be constructed without adjustment for multiplicity.

The RRatio will be analyzed using an analysis of covariance (ANCOVA) model including treatment and the baseline seizure frequency per week as a covariate. The differences between the treatment dose group and placebo will be estimated based on the least square mean (LSMean) difference between each CVL-865 dose group vs placebo and combined CVL-865 dose groups vs placebo with corresponding 90% confidence interval (CI) and P-value.

5.8.4. Sensitivity Analyses

5.8.4.1. Treatment Effect based on Actual Treatment Received

Should a discrepancy between the study treatment received and the randomized treatment assignment occurred in 4 or more subjects, a sensitivity analysis may be conducted based on the study treatments that subjects actually received using the analysis method described in Section 5.8.3.

5.8.4.2. Impact of Low eDiary Entry Compliance

To evaluate the impact of subject's low compliance of eDiary entry on the results from the main analysis, a sensitivity analysis that treat these cases as missing at random will be performed. Specifically, if a subject has more than 50% of their diary entries missing over a period (baseline, maintenance, etc), the seizure frequency for that period will be treated as missing. Multiple imputations under missing at random assumption will be performed. The Markov chain method implemented in SAS PROC MI will be utilized based on the mITT population. The imputations will be performed on the logarithmic scale (ln(X+1)), where X represents the 7 day average seizure frequency for a period, and back transformed to conform to the multivariate normality distribution and the imputed values will then be back transformed to the original scale. SAS PROC MI will be used to generate 10 possible imputed datasets using the following SAS code:

```
proc mi data=mcmc1 seed=SEED1 nimpute=10 minimum=0 out=Out1X;
mcmc chain=multiple displayinit initial=em(itprint);
var TRT y0 y;
run;
```

Where TRT is an indicator variable representing treatment with the two treatment groups of 'CVL-865 7.5 mg BID', 'CVL-865 25 mg BID' or 'Placebo', y represents ln(7 day average seizure frequency over maintenance period + 1), y0 is ln(7 day average seizure frequency over the baseline period+1), and SEED1 is a random number.

Each of these datasets will be analyzed using the same ANCOVA model through SAS PROC MIXED as described in Section 5.8.3. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

5.8.4.3. Impact of Discontinuation Potentially Related to Treatment

The seizure frequency data of subjects who discontinue of from the trial on or before Week 6 (Visit 3) for the following reasons are potentially missing not at random (MNAR).

- AE with AEHLGT eq 'Seizures (incl subtypes)'
- WITHDRAWAL BY SUBJECT
- LACK OF EFFICACY
- LOST TO FOLLOW-UP

In this assessment, the subjects with MNAR (to be identified and documented in Section 9.5 before database lock) will be imputed by jump to reference approach.

Specifically, the missing values in each of the active group will be imputed using the multiple imputation procedure described above except that the missing observations in CVL-865 group are not constructed from the observed data in the respective groups, but rather from the observed data in the placebo group. Any missing data from the placebo group is imputed using the observed data from the placebo group. The data will be log transformed using convention log(X+1) and back transformed to conform to the multivariate normality distribution. The

```
proc mi data = mcmc1 (where=( ((y = . or y0=.) and trt ne 'Placebo')  or (trt='Placebo' and (y0  ne . and y ne .)) )) seed = SEED1 nimpute = 10 minimum =0 minmaxiter = 1000 out= Out1X;
mcmc chain = multiple displayinit initial=em(itprint);
 var  y0 y;
run;
```

Where y represents ln(7 day average seizure frequency over maintenance period + 1), y0 is ln(7 day average seizure frequency over the baseline period+1), and SEED1 is a random number. Each of these datasets will be analyzed using the same ANCOVA model through SAS PROC MIXED as described in Section 5.8.3. The results of the analyses of the datasets will be combined using PROC MIANALYZE to produce an inferential result.

5.8.5. Subgroup Analyses

The mITT population is defined as all randomized subjects who receive at least 1 dose of IMP and have both an eDiary baseline compliance ≥ 20% and at least 1 post baseline entry in the seizure diary during maintenance phase. To further assess the impact of the eDiary compliance, sensitivity analyses based on the subgroup with a baseline compliance ≥ 50% and a maintenance phase compliance ≥ 50% may be conducted if the sample size allows.

In addition, the following subgroup analyses will be conducted:

1. subjects with baseline eDiary compliance ≥ 80%.
2. subgroup analysis of baseline disease characteristics based on seizure frequency, defined: Low frequency= up to 20 seizures a week; High frequency = 21 and above, including all subjects with "uncountable" seizures will be conducted.

5.9. Key Secondary Efficacy Analyses

5.9.1. Derivation of Key Secondary Efficacy Endpoints

5.9.1.1. Change in Log-Transformed Seizure Frequency from Baseline

The 7-day adjusted seizure frequency will be log-transformed using the convention ln(X+1), where X represents the focal onset seizure frequency. This will be summarized for the Titration Phase and Maintenance Phase.

5.9.1.2. 50% Responder

Responder status (yes or no) for a subject is determined by the percent reduction in 7-day adjusted seizure frequency during the Maintenance Phase from Baseline. A subject is defined as

a 50% responder if subject has at least a 50% reduction in the focal onset seizure frequency during the Maintenance Phase relative to the Baseline Period.

5.9.2. First Key Secondary Estimand

The key research question for the first secondary efficacy variable will be addressed with an estimand based on the following attributes:

1. Treatments: treatments as randomized regardless of the actual treatment received.
2. Target study population of interest: subjects in the modified intent-to-treat (mITT) population.
3. Endpoint (variable) of interest: change from baseline in focal onset seizure frequency in logarithmic scale.
4. Population level summary of interest: estimated mean difference between CVL-865 treated and placebo subjects in change from baseline in focal onset seizure frequency per week in logarithmic scale during the Maintenance Phase.
5. Strategy for Intercurrent events (ICEs): a hypothetical strategy will be used to address intercurrent events (ICEs) of potential death, and treatment discontinuations. The data after treatment discontinuations will typically be missing or be treated as missing even if collected. Under the hypothetical strategy, these missing values as the result of ICEs of discontinuation will be assumed to follow the observed trajectory of the subject and thus the endpoint will include only eDiary based response data that occur before discontinuation of treatment. It should be noted that the use of protocol defined rescue medication will not be considered as an ICE.

5.9.3. Main Analytical Approach for First Key Secondary Endpoint

The change from baseline in log-transformed seizure frequency will be analyzed using an ANCOVA, including treatment as a factor and the log-transformed baseline focal onset seizure frequency per week as a covariate. The comparisons between the treatment groups will be based on the LS Mean difference between each CVL-865 dose group and placebo with corresponding 90% CI and P-value.

The LS Mean and 90%CI for each treatment group in log scale will be exponentiated to derive the model-estimated mean percent change from baseline using the following formula:

Estimated Mean % Change from Baseline=100*[1-exp(LSMean)]

The percent reduction relative to placebo and 90%CI will be constructed by exponentiating the LSMean difference and 90%CI between each CVL-865 treatment group and placebo from the ANOCOVA model using the following formula:

$$\%\frac{Reduction}{Placebo} = 100 * [1 - \exp(LSMean_{CVL-865} - LSMean_{Placebo})]$$

5.9.4. Sensitivity Analyses

The sensitivity analyses to assess the impact of low eDiary compliance and that of discontinuation potentially related to treatment described in Section 5.8.4 for the primary estimand will also be performed for the key secondary efficacy estimand.

Two additional sensitivity analyses will be performed to assess the impact of the logarithmic transformation ln(X+1) of seizure frequency. The first one will be based on a slightly modified logarithmic transformation ln(X+0.1). This sensitivity analysis is to assess if the correction for zero in seizure frequency may have undue effect on other low seizure frequencies. In addition, the percent change from baseline in seizure frequency in Titration Phase and Maintenance Phase will also be analyzed using a nonparametric approach (in the original scale) of Wilcoxon rank sum test followed by the Mann-Whitney test for the comparison of each active treatment group to placebo.

5.9.5. Subgroup Analysis

The following subgroup analyses will be conducted:

1. subjects with baseline eDiary compliance ≥ 80%.
2. subgroup analysis of baseline disease characteristics based on seizure frequency, defined: Low frequency= up to 20 seizures a week; High frequency = 21 and above, including all subjects with “uncountable” seizures will be conducted.

5.9.6. Supplemental Analysis

A supplemental analysis will be conducted using a Poisson Regression model on the untransformed data for the raw number of seizures. A generalized linear model assuming a Poisson distribution and canonical log link function will be applied to the raw seizure count over the Maintenance Phase. The model will have an off-set parameter for the number of non-missing eDiary days (i.e., ln(days)) the subject was in the maintenance phase. Independent variables will include treatment and baseline seizure count.

5.10. Second Key Secondary Efficacy Analysis

The second key secondary efficacy endpoint is 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.

5.10.1. Second Key Secondary Estimand

The key research question for the second key secondary efficacy variable will be addressed with an estimand based on the following attributes:

1. Treatments: treatments as randomized regardless of the actual treatment received.
2. Target study population of interest: subjects in the modified intent-to-treat (mITT) population.
3. Endpoint (variable) of interest: 50% responder rate in the Maintenance Phase.

4. Population level summary of interest: the 50% responder rate in the Maintenance Phase relative to the baseline period between CVL-865 treated and placebo subjects.
5. Strategy for Intercurrent events (ICEs): a hypothetical strategy will be used to address intercurrent events (ICEs) of potential death, and treatment discontinuations. The data after treatment discontinuations will typically be missing or be treated as missing even if collected. These missing values as the result of ICEs of discontinuation will be assumed to follow the observed trajectory of the subject and thus the endpoint will include only eDiary based response data that occur before discontinuation of treatment. However, subjects with greater than 80% missing seizure diary entries will be treated as non-responders. It should be noted that the use of protocol defined rescue medication will not be considered as an ICE.

5.10.2. Main Analytical Approach for Second Key Secondary Endpoint

The second key secondary endpoint, 50% responder rate, will be analyzed for the mITT population using a logistic regression model with effects for treatment and baseline seizure frequency. The binary outcome will be defined as having at least a 50% reduction in the maintenance phase relative to the baseline period or not having a 50% reduction. Odd ratios will be constructed for each CVL-865 treatment dose group compared with placebo and will be summarized with 90% confidence intervals. Subjects with greater than 80% missing seizure diary entries will be treated as non-responders for this analysis. Should a logistic regression model fail to converge, paired Fisher's exact tests will be used instead.

5.10.3. Sensitivity Analyses

The sensitivity analyses to assess the impact of low eDiary compliance and that of discontinuation potentially related to treatment described in Section 5.8.4 for the primary estimand will also be performed for the second key secondary efficacy estimand. The 50% responder rate will be constructed off the results from the primary sensitivity analysis. This will be conducted for the two different sensitivity assessments will be conducted to assess the impact of this missingness (data are missing at random and data are not missing at random).

5.11. Other Efficacy Analyses

5.11.1. Other Secondary Efficacy Endpoints

Other protocol-defined secondary efficacy endpoints will be summarized using descriptive statistics by treatment group and visit, if appropriate. Statistical analysis method for each endpoint is described below in Table 11. Statistical comparisons for each endpoint will be constructed without adjustment for multiple endpoints.

Table 11: Summary of Other Secondary Efficacy Analyses

Endpoint	Analysis Population	Analysis Method
Seizure Freedom	mITT	Seizure freedom is defined as no seizures during the maintenance period. A logistic regression model with treatment as a fixed effect will be used. Odd ratios will be constructed for each CVL-865 treatment dose group compared with placebo and will be summarized with 90% confidence intervals. Should a logistic regression model fail to converge, paired Fisher's exact tests will be used instead.
Seizure Rate over Time	mITT	Seizure rate over time during the maintenance period will be analyzed using an MMRM. Only focal onset seizure will be included in this analysis. Data will be log-transformed using the convention ln(X+1), where X represents the seizure rate at each time point. 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, and log-transformed baseline rate will be included as a covariate. Subject will be included as a random effect, and an unstructured covariance structure will be used for the repeated measures. The difference between each CVL-865 level versus placebo at each visit will be estimated based on the LSMeans from the MMRM. The model estimated mean percent change from baseline and percent reduction versus placebo at each visit will be derived from back-transformed statistics the same way as described in Section 5.9.3 . A Mann-Whitney U test will also be used to compare each treatment level versus placebo at each visit.
PGI-C Score at Visits 2, 3, and 4	mITT	PGI-C score over time will be analyzed using a Mixed Model for Repeated Measures (MMRM) analysis. 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. Subject will be included as a random effect, and an unstructured covariance structure will be used for the repeated measures. The difference between each CVL-865 level versus placebo at each visit will be estimated based on the LSMeans from the MMRM.
CGI-S Score - Change from Baseline to Visits 2, 3, and 4	mITT	Change from baseline in CGI-S score over time will be analyzed using similar MMRM model as described above for PGI-C score.
CGI-I Score at Visit 2, 3, and 4	mITT	CGI-S score over time will be analyzed using similar MMRM model as described above for PGI-C score.
QOLIE-31 Overall and Domain Score - Change from Baseline to Visit 4	mITT	Changes from baseline in QOLIE-31 Overall Scores will be compared using an ANCOVA model with the baseline score as a covariate and treatment group included in the model as fixed effects in the mITT population. This estimand will include available post-baseline response data that occur before discontinuation of treatment or addition of rescue medication. The differences between each treatment dose group and placebo will be estimated based on the LSMeans difference between each CVL-865 dose group and placebo with corresponding 90% CI. The QOLIE-31 Domain Scores will be analyzed the same way, by each of the following categories: Energy, Emotions, Daily

Endpoint	Analysis Population	Analysis Method
		Activities, Mental Activity, Medication Effects, Seizure Worry, and Overall Quality of Life.
HUI Utility Score - Change from Baseline to Visit 4	mITT	Overall Health-Related Quality of Life (HRQL) Utility Scores (HUI-3 and HUI-2) will be analyzed using an ANCOVA model as described above for QOLIE-31 Overall Scores.

5.12. Additional Exploratory Analyses

An exploratory analysis may be conducted to evaluate the percentage of subjects reaching 75% seizure frequency reduction from baseline during the maintenance period if sample size warrants. Fisher's exact test may be used for the comparisons.

A second exploratory analysis may also be conducted to evaluate the percentage of subjects with use of protocol defined rescue medications.

5.13. Interim and Final Analysis

No interim analysis is planned for this trial.

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.

5.14. Safety Analyses

All safety analyses will be performed on the Safety analysis set (FAS). Should any subjects receive a treatment other than their randomized treatment, the treatment as received will be used in the safety presentation.

5.14.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or higher preferred term and system organ class. If a subject experiences multiple events that map to a single preferred term, the greatest intensity and strongest investigator assessment of relation to IMP will be assigned to the preferred term for the appropriate summaries. Events with missing intensity or relationship will be classified as outlined in Section 3.2.1. Summaries of treatment-emergent AEs 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 treatment group using preferred terms, system organ classes, and severity. Separate summaries of treatment-emergent serious adverse events (TESAEs), TEAEs related to IMP, AESIs, AESIs not leading to discontinuation of IMP, TEAEs leading to death and events leading to the discontinuation of IMP will be generated respectively. A presentation of AEs by phase, by dose at event onset and AESIs by dose at event onset will be prepared. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. All adverse events that occurred prior to the initiation of study will be excluded from the tables but will be included in the listings.

Furthermore, TEAEs with ≥2% incidence in the treatment group and a greater incidence than the placebo group will be summarized by treatment group using preferred term in descending order of the incidence in the treatment group.

Missing onset dates will be imputed as previously outlined in Section 4.1.11 as required to determine treatment-emergent events.

5.14.2. Concomitant Medications and Non-Drug Therapy/Procedures

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

Prior and concomitant medications will be coded using the World Health Organization (WHO) dictionary (Version: Global B3, March 2020 or higher). Each concomitant medication will be classified as either an AED or a non-AED medication. Non-AED concomitant medications will be summarized by treatment group, 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 medications will be coded using the World Health Organization (WHO) drug dictionary (WHODrug Version: Global B3 September 2019 or later). Concomitant medications will be summarized by treatment group, frequency of drug classification, and generic drug name. Incidence of dosage adjustment of levodopa (L-Dopa) or equivalent, prohibited by the protocol, for duration longer than one week will be summarized. Prior and concomitant medications will be presented in a data listing.

Prior and concomitant non-drug therapy/procedures will be coded using MedDRA Version 26.1 or higher. Concomitant non-drug therapy/procedures will be summarized by treatment group, frequency of system organ class and preferred term. Prior and concomitant non-drug therapy/procedures will be presented in a data listing.

5.14.2.2. Concomitant AED Medication and Therapy/Procedures

Concomitant AED medications will be summarized by treatment group, frequency of drug classification and generic drug name. Number of AEDs taken at study entry and number of subjects with RNS/VNS will also be summarized by treatment group.

5.14.3. Clinical Laboratory Assessments

Descriptive summaries of selected (quantitative) clinical laboratory results will be presented by treatment group and study visit. Laboratory values outside the normal range for each systematically collected hematology, blood chemistry, and urinalysis parameter will be identified. 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. Each subject's qualitative urinalysis results will be flagged as "normal" or "abnormal." In addition, the severity of laboratory abnormality will be graded based on toxicity criteria specified in Section 9.6 in reference to Common Terminology Criteria for Adverse

Events (CTCAE) Version 5.0. The result of each laboratory test for individual subjects will be presented in a listing with the normal range defined by the central laboratory, the status relative to the normal range, and the toxicity grade.

Shift table will be used to summarize shifts from baseline toxicity grades to greatest (worst) treatment-emergent laboratory toxicity. For hematology and, blood chemistry, and quantitative urinalysis parameters that toxicity grade was not defined, a shift table for each laboratory test will be based on the shift from baseline high/normal/low status to the status of the maximum post-baseline value and the minimum post-baseline value (including test results from unscheduled visits, if any). Similarly, for qualitative urinalysis parameters, shifts from baseline normal/abnormal status to the worst post-baseline status will be summarized.

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 > 3 × ULN and > 5 × ULN elevation criteria.

- ALT and/or AST > 3 × ULN and total bilirubin > 1.5 or 2 × ULN
- 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.

Other tests (drug screen, pregnancy testing, serology) will be presented in listings.

5.14.4. Vital Signs

Vital sign measurements will include body temperature (oral or tympanic), respiratory rate, body weight, 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 baseline will be summarized by visit and treatment group using descriptive statistics.

Number and percent of subjects with out-of-range post-baseline vital signs will be summarized based on the following criteria:

- Systolic Blood Pressure
  - < 90 mmHg,
  - > 140 mmHg
- Diastolic Blood Pressure
  - < 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 also be presented as listing with the out-of-range value flagged based on the above criteria.

5.14.5. Electrocardiograms (ECGs)

Electrocardiogram recordings will be obtained after the subject has been supine and at rest for at least 5 minutes. If during screening, any abnormal ECG finding is deemed medically significant or meets and exclusion criteria, it will be repeated once at screening with 3 consecutive ECG recordings to ensure reproducibility of the abnormality before excluding the subject. Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF. If a subject in the FAS population has more than one ECG within a time point, an average of each ECG measurement at that time point will be used for summary analysis.

ECGs measurements and corresponding changes from baseline will be listed. ECG variables will include heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected for heart rate using Fridericia's correction, QTcF.

The number and proportion of subjects having a worst post-baseline QTcF value from > 450 msec to 480 msec, > 480 msec to 500 msec, and > 500 msec will be summarized.

In addition, subjects with an increase from baseline of > 30 msec to 60 msec and > 60 msec will be summarized.

Important abnormalities in ECG waveform that are changes from baseline readings will also be reported in a listing.

5.14.6. Physical and Neurological Examinations

Physical and Neurological examination data will be listed.

5.14.7. 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 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.

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

The clinician-observed assessment section has been removed for the modified version of Clinical Institute Withdrawal Assessment – Benzodiazepines (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 and contacts by treatment group in addition to change from last on treatment assessment prior to or on Day 71 (Visit 4).

5.15. 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 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. An additional PK sample will be obtained at Visit 6 to document complete washout of IMP.

5.15.1. Pharmacokinetic Data Analysis

Plasma concentrations of CVL-865 in unit as reported by the analytical laboratory will be summarized by treatment and nominal time point using descriptive statistics. Summaries will include mean, standard deviation and coefficient of variation, median, minimum, maximum, and geometric mean. The mean concentration (SD) plot over time in the original scale and log-scale will be plotted based on nominal visit week.

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/PD analyses. Any population PK analysis and exploratory biomarker analyses (if completed) will be presented separately from the main CSR.

5.16. Protocol Deviations

All protocol deviations will be reviewed by the project team prior to unblinding to identify subjects with important protocol deviations. The number and percentage of subjects with important deviations will be tabulated by treatment and further tabulated by category and treatment. 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 final approved (prior to database lock and unblinding) 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.

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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

National Research Council. The Prevention and Treatment of Missing Data in Clinical Trials; 2010.

Rausch R, Crandall PH. Psychological status related to surgical control of temporal lobe seizures. Epilepsia. 1982;23(2):191-202.

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9. APPENDICES

9.1. Schedule of Assessments

Table 12: 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		

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-S			X		X		X		X				X		
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]	←----------														----------→

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**											
Laboratory															
Safety laboratory blood sample	X		X		X		X		X			X	X		X
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												

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**											
Other															
IMP dispensing			X		X		X		X						
Collect final eDiary device															X
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.

9.2. Quality of Life in Epilepsy – 31 (QOLIE-31)

Table 13: QOLIE-31 Scoring Form

Scale Question	Response 1	2	3	4	5	6	Subtotal		Final Scale Score (0-100) (Domain Score)
A. Energy (tiredness)									
How much of the time during the past 4 weeks…									
Did you feel full of pep?[1]	100	80	60	40	20	0			
Did you have a lot of energy?[1]	100	80	60	40	20	0			
Did you feel worn out?[1]	0	20	40	60	80	100			
Did you feel tired?[1]	0	20	40	60	80	100			
						TOTAL:		÷ 4 =	
How much do the above problems and worries about energy **distress** you overall?[9]	100%	75%	50%	25%	10%				
B. Emotions (mood)									
How much of the time during the past 4 weeks…									
Have you been a very nervous person?[1]	0	20	40	60	80	100			
Have you felt so down in the dumps that nothing could cheer you up?[1]	0	20	40	60	80	100			
Have you felt calm and peaceful?[1]	100	80	60	40	20	0			
Have you felt downhearted and blue?[1]	0	20	40	60	80	100			
Have you been a happy person?[1]	100	80	60	40	20	0			
						TOTAL:		÷ 5 =	

Scale Question	Response 1	2	3	4	5	6	Subtotal	Final Scale Score (0-100) (Domain Score)
How much do the above problems and worries about energy **distress** you overall?[9]	100%	75%	50%	25%	10%			
C. Daily Activities (work, drive, social)								
How much of the time during the past 4 weeks…								
Has your health limited your social activities (such as visiting with friends or close relatives)?[1]	0	20	40	60	80	100		
How much of the time during the past 4 weeks your epilepsy or antiepileptic medication has caused trouble with...								
Leisure activities (such as hobbies, going out)?[2]	0	25	50	75	100	--		
Driving (or transportation)?[2]	0	25	50	75	100	--		
How much do your work limitations bother you?[3]	100	75	50	25	0	--		
How much do your social limitations bother you?[3]	100	75	50	25	0	--		
						TOTAL:	_____	÷ 5 = _____
How much do the above problems and worries about energy **distress** you overall?[9]	100%	75%	50%	25%	10%			

Scale Question	Response 1	2	3	4	5	6	Subtotal		Final Scale Score (0-100) (Domain Score)
D. Mental Activity (thinking, concentrating, memory)									
How much of the time during the past 4 weeks...									
Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?[1]	0	20	40	60	80	100	_____		
In the past 4 weeks, have you had any trouble with your memory?[4]	0	33.3	66.7	100	--	--	_____		
In the past 4 weeks, how often have you had...							_____		
Trouble remembering things people tell you?[1]	0	20	40	60	80	100	_____		
Trouble concentrating on reading?[1]	0	20	40	60	80	100	_____		
Trouble concentrating on doing one thing at a time?[1]	0	20	40	60	80	100	_____		
How much do your memory difficulties bother you?[3]	100	75	50	25	0	--	_____		
						TOTAL:	_____	÷ 6 =	_____
How much do the above problems and worries about energy **distress** you overall?[9]	100%	75%	50%	25%	10%				

Scale Question	Response 1	2	3	4	5	6	Subtotal	Final Scale Score (0-100) (Domain Score)
E. Medication Effects (physical, mental)								
During the past 4 weeks...								
How much do physical effects of antiepileptic medication bother you?[3]	100	75	50	25	0	--	_____	
How much do mentals effects of antiepileptic medication bother you?[3]	100	75	50	25	0	--	_____	
How worried are you that medications you are taking will be bad for you if taken for a long time?[5]	0	33.3	66.7	100	0	--	_____	
						TOTAL:	_____ ÷ 3 =	_____
How much do the above problems and worries about energy **distress** you overall?[9]	100%	75%	50%	25%	10%			
F. Seizure Worry (impact of seizures)								
How much of the time during the past 4 weeks...								
Have you worried about having another seizure?[1]	0	20	40	60	80	100	_____	
How fearful are you of having a seizure during the next month?[6]	0	33.3	66.7	100	--	--	_____	
Do you worry about hurting yourself during a seizure?[7]	0	50	100	--	--	--	_____	
How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?[5]	0	33.3	66.7	100	--	--	_____	
How much do your seizures bother you?[3]	100	75	50	25	0	--	_____	
						TOTAL:	_____ ÷ 5 =	_____
How much do the above problems and worries about energy **distress** you overall?[9]	100%	75%	50%	25%	10%			

Scale Question	Response 1	2	3	4	5	6	Subtotal		Final Scale Score (0-100) (Domain Score)
G. Overall Quality of Life									
Overall, how would you rate your quality of life? (10 = Best Possible Quality of Life; 0 = Worst Possible Quality of Life)	(multiply response by 10)						_____		
How has the quality of life been during the past 4 weeks?[8]	100	75	50	25	0	--	_____		
						TOTAL:	_____	÷ 2 =	_____
How much does the state of your quality of life **distress** you overall?[9]	100%	75%	50%	25%	10%				

Note: The total number of items in each scale is listed as the divisor for each subtotal. However, due to missing data, the divisor might actually be less than that as noted. The divisor should be the number of items that the respondent answered within the scale.

[1]1=All of the time, 2=Most of the time, 3=A good bit of the time, 4=Some of the time, 5=A little of the time, 6=None of the time
[2]1=A great deal, 2=A lot, 3=Somewhat, 4=Only a little, 5=Not at all
[3]1= Not at all bothersome and 5 = Extremely bothersome
[4]1= Yes, a great deal, 2=Yes, somewhat, 3=Only a little, 4=No, not at all
[5]1=Very worried, 2=Somewhat worried, 3=Not very worried, 4=Not at all worried
[6]1=Very fearful, 2=Somewhat fearful, 3=Not very fearful, 4=Not fearful at all
[7]1=Worry a lot, 2=Occasionally worry, 3=Don't worry at all
[8]1=Very well: could hardly be better, 2=Pretty good, 3=Good and bad parts about equal, 4=Pretty bad, 5=Very bad: could hardly be worse
[9]1=Not at all, 2=Somewhat, 3=Moderately, 4=A lot, 5=Very Much

A QOLIE-31 overall score is obtained using a weighted average of the multi-item scale scores found in the table below (Table 15). If a value for Final Scale Score or Distress Score % is missing, the Weighted Subtotal cannot be calculated. However, if the Distress Score % is available, it can be used for the Sum Distress

Table 14: Formula for Calculating QOLIE-31 Overall Score

QOLIE-31 Scale	Final Scale Score (Domain Score)		Distress Score %		Weighted Subtotal
A. Energy	_____	x	_____	=	_____
B. Emotions	_____	x	_____	=	_____
C. Daily Activities	_____	x	_____	=	_____
D. Mental Activity	_____	x	_____	=	_____
E. Medication Effects	_____	x	_____	=	_____
F. Seizure Worry	_____	x	_____	=	_____
G. Overall QoL	_____	x	_____	=	_____
	Sum Distress=		_____	Sum Weights=	_____

OVERALL QOLIE-31-P SCORE = Sum Weights/Sum Distress * 100 = _____

9.3. Health Utilities Index (HUI)

HUI Utility Score

The 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. The HUI-3 health status classification system evolved from applications of the HUI-2 system and is considered to be complementary to the HUI-2 health status classification system. They both provide a descriptive measure of ability or disability for each subject on each HUI-2 and HUI-3 attribute, as well as a composite description of overall health status according to both systems.

The 15-item family of questionnaires for self-completion have been designed to collect the minimum amount of information required to classify subjects' health status according to both the HUI-2 and HUI-3 classification systems. The standard HUI 15-item questionnaires for self-completion are as follows:

1. Which one of the following best describes your ability, during the past week, to see well enough to read ordinary newsprint?
    a) Able to see well enough without glasses or contact lenses
    b) Able to see well enough with glasses or contact lenses
    c) Unable to see well enough even with glasses or contact lenses
    d) Unable to see at all

2. Which one of the following best describes your ability, during the past week, to see well enough to recognize a friend on the other side of the street?
    a) Able to see well enough without glasses or contact lenses
    b) Able to see well enough with glasses or contact lenses
    c) Unable to see well enough even with glasses or contact lenses
    d) Unable to see at all

3. Which one of the following best describes your ability, during the past week, to hear what was said in a group conversation with at least three other people?
    a) Able to hear what was said without a hearing aid
    b) Able to hear what was said without a hearing aid
    c) Unable to hear what was said even with a hearing aid
    d) Unable to hear what was said, but did not wear a hearing aid
    e) Unable to hear at all

4. Which one of the following best describes your ability, during the past week, to hear what was said in a conversation with one other person in a quiet room?
    a) Able to hear what was said without a hearing aid
    b) Able to hear what was said without a hearing aid
    c) Unable to hear what was said even with a hearing aid
    d) Unable to hear what was said, but did not wear a hearing aid
    e) Unable to hear at all

5. Which one of the following best describes your ability, during the past week, to be understood when speaking your own language with people who do not know you?
    a) Able to be understood completely
    b) Able to be understood partially
    c) Unable to be understood
    d) Unable to speak at all

6. Which one of the following best describes your ability, during the past week, to be understood when speaking with people who know you well?
    a) Able to be understood completely
    b) Able to be understood partially
    c) Unable to be understood
    d) Unable to speak at all

7. Which one of the following best describes how you have been feeling during the past week?
    a) Happy and interested in life
    b) Somewhat happy
    c) Somewhat unhappy
    d) Very unhappy
    e) So unhappy that life was not worthwhile

8. Which one of the following best describes the pain and discomfort you have experienced during the past week?
    a) Mild to moderate pain or discomfort that prevented no activities
    b) Moderate pain or discomfort that prevented no activities
    c) Moderate to severe pain or discomfort that prevented no activities
    d) Severe pain or discomfort that prevented most activities

9. Which one of the following best describes your ability, during the past week, to walk?
    Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.
    a) Able to walk around the neighborhood without difficulty, and without walking equipment.
    b) Able to walk around the neighborhood with difficulty; but did not require walking equipment or the help of another person
    c) Able to walk around the neighborhood with walking equipment, but without the help of another person
    d) Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighborhood
    e) Unable to walk alone, even with walking equipment.
    f) Able to walk short distances with the help of another person, and required a wheelchair to get around the neighborhood
    g) Unable to walk at all

10. Which one of the following best describes your ability, during the past week, to use your hands and fingers?
    Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.
    a) Full use of two hands and ten fingers
    b) Limitations in the use of hands or fingers, but did not require special tools or the help of another person
    c) Limitations in the use of hands or fingers, independent with use of special tools (did not require the help of another person)
    d) Limitations in the use of hands or fingers, required the help of another person for some tasks (not independent even with use of special tools)
    e) Limitations in the use of hands or fingers, required the help of another person for most tasks (not independent even with use of special tools)
    f) Limitations in the use of hands or fingers, required the help of another person for all tasks (not independent even with use of special tools)

11. Which one of the following best describes your ability, during the past week, to remember things?
    a) Able to remember most things
    b) Somewhat forgetful
    c) Very forgetful
    d) Unable to remember anything at all

12. Which one of the following best describes your ability, during the past week, to think and solve day to day problems?
    a) Able to think clearly and solve day to day problems
    b) Had a little difficulty when trying to think and solve day to day problems.
    c) Had some difficulty when trying to think and solve day to day problems.
    d) Had a great difficulty when trying to think and solve day to day problems.
    e) Unable to think or solve day to day problems.

13. Which one of the following best describes your ability, during the past week, to perform basic activities?
    a) Eat, bathe, dress and use the toilet normally
    b) Eat, bathe, dress or use the toilet independently with difficulty
    c) Required mechanical equipment to eat, bathe, dress or use the toilet independently
    d) Required the help of another person to eat, bathe, dress or use the toilet

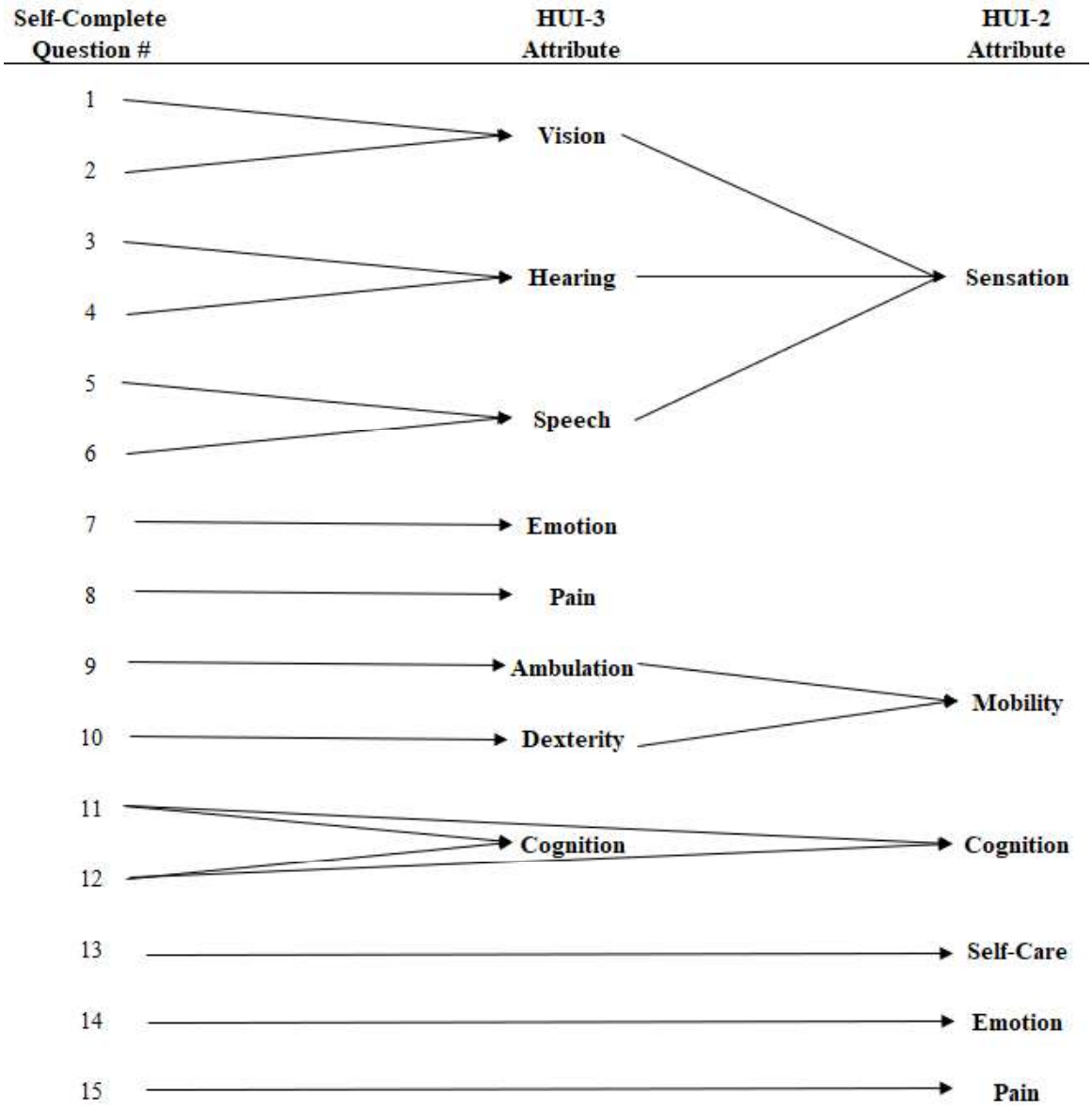
14. Which one of the following best describes how you have been feeling during the past week?
    a) Generally happy and free from worry
    b) Occasionally fretful, angry, irritable, anxious or depressed
    c) Often fretful, angry, irritable, anxious or depressed
    d) Almost always fretful, angry, irritable, anxious or depressed
    e) Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help

15. Which one of the following best describes the pain or discomfort you have experienced during the past week?
    a) Free of pain and discomfort.
    b) Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.
    c) Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities
    d) Frequent pain or discomfort; frequent disruption of normal activities Discomfort required prescription narcotics for relief.
    e) Severe pain or discomfort. Pain not relieved by drugs and constantly disrupted normal activities.

16. Overall, how would you rate your health during the past week?
    a) Excellent
    b) Very good
    c) Good

17. How did you complete the questionnaire? Please select the one answer that best describes your situation
    a) By myself, without any help from anyone else
    b) By myself, except someone else circled the answers on the questionnaire form for me
    c) With the help of someone else
    d) This questionnaire was completed by a family member, without help from the subject or patient
    e) This questionnaire was completed by a nurse or other health professional, without help from the subject or patient
    f) This questionnaire was completed by another person, without help from the subject or patient

The mappings of the self-complete questions to the HUI-3 and HUI-2 attribute levels are as follows:



From the standard HUI 15-item questionnaire data we are able to determine 8 scores (with differing number of variables in the scoring) which are used to calculate an overall utility score for HUI-3 and HUI-2:

1. HUI-3 attribute levels (8 variables; calculated from HUI 15-item questionnaire data)
2. HUI-3 single-attribute utility scores (8 variables; calculated from the HUI-3 attribute levels)
3. HUI-3 comprehensive health state (1 variable; 8-element vector from HUI-3 attribute levels)
4. HUI-3 overall multi-attribute utility score (1 variable; calculated from single-attribute utility scores)
5. HUI-2 attribute levels (7 variables; calculated from the HUI-3 attribute levels)
6. HUI-2 single-attribute utility scores (7 variables; calculated from the HUI-2 attribute levels)
7. HUI-2 comprehensive health state (1 variable; 7-element vector from HUI-3 attribute levels)
8. HUI-2 overall multi-attribute utility score (1 variable; calculated from single-attribute utility scores)

The statistical analysis will be completed utilizing the **OVERALL MULTI-ATTRIUBUTE UTILITY SCORES for HUI-3 and HUI-2**.

The HUI-2 and HUI-3 multi-attribute utility score scales are each defined such that the score for dead is set to 0.00. The score for perfect health (defined as the state having all attributes at level 1) is set to 1.00. The HUI-2 multi-attribute utility scale is defined for the interval -0.03 to 1.00; the HUI-3 multi-attribute utility scale is defined for the interval -0.36 to 1.00. Negative scores represent states considered worse than dead.

The following instructions guide the user in the determination of HUI-3 and HUI-2 attribute levels and overall multi-attribute utility scores for each subject:

1. Determining HUI-3 Attribute Levels (8 variables)
   The levels are Vision, Hearing, Speech, Emotion, Pain, Ambulation, Dexterity, and Cognition. Four of these attributes (vision, hearing, speech, and cognition) each require input from sets of two questions to determine the attribute level.

   The scoring methods for HUI-3 Attribute Levels can be found in Tables 15-19:

Table 15: HUI-3 Vision Attribute Level Decision Table

(based on self-complete questionnaire responses)

Question #1 Response	Question #2 Response			
	a	b	c	d
a	1	2	3	3
b	2	2	3	3
c	4	4	5	5
d	6	6	6	6

Table 16: HUI-3 Hearing Attribute Level Decision Table

(based on self-complete questionnaire responses)

Question #3 Response	Question #4 Response				
	a	b	c	d	e
a	1	1	1	1	1
b	2	3	3	3	3
c	4	5	6	6	6
d	4	5	6	6	6
e	6	6	6	6	6

Table 17: HUI-3 Speech Attribute Level Decision Table

(based on self-complete questionnaire responses)

Question #5 Response	Question #6 Response			
	a	b	c	d
a	1	1	1	1
b	2	3	5	5
c	4	4	5	5
d	4	4	5	5

Table 18: HUI-3 Cognition Attribute Level Decision Table

(based on self-complete questionnaire responses)

Question #11 Response	Question #12 Response				
	a	b	c	d	e
a	1	2	2	5	6
b	3	4	4	5	6
c	5	5	5	5	6
d	6	6	6	6	6

Table 19: Ambulation, Dexterity, Emotion and Pain Attribute Level Decision Table

(based on self-complete questionnaire responses)							
	Question Response						
Attribute	Question #	a	b	c	d	e	f
Ambulation	9	1	2	3	4	5	6
Dexterity	10	1	2	3	4	5	6
Emotion	7	1	2	3	4	5	n/a
Pain	8	1	2	3	4	5	n/a

The standard, and somewhat arbitrary, HUB attribute levels for comatose study subjects are defined as follows: Vision= Level 6; Hearing= Level 6; Speech= Level 5; Ambulation= Level 6; Dexterity= Level 6; Emotion= Level 3; Cognition= Level 6; and Pain= Level 3.

2. Determining HUI-2 Attribute Levels (7 variables)
The levels are Sensation, Mobility, Cognition, Self-Care, Emotion, Pain, and Fertility. HU1-2 level codes for sensation and mobility attributes are derived directly from previously determined HUI-3 attribute level codes. Note: To distinguish clearly previously determined HUI-3 levels from HUI-2 levels being determined, the HUI-3 levels are printed as words and the HUI-2 levels are specified using numerals.

   The scoring methods for HUI-2 Attribute Levels can be found in Tables 20-24:

Table 20: HUI-2 Sensation Attribute Level Decision Table

(based on levels of HUI-3 attributes of vision, hearing, and speech)

HUI-3 Levels		HUI-3 Levels of Speech				
Vision	**Hearing**	One	Two	Three	Four	Five
One	One	1	3	3	3	4
One	Two	2	3	3	3	4
One	Three	2	3	3	3	4
One	Four	3	3	3	3	4
One	Five	3	3	3	3	4
One	Six	4	4	4	4	4
Two	One	2	3	3	3	4
Two	Two	2	3	3	3	4
Two	Three	2	3	3	3	4
Two	Four	3	3	3	3	4
Two	Five	3	3	3	3	4
Two	Six	4	4	4	4	4
Three or Four or Five	One	3	3	3	3	4
Three or Four or Five	Two	3	3	3	3	4
Three or Four or Five	Three	3	3	3	3	4
Three or Four or Five	Four	3	3	3	3	4
Three or Four or Five	Five	3	3	3	3	4
Three or Four or Five	Six	4	4	4	4	4
Six	One	4	4	4	4	4
Six	Two	4	4	4	4	4
Six	Three	4	4	4	4	4
Six	Four	4	4	4	4	4
Six	Five	4	4	4	4	4
Six	Six	4	4	4	4	4

Table 21: HUI-2 Mobility Attribute Level Decision Table

(based on levels of HUI-3 attributes of ambulation and dexterity)

HUI-3 Levels of Ambulation	HUI-3 Levels of Dexterity					
	One	Two	Three	Four	Five	Six
One	1	1	1	1	1	1
Two	2	2	2	2	2	2
Three	3	3	3	3	3	3
Four	3	3	3	3	3	3
Five	4	4	4	4	4	4
Six	4	4	4	4	4	5

Table 22: HUI-2 Cognition Attribute Level Decision Table

(based on self-complete questionnaire responses)					
Question #11 Response	Question #12 Response				
	a	b	c	d	e
a	1	2	2	3	4
b	2	2	2	3	4
c	2	3	3	3	4
d	4	4	4	4	4

Table 23: HUI-2 Self-Care, Emotion, and Pain Attributes Level Decision Table

(based on self-complete questionnaire responses)						
		Question Response				
Attribute	Question #	a	b	c	d	e
Self-Care	13	1	2	3	4	n/a
Emotion	14	1	2	3	4	5
Pain	15	1	2	3	4	5

Table 24: HUI-2 Fertility Attributes Level Decision Table

The HUI2 fertility attribute level code is assumed to be level 1

The standard, and somewhat arbitrary, HUI-2 attribute levels for comatose study subjects are as follows: Sensation= Level 4; Mobility= Level 5; Emotion= Level 3; Cognition Level 4; Self-Care= Level 4; Pain= Level 3; and Fertility= Level 1.

3. Determining Single-Attribute HUI-3 Utility Scores (8 variables)
Single-attribute utility functions provide preference scores of relative desirability for functional capacity within single attributes defined by the HUI-3 health status classification system. The HUI-3 levels are labelled using integers. Each single-attribute utility function is defined on a scale from 0.00 to 1.00.

The most disabled level of an attribute has a single-attribute utility score of 0.00, and no disability of an attribute has a single-attribute utility score of 1.00.

Scoring is as follows:

Attribute Level	Vision u_1	Hearing u_2	Speech u_3	Ambulation u_4	Dexterity u_5	Emotion u_6	Cognition u_7	Pain u_8
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.95	0.86	0.82	0.83	0.88	0.91	0.86	0.92
3	0.73	0.71	0.67	0.67	0.73	0.73	0.92	0.77
4	0.59	0.48	0.41	0.36	0.45	0.33	0.70	0.48
5	0.38	0.32	0.00	0.16	0.20	0.00	0.32	0.00
6	0.00	0.00	n/a	0.00	0.00	n/a	0.00	n/a

Legend: u_x: single-attribute utility function for attribute x, n/a: not applicable
Note: The mean single-attribute utility score for level 3 cognition is greater than the mean single-attribute utility score for level 2 cognition.

4. Determining Single-Attribute HUI-2 Utility Scores (7 variables)
Single-attribute utility functions provide preference scores of relative desirability for functional capacity within single attributes defined by the HUI-2 health status classification system. The HUI-2 levels are labelled using integers. Each single-attribute utility function is defined on a scale from 0.00 to 1.00.

The lack of functional capacity, or most disabled level, in an attribute has a single-attribute utility score of 0.00, and full function, or no disability, for an attribute has a single-attribute utility score of 1.00.

Scoring is as follows:

Attribute Level	Sensation u_1	Mobility u_2	Emotion u_3	Cognition u_4	Self-Care u_5	Pain u_6	Fertility u_7
1	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.87	0.92	0.86	0.86	0.85	0.95	0.75
3	0.65	0.61	0.60	0.66	0.55	0.75	0.00
4	0.00	0.34	0.37	0.00	0.00	0.42	n/a
5	n/a	0.00	0.00	n/a	n/a	0.00	n/a

Legend: u_x: single-attribute utility function for attribute x, n/a: not applicable

5. Determining Overall Health-Related Quality of Life (HRQL) Utility Scores Using HUI-3 Utility Function (1 variable)
To calculate the HUI-3 HRQL Utility Score, the above-determined single-attribute levels are entered into the following health utility formula **or subjects who do not have missing data from the 15-item questionnaire**:
U=1.371(Vison*Hearing*Speech*Ambulation*Dexterity*Emotion*Cognition*Pain)–0.371

HUI-3 allows for negative scores of HRQL that represent health states considered worse than dead. The lowest possible HUI-3 score is -0.3. Note that the overall HRQL utility score for deceased subjects cannot be calculated using the HUB multi-attribute utility function and that this variable should be assigned a score of 0.00. (Dead is an anchor state of the conventional dead=0.00 to perfect health=1.00 overall HRQL utility scale and, therefore, **the score for dead is 0.00** by definition.)

6. Determining Overall Health-Related Quality of Life (HRQL) Utility Scores Using HUI-2 Utility Function (1 variable)
   To calculate the HUI-2 HRQL Utility Score, the above-determined single-attribute levels are entered into the following health utility formula **for subjects who do not have missing data from the 15-item questionnaire**:
   U=1.06(Sensation*Mobility*Emotion*Cognition*Self-Care*Pain*Fertility)–0.06

   HUI-2 allows for negative scores of HRQL that represent health states considered worse than dead. The lowest possible HUI-2 score is -0.03. Note that the overall HRQL utility score for deceased subjects cannot be calculated using the HUB multi-attribute utility function and that this variable should be assigned a score of 0.00. (Dead is an anchor state of the conventional dead=0.00 to perfect health=1.00 overall HRQL utility scale and, therefore, **the score for dead is 0.00** by definition.)

9.4. 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.

9.5. MNAR Cases Identified Prior to Database Lock

Site	Subject ID	IMP Start Date	IMP End Date	Intercurrent Event
0036	0032	19-Jan-21	22-Mar-21	LACK OF EFFICACY
0038	0052	8-Apr-21	6-May-21	LOST TO FOLLOW-UP
0090	0196	16-Nov-22	10-Jan-23	WITHDRAWAL BY SUBJECT

9.6. 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.

- 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 Payne's formula:

Corrected calcium = measured Ca (mg/dL) + 0.8 × (4.0 g/dL – patient albumin (g/dL)).

(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

- 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

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 using the WHO criterion 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

Uric Acid will not be CTCAE graded.

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	-	-	-	-

Bicarbonate or CO2 will not be CTCAE graded.

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

Phosphorus or Phosphate will not be CTCAE graded.

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 be graded in Grade 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 be graded in Grade 1-3 without baseline factor

- 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	-	-

Eosinophils will not be CTCAE graded

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

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	-

Platelet count will not be CTCAE graded

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 grades 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

Urine blood will not be CTCAE graded

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

9.7. 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, listing, and figure will clearly specify the analysis population being summarized/listed. 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 treatment, 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.
- The presentation of numerical values will adhere to the following guidelines (exceptions may be necessary in some circumstances for derived analysis variables to allow readability):
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the eCRFs.
    - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.
    - Means will be reported to the one decimal place beyond the number of decimal places the original parameter is presented.
    - Calculated percentages will be reported with one decimal place.

- ♦ 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 eCRFs.
- 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.

9.8. Abbreviations

Abbreviation	Definition
AE	Adverse event
AED	Anti-epileptic drug
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BID	Twice daily
BMI	Body mass index
BZD	Benzodiazepine
CGI-S	Clinical Global Impression – Severity of Symptoms
CGI-I	Clinical Global Impression – Improvement
CI	Confidence interval
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
DBS	Deep brain stimulator
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HUI	Health Utilities Index
ICF	Informed consent form
ILAE	International League Against Epilepsy
IMP	Investigational medicinal product
LLN	Under the lower limit of normal
LOQ	Limit of quantification
mCIWA-B	Modified Clinical Institute Withdrawal Assessment – Benzodiazepines
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MHI	Medication Handling Irregularities
MMRM	Mixed Measures of Repeated Model
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
QOLIE-31	Quality of Life in Epilepsy-31
QTc	QT interval value corrected for heart rate
QTcF	QT interval value corrected for heart rate using Fridericia's formula
RNS	Responsive neurostimulator
RRatio	Response Ratio
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SF	Screen Failure
SIF/DRF	Seizure Identification and Diagnostic Review Form
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESC	The Epilepsy Study Consortium
ULN	Above the upper limit of normal
VNS	Vagus Nerve Stimulator
WBC	White Blood Cell
WHO	World Health Organization