Official Title: A Phase 1, Double-blind (Investigator and Participant), First-in-Human Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of CVL-354 in Healthy Participants

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16.1.9 DOCUMENTATION OF STATISTICAL METHODS

STATISTICAL ANALYSIS PLAN

A PHASE 1, DOUBLE-BLIND (INVESTIGATOR AND PARTICIPANT), FIRST-IN-HUMAN TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE AND MULTIPLE ASCENDING DOSES OF CVL-354 IN HEALTHY PARTICIPANTS

Protocol Number: CVL-354-1001

Compound: CVL-354

Trial Phase: 1

Short Title: A Single and Multiple Ascending Dose Trial of CVL-354 in Healthy Participants

Sponsor Name: Cerevel Therapeutics, LLC

Protocol Version: **Version 3.0: 25 May 2022**
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Analysis Plan Version: **Final 1.0: 17 Mar 2023**

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the planned data summary and analysis of disposition, demographics, and safety data from Protocol CVL-354-1001. The statistical analysis plan (SAP) is based on:

- Protocol CVL-354-1001, Version 3.0: 25 May 2022
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)

Background information is provided for the overall study design and objectives. Further details of study conduct, and data collection are provided in the study protocol and case report forms (CRFs). A standalone Pharmacokinetic (PK) Analysis Plan containing details regarding the planned analysis of plasma concentrations is provided as an appendix of this document.

1.1. Study Overview

CVL-354-1001 is a Phase 1, double-blind (investigator and participant), randomized, placebo-controlled, single-center trial that will be conducted in 2 sequential parts to evaluate safety, tolerability, and PK of CVL-354 following single and multiple doses in healthy participants.

1.1.1. Part A (Single Ascending Dose: Cohorts 1 and 2)

Part A (Cohort 1 and Cohort 2) will employ a 4-period crossover, single ascending dose methodology. Up to 2 cohorts of participants may be evaluated during the Part A.

Cohorts 1 and 2 will be dosed in a sequential manner for up to 4 periods each. Progression to each dose level will occur following evaluation of all available cumulative safety, tolerability, PK, and other emergent data from the previous cohorts and periods.

The current trial may evaluate up to 8 different dose levels in Cohorts 1 and 2; however, some doses may be repeated, if required. The starting dose for Part A will be 0.5 mg. Doses, in general, will be escalated in Cohort 1 and Cohort 2 until the maximum tolerated dose is achieved or the CVL-354 exposures (C_{max} and AUC_{24}) reach, or are projected to reach, the predefined human exposure limits [redacted] Dose escalation may also be stopped if it is determined that sufficient exposures are achieved, based on estimated target occupancy. Based on emergent data, the actual doses may change; however, new doses will not exceed half-log increments (3.3-fold) from previous dose. Smaller increments (eg, ≤2-fold) will be evaluated as exposures approach the proposed stopping criteria. All dosing decisions will be made jointly by the sponsor and the investigator after review of all available safety, tolerability (through 72 hours postdose), and PK data (through 24 hours postdose) at a Safety Review Team (SRT) meeting.

During dose escalation, Cohorts 1 and 2 will employ sentinel dosing (n=2; 1 CVL-354 and 1 placebo) during each period to ensure safety and tolerability before proceeding to dosing of non-sentinel participants for that period. The investigator will review AEs (serious and nonserious) and all available safety data from the first 24 hours after dosing for the 2 sentinel participants. If clinically significant safety concerns are observed in sentinel participants, dosing of the rest of the cohort will be paused in order for the SRT to discuss the findings and determine

subsequent actions. If no safety concerns are observed in the sentinel participants, the investigator will provide written documentation for sponsor confirmation before proceeding to dosing of non-sentinel participants.

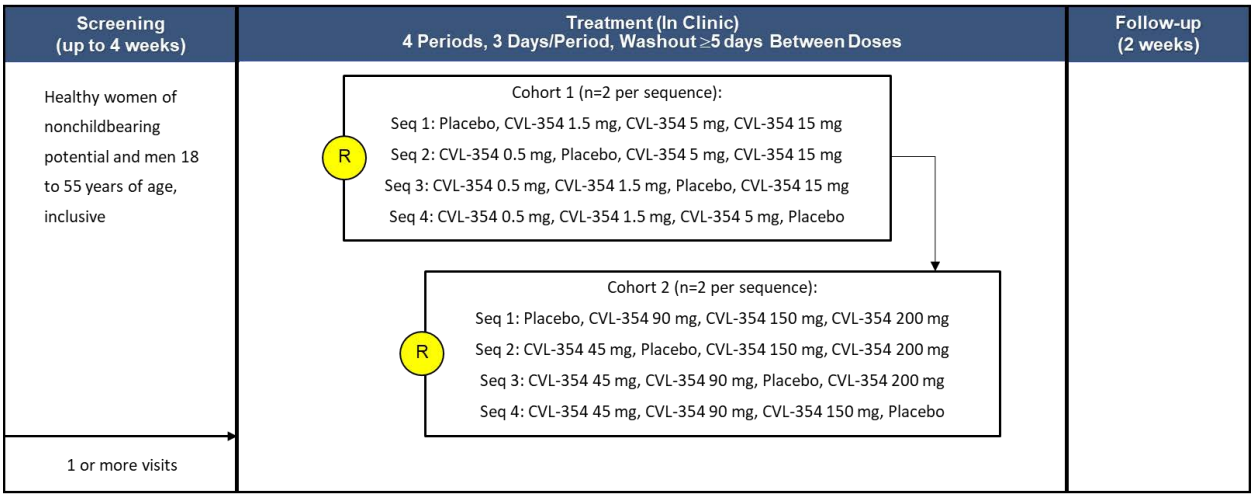
Check-in assessments conducted on Day -1 of each period will include both sentinel and non-sentinel participants. No additional check-in assessments will be required for non-sentinel participants prior to dosing if the Check-in assessments are performed within 48 hours prior to dosing.

Each dosing period for the dose escalation portion of Part A will be separated by a washout period of at least 5 days (ie, administration of subsequent doses of investigational medicinal product [IMP] will not occur until at least 5 days after the previous dose of IMP).

Cohorts 1 and 2 will comprise approximately 8 participants each (3:1 ratio of CVL-354 to placebo within each treatment period). All participants will receive single oral doses of CVL-354 or placebo during each period. All doses during dose escalation will be administered under fasted conditions following a 10-hour overnight fast. Participants will continue to fast for 4 hours following dosing on Day 1.

The planned trial design for Part A: Cohorts 1 and 2, is depicted in Figure 1.

Figure 1: Trial Schematic - Part A (Single Ascending Dose, Cohorts 1 and 2)



Abbreviations: IMP=investigational medicinal product; R=randomization; Seq=sequence.
For each period, Check-in is on Day -1 and Check-out is on Day 3.
Follow-up consists of a contact to check on status 14±3 days after a participant's final dose of IMP in the trial.
Doses/treatment may be modified based on emergent safety, tolerability, and pharmacokinetic data.
Doses may be repeated to confirm safety/tolerability.

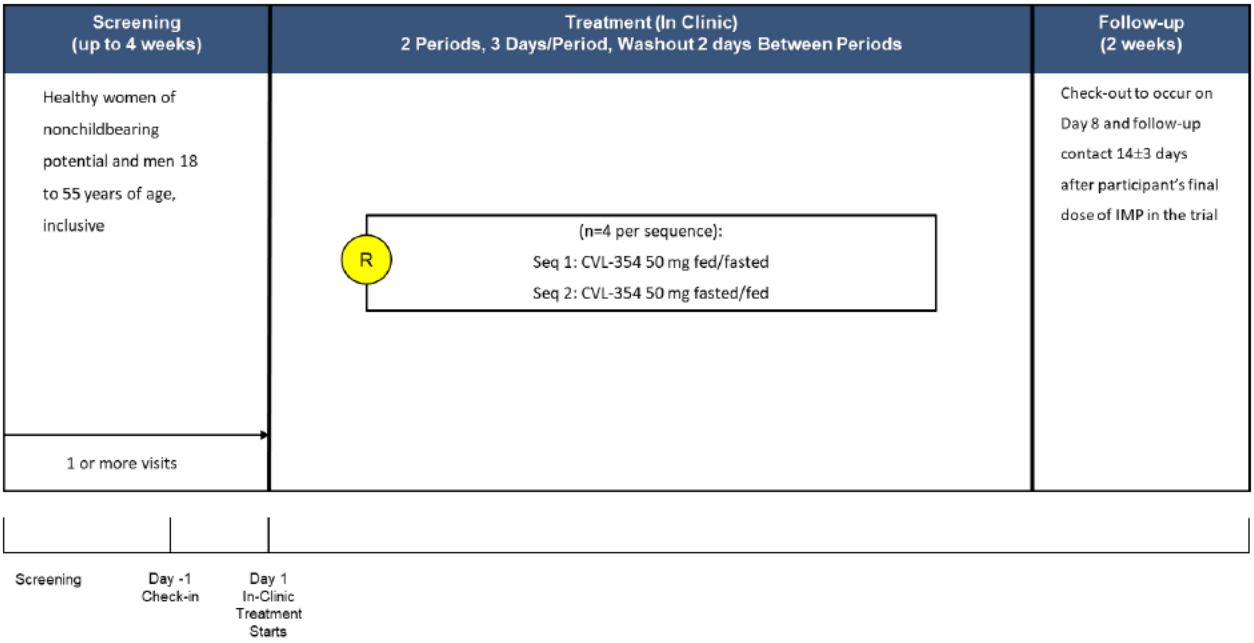
1.1.2. Part A (Food Effects: Cohort 3)

Cohort 3 will be scheduled after completion of single dose escalation to evaluate the effect of food on CVL-354 exposures after a single 50 mg dose. The selected dose is 4-fold lower than the top single CVL-354 200 mg dose that is considered to be safe and tolerated. For evaluation of food effect, a 2-period crossover design will be utilized, with approximately 8 participants randomized to 1 of 2 sequences (fed/fasted or fasted/fed). Sentinel dosing will not be employed for evaluation of food effect.

Participants will remain domiciled after Check-in for both periods of the food effect evaluation. The duration of each period will be 3 days, with a 2-day washout between Period 1 and Period 2.

The trial design for Part A (Food Effects, Cohort 3) is in Figure 2.

Figure 2: Trial Schematic - Part A (Food Effect, Cohort 3)



Abbreviations: IMP=investigational medicinal product; R=randomization; Seq=sequence.
The treatment phase will comprise 2 periods with a 2-day washout between Periods 1 and 2. Participants will be discharged from the clinic on Period 2 Day 3 (Check-out).
Follow-up consists of a contact to check on status 14±3 days after a participant's final dose of IMP in the trial.

1.1.3. Part B (Multiple Ascending Dose)

The safety and PK of double-blind (investigator and participant), multiple-dose administration of CVL-354 will be evaluated in Part B of the trial after completion of dose escalation in Part A. Part B may overlap with Part A Cohort 3 (evaluation of food effect on CVL-354 exposures).

Up to 5 sequential cohorts of 10 participants each will be evaluated in Part B. Participants will receive oral doses of either CVL-354 or placebo for up to 14 days. Eligible participants will be admitted to the clinic on Day -1 and will be randomized in a 4:1 ratio (8 participants active treatment: 2 participants placebo). Cohorts will be initiated in a sequential manner after review of all available safety, tolerability, and PK data (at least up to Day 15) from previous cohorts.

Each dose of CVL-354 will be administered once daily (QD) throughout Part B of the trial based on data obtained during Part A of the trial.

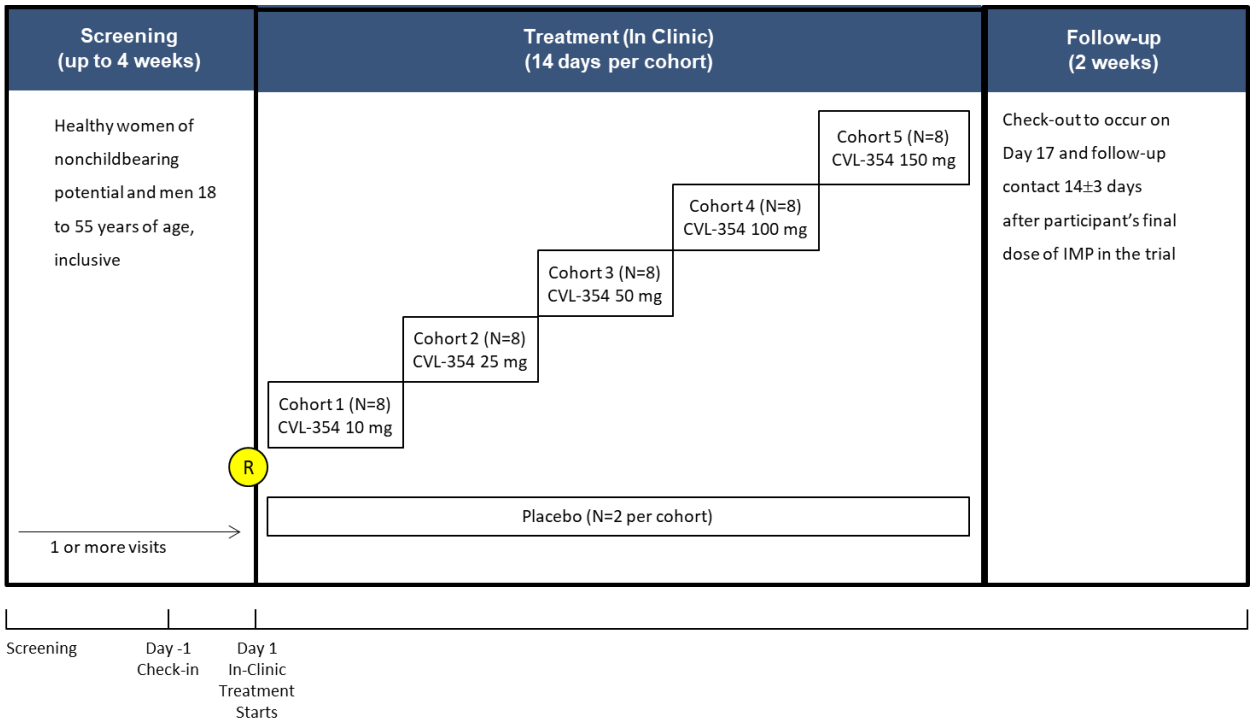
The starting dose for Part B will be 10 mg QD. In Part A, a single oral CVL-354 dose of 200 mg was deemed to be safe and well tolerated. The exposures from daily doses of 10 mg QD are expected to be well below the highest exposures investigated in the SAD part [redacted] Only the 10 mg QD dose will be administered as an extemporaneously prepared solution (same formulation as Part A) in Part B. All other subsequent doses will be

administered as capsule. During Part B, all preceding doses should be deemed safe and tolerated before progressing to higher doses. Similar to Part A, dose increments in Part B will not exceed half-log increments (3.3-fold) early in escalation and smaller escalation steps (≤2-fold) will be implemented at doses closer to stopping criteria. Standard safety laboratory assessments, vital sign measurements, safety electrocardiograms (ECGs), and AE data will provide the relevant safety data up to Day 17 to make the dose-escalation decision. Furthermore, dose-escalation decisions will be made by the SRT.

On days with intensive PK sampling (Days 1 and 14), IMP will be administered under fasted conditions following a 10-hour overnight fast. Participants will continue to fast for 4 hours following dosing on these intensive PK sampling days. On other days, each dose of IMP will be administered at approximately the same time each morning at least 1 hour following the morning meal. Each dose of IMP will be administered orally with approximately 240 mL of water.

The Trial Design for Part B is in Figure 3.

Figure 3: Trial Schematic - Part B (Multiple Ascending Dose, Cohorts 1-5)



Abbreviations: IMP=investigational medicinal product; R=randomization.
Doses will be selected following completion of Part A.

1.2. Sample Size Considerations

The sample size is not based on statistical hypothesis testing. Based on historical precedent, it is expected that the proposed sample sizes of 8 participants per cohort in Part A (SAD, food effect) and 10 participants per cohort in Part B (MAD) will address the overall aim of the trial.

In the event of higher than anticipated early terminations, Cerevel may extend enrollment in order to achieve trial objectives.

1.3. Measures to Minimize Bias: Randomization and Blinding

1.3.1. Subject Assignment to Treatment

Treatment assignments will be based on a computer-generated randomization code provided by the sponsor or designee.

For the food effect evaluation (Part A, Cohort 3), participants will receive the same 50 mg dose and will be randomized to a treatment sequence (fed/fasted or fasted/fed).

Participants who discontinue may be replaced at the discretion of the sponsor and investigator. If a participant is replaced, he or she will receive a mirror randomization number (such that the same sequence [Part A, Cohorts 1 and 2] or treatment [Part B] assigned to the original discontinued participant would be assigned to the replacement participant). Participants who discontinue during Part A (SAD portion) of the trial may be replaced; however, the replacement participant will only need to complete the trial periods that were not completed by the original participant.

1.3.2. Blinding

During the entire trial, treatment will be blinded such that participants and the investigator and other site personnel (with the exception of pharmacy staff) will not have knowledge of the treatment assignment at any visit.

Treatment assignment will not be blinded for the food effect portion of the trial.

At the initiation of the trial, investigators and site personnel will be instructed on the method for breaking the blind. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of the treatment assignment for an individual participant is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor before unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. The sponsor must be notified within 24 hours after breaking the blind for a trial participant.

Documentation of unblinding should be recorded in the participant's medical record, including 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 participant, treatment with the IMP may not be reinitiated for that participant.

A list of sponsor personnel who will be unblinded to treatment allocation for the purposes of dose escalation and safety monitoring (SRT) will be provided in a separate document.

2. OBJECTIVES AND ENDPOINTS

The trial objectives and endpoints are summarized in Table 1 and Table 2.

Table 1: Part A (Single Ascending Dose)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of single ascending doses of CVL-354 administered orally to healthy participants	• Treatment-emergent AEs, including AEs potentially related to abuse • Clinically significant changes in ECGs, vital signs, clinical laboratory assessments, and physical and neurological examination results • Changes in suicidality assessed using the C-SSRS
Secondary	
• To evaluate the plasma pharmacokinetics of CVL-354 following single ascending doses administered orally to healthy participants	• Pharmacokinetic parameters of CVL-354 following single oral doses: ○ C_{max} ○ T_{max} ○ AUC_{24} ○ AUC_{last} ○ AUC_{inf} ○ CL/F ○ V_z/F ○ $t_{½}$
• To evaluate the effect of food following single doses of CVL-354 administered orally to healthy participants	• Pharmacokinetic parameters of CVL-354 following single oral doses: ○ C_{max} ○ T_{max} ○ AUC_{24} ○ AUC_{last} ○ AUC_{inf} ○ CL/F ○ V_z/F ○ $t_{½}$

Abbreviations: AE=adverse event; AUC=area under the concentration-time curve; CL/F=apparent clearance of drug from plasma; C_{max}=maximum plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; $t_{½}$=apparent terminal half-life; SAD=single ascending dose; T_{max}=time to maximum plasma concentration; Vz/F=apparent volume of distribution during terminal phase.

Table 2: Part B (Multiple Ascending Dose)

Objectives	Endpoints
Primary	
• To explore the safety and tolerability of multiple ascending doses of CVL-354 administered orally to healthy participants	• Treatment-emergent AEs, including AEs potentially related to abuse • Clinically significant changes in ECGs, vital signs, clinical laboratory assessments, and physical and neurological examination results • Changes in suicidality assessed using the C-SSRS
Secondary	
• To evaluate the plasma pharmacokinetics of CVL-354 following multiple ascending doses administered orally to healthy participants	• Pharmacokinetic parameters for CVL-354 on Days 1 and 14: ○ C_{max} ○ T_{max} ○ C_{trough} ○ AUC_{τ} ○ CL/F (Day 14 only) ○ V_Z/F (Day 14 only) ○ PTR (Day 14 only) ○ Rac, C_{max} (Day 14 only) ○ Rac, AUC (Day 14 only) ○ $t_{½}$ (Day 14 only) ○ Ae (amount eliminated unchanged in urine at steady state on Day 14) ○ Renal clearance

Abbreviations: AE=adverse event; AUC=area under the concentration-time curve; CL/F=apparent clearance of drug from plasma; C_{max}=maximum plasma concentration; C_{trough}=trough plasma concentration; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; PTR=peak to trough ratio; Rac=accumulation ratio; $t_{½}$=apparent terminal half-life; T_{max}=time to maximum plasma concentration; Vz/F=apparent volume of distribution during terminal phase.

3. KEY ASSESSMENTS AND DERIVATIONS

3.1. Efficacy Assessments

No efficacy assessments will be performed for this Phase 1 first-in-human trial.

3.2. Screening and Baseline Assessments

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants who are screened and to confirm eligibility or record reasons for screening failure, as applicable.

3.4. Safety Assessments

3.4.1. Vital Signs

Vital signs include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Supine blood pressure and heart rate measurements will be obtained after at least 3 minutes of rest.

At specified time points, the supine measurements will be followed by measurements in the standing position (after standing for at least 3 minutes) to allow for orthostatic assessments. Orthostatic hypotension is defined as a decrease of ≥20 mmHg in systolic blood pressure upon standing compared with the supine blood pressure measurement (at Screening, relative to the average measurement).

3.4.2. Electrocardiograms

3.4.2.1. Continuous Electrocardiogram Recordings

During the SAD portion of the trial (Part A), a one-time baseline report of continuous ECG telemetry will be recorded for each participant by the site for a minimum of 12 hours starting on Day -1 prior to first dose. This baseline report will also be required for any replacement

participants during Part A. The investigator is required to review the baseline telemetry report prior to randomizing each participant.

During the SAD and MAD portions of the trial, continuous ECGs will be recorded for a minimum of 26 hours, starting at least 2 hours predose and continuing until 24 hours postdose on the days indicated in the Schedule of Assessments (Appendix 9.1). Electrocardiograms will be extracted from the continuous recording by a central ECG service.

3.4.2.2. Standard 12-Lead Electrocardiograms

Electrocardiogram recordings will be obtained after the participant has been supine and at rest for approximately 3 minutes. During the SAD and MAD portions of the trial, 12-leads ECG will be performed according to the Schedule of Assessments (Appendix 9.1). The central ECG service will provide the QTcF corrections and average of the 3 ECGs performed.

3.4.3. Clinical Safety Laboratory Assessments

Clinical laboratory tests will be performed according to the Schedule of Assessments (Appendix 9.1).

3.4.4. Suicidal Ideation and Behavior Risk Monitoring

Suicidality will be monitored during the trial using the C-SSRS. This semi-structured interview was originally developed to evaluate the link between antidepressants and suicidal behavior and ideation in youth and adverse events from pediatric clinical trials (Posner et al, 2011). It was designed to quantify the severity of suicidal ideation and behavior. Trial personnel administering the C-SSRS must have completed the appropriate training and have valid certification. Access to training on the scale will be provided by the sponsor or designee.

This trial will use the “Baseline/Screening” and “Since Last Visit” versions of the scale. The “Baseline/Screening” version, which assesses the lifetime experience of the participant 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 participants at screening to determine eligibility.

The “Since Last Visit” C-SSRS form will be completed at all specified time points after screening. The investigator will review the results of the “Since Last Visit” C-SSRS during the trial to determine whether it is safe for the participant to continue in the trial. If a participant has any “YES” answers on the C-SSRS for the suicidal ideation or suicidal behavior items, the investigator will evaluate whether a risk assessment by a qualified mental health professional (or the investigator alone if the investigator is a qualified mental health professional) is needed and discuss with the medical monitor whether the participant should continue in or be discontinued from the trial.

3.4.5. Physical/Neurological Examinations

The full physical examination will include a review of the following body systems: head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, and musculoskeletal systems.

The abbreviated physical examinations will include evaluation of cardiovascular, pulmonary, and gastrointestinal systems.

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

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.

3.4.6. Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject, temporally associated with the use of trial intervention, whether considered related to the trial intervention.

All adverse events will be recorded on the ADVERSE EVENTS CRF. Adverse events with missing severity will have the severity imputed as 'Grade 3' 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 intensity and/or relationship will be presented as missing.

3.4.6.1. Adverse Events of Special Interest

The following events will be reported as AESIs:

- AEs that result in the discontinuation of IMP
- Events that satisfy the criteria for suspected Hy's Law (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3 × upper limit of normal [ULN], AND serum bilirubin ≥2 × ULN
  - Repeat for confirmation and notify the medical monitor immediately
- QTcF >500 ms or increase >60 ms from baseline
  - Repeat for confirmation and notify the medical monitor immediately
- Grade 2 moderate AEs that are related to the gastrointestinal system (eg, nausea, vomiting, diarrhea, constipation, dyspepsia, etc)
- Grade 2 moderate AEs that are related to the central nervous system (eg, headache, dizziness, syncope, irritability, anxiety, etc)
- AEs potentially related to abuse (refer to the APMP document for details)

The primary objective of the APMP is to monitor events that may suggest that CVL-354 produces drug effects that could be sought out for abuse purposes. In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue will also receive special attention. As part of the APMP, AEs potentially related to abuse and medication handling irregularities related to suspected or known abuse of IMP must be reported

as AESIs. Investigators and site staff at each trial site will be trained on reporting potentially abuse-related AEs. While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search by the sponsor of all relevant Medical Dictionary for Regulatory Activities (MedDRA) terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, consistent with US FDA guidance (FDA, 2017).

3.5. Pharmacokinetics

Plasma and urine samples for pharmacokinetics assessments will be processed, stored, and shipped to the bioanalytical facility according to the instructions provided to the investigator in advance of the trial. A fully validated bioanalytical method will be used to quantitate the concentrations of CVL-354 in plasma and in urine. Plasma and urine PK samples from this trial may be used for further evaluation of bioanalytical methods and identification of additional metabolites.

The results from metabolite scouting work (plasma and urine) will be captured in an exploratory metabolite scouting report, which will not be included in the CSR.

4. DATA CONVENTIONS AND VISIT WINDOWS

4.1. Data Conventions

4.1.1. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized. In situations where it is not possible to obtain all data, it may be necessary to impute missing data. These situations are described below. Unless otherwise specified, all other missing data will not be imputed.

4.1.1.1. Missing Severity or Relationship for Adverse Events

Adverse events (AEs) with missing severity (Common Terminology Criteria for Adverse Events [CTCAE] toxicity grade) will have the severity imputed as 'Grade 3' or 'Severe'. Adverse events with missing relationship to IMP will have the relationship imputed as 'Related' if the AE started after the first dose of IMP. Actual values will be presented in the data listings.

4.1.1.2. Incomplete or Missing Dates

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

For many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (ie, 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 dosing of IMP, then the start day of the IMP will be assigned to the day of first dose of IMP.
    - 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 dosing, 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.
- Missing all components of a start date:
    - Assign the date of 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/discontinuation.
  - However, if study completion/discontinuation year is greater than the year of the event, then the day and month will be set to 31 December.

- In the event of a completely missing end date (year not present and ongoing not checked), the end date will be considered as 'ongoing' and will not be imputed.

If any imputed date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date. If any imputed date causes the start date of the event to occur after the end date of the event, the end date of the event will be used for the imputation of the start 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 (ie, imputed values will not be listed).

4.1.1.3. Missing Time

If time is missing for a laboratory assessment taken on the first day of IMP administration, ie Day 1, but the time of IMP administration is available, then time for the laboratory assessment will be assumed to have occurred prior to IMP administration and will serve as the baseline value, assuming that the timepoint for the assessment was designated as predose. If the timepoint for the assessment was designated as postdose, then the assessment will be assumed to have been taken postdose.

4.1.1.4. Imputation for 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, the following imputation rules will be employed: the lower limit of quantification will be replaced with ½ the value of the lower limit. For example, < 0.1 will be replaced with 0.05.

The upper limit of quantitation will be increased by one level of precision that precedes the value. For example, ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1".

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

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

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

4.1.1.5. Derived and Transformed Data

There are no planned derivations or transformations.

4.1.2. Definitions and Terminology

4.1.2.1. Screen Failure

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized in the trial.

4.1.2.2. Analysis Period

Given the crossover design of Part A, in which each unique subject receives four treatments in a randomly ordered sequence, Period 1 is the subset of study days between the start of dosing for the initial treatment in the sequence until the dosing for Period 2, the second treatment in the sequence. This includes the washout period between dose 1 and dose 2. Period 2 is the subset of study days between the start of dosing for the second treatment until the dosing for Period 3, including the washout period between dose 2 and dose 3. Period 3 is the subset of study days between the start of dosing for the third treatment until the dosing for Period 4, including the washout period between dose 3 and dose 4. Period 4 is the subset of study days between the start of dosing for the fourth period until the end of study.

4.1.2.3. Age

Age is defined as age at the time of signing the ICF.

4.1.2.4. Baseline Value

For purposes of analysis, the baseline value is defined as the last value obtained prior to initiation of IMP. For ECG via Holter monitoring, the baseline value will be the average of the -15, -30, and -45 timepoints.

Period Baseline Value (Part A)

For purposes of analysis of data within each Study Period, the period baseline value will be defined as the last valid evaluation done before the IMP administration within each of the treatment periods.

Day 1 (Baseline) (Part B)

Baseline for Part B (Day 1) is defined as the day IMP is first initiated.

Period Day (Part A)

For Part A, within each period, Period Day is defined relative to the first day of the sentinel dosing within each phase. Thus, the period day of an event is calculated as:

Period Day = event date – first date of period dosing (+1, if event date ≥ date of Period Day 1)

This calculation will result in negative period days being assigned to visits occurring prior to treatment with IMP within each period, and positive study days being assigned on or after the start of IMP.

Study Day (Part B)

Study Day is defined relative to Baseline (Day 1). Thus, the study day of an event is calculated 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 being assigned to visit occurring prior to the start of IMP and positive study days being assigned on or after the start of IMP. There will be no Day 0 value to match the schedule of events.

Change from Baseline

Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Days on Study

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

Days on IMP (Part B)

Days on IMP is the number of days from Study Day 1 to the date of last dose of IMP as recorded on the End of Treatment eCRF page.

Cumulative Dose of IMP (Part B)

The cumulative dose of IMP is calculated in milligrams and is calculated as the sum of each daily dose on IMP as recorded on the Exposure eCRF page.

Treatment-emergent Adverse Event (TEAE)

Any event reported on the eCRF that occurs on or after the initiation of IMP and up to the final 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 may have occurred after the initiation of IMP. Hence, Adverse Events occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

For Part A, treatment-emergent adverse events will be attributed to a period based on the start date. An adverse event starting on or after the initiation of IMP in Period 1 and before dosing with IMP for Period 2, or through follow-up contact if subject discontinues prior to Period 2, is considered a Period 1 TEAE. For Cohort 1 and 2, an adverse event starting on or after the initiation of IMP in Period 2 and before dosing with IMP for Period 3, or through follow-up contact if subject discontinues prior to Period 3 is considered a Period 2 TEAE. An adverse event starting on or after the initiation of IMP in Period 3 and before dosing with IMP for Period 4, or through follow-up contact if subject discontinues prior to Period 4, is considered a Period 3

TEAE. An adverse event occurring after dosing for Period 4, through follow-up contact, is considered a Period 4 TEAE.

Treatment-emergent Laboratory Abnormality

A treatment-emergent laboratory abnormality is defined as value outside the normal range which occurs on or after the start of IMP and up to the follow-up contact following discontinuation of IMP of a given analysis period.

In Part A, treatment-emergent laboratory abnormalities will be attributed to a period based on the start date. A laboratory abnormality occurring on or after the initiation of IMP in Period 1 and before dosing with IMP for Period 2, or through the follow-up contact if subject discontinues prior to Period 2, is considered a Period 1 laboratory abnormality. For Cohort 1 and 2, a laboratory abnormality occurring on or after the initiation of IMP in Period 2 and before dosing with IMP for Period 3, or through the follow-up contact if subject discontinues prior to Period 3, is considered a Period 2 laboratory abnormality. A laboratory abnormality occurring on or after the initiation of IMP in Period 3 and before dosing with IMP for Period 4, or through the follow-up contact if subject discontinues prior to Period 4, is considered a Period 3 laboratory abnormality. A laboratory abnormality occurring after dosing for Period 4 through the follow-up contact is considered a Period 4 treatment-emergent laboratory abnormality.

Treatment-emergent Laboratory Toxicity

A treatment-emergent laboratory toxicity is defined as an increase of at least one toxicity grade from the baseline assessment at any post baseline visit. The post baseline visit must occur after the administration of IMP and through the follow-up contact. For defining treatment-emergent laboratory events, it is assumed that a laboratory assessment obtained on Day 1 with missing collection times occurred prior to the initiation of IMP unless a protocol deviation is identified. If the relevant baseline assessments are missing, then any graded toxicity (ie, at least Grade 1) is considered treatment-emergent.

For Part A, treatment-emergent laboratory toxicities will be attributed to a period based on the start date. A laboratory toxicity occurring on or after the initiation of IMP in Period 1 and before dosing with IMP for Period 2, or through the follow-up contact if subject discontinues prior to Period 2, is considered a Period 1 treatment-emergent toxicity. For Cohort 1 and 2, a laboratory toxicity occurring after dosing for Period 2 and before dosing with IMP for Period 3, or through the follow-up contact if subject discontinues prior to Period 3, is considered a Period 2 treatment-emergent toxicity. A laboratory toxicity occurring on or after the initiation of IMP in Period 3 and before dosing with IMP for Period 4, or through the follow-up contact if subject discontinues prior to Period 4, is considered a Period 3 laboratory toxicity. A laboratory toxicity occurring after dosing for Period 4 through the follow-up contact post Period 4 is considered a Period 4 treatment-emergent toxicity.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is comprised of 10 categories with binary responses. Details of the assessments and definitions are provided in Appendix 9.2.

Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a trial participant, at a dose above that which is assigned to that individual participant according to the protocol.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of IMP. These medications include those medications started before the initiation of IMP and continuing post Day 1. Concomitant medications will be classified by treatment. Medications taken during a washout period will be applied to the treatment received immediately prior. Medications taken across multiple treatments will be assigned to those treatments. These medications will be recorded in the Concomitant Medications page of the eCRF.

Prior Medications

Prior medications are those medications taken prior, and ended prior, to the first initiation of IMP. Medications and therapies are to be recorded in the eCRF if taken by the subject at any time 30 days prior to signing of informed consent.

Orthostatic Vital Sign Change

Orthostatic change for blood pressure and heart rate is calculated as the difference in the standing value from the supine value (ie, supine value – standing value) both collected at the same visit, date, and timepoint.

[redacted]

Loss to Follow-Up

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

Study Withdrawal

A participant is considered to have withdrawn from the study if they withdraw their consent from further participation in the trial at any time. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. If a subject is determined to be lost to follow-up, he/she will be considered to have withdrawn from the trial. Participants cannot withdraw consent for use of data already collected as part of the trial, but only for future participation.

Completed Subject

A participant is considered to have completed the trial if he/she has completed all periods of the trial including the last in-clinic visit (Day 3 in Period 4 [Part A] or Day 17 [Part B]), as shown in the Schedule of Assessments (Appendix 9.1).

End of Trial

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

End of Period

For purposes of analysis of data within each study period, the End of Period value will be defined as the last valid evaluation done before the IMP administration for the next period. For the last period in the study, there will be no end of period value. For [redacted], ECG, Lab, and Vital tables, End of Period values will not be presented.

4.2. Visit Windows

4.2.1. Method of Aligning Measurements to Treatment for Part A (SAD)

Given the crossover nature of Part A, measurements will be assigned to treatment based on treatment received at each analysis period. The start of a given analysis period will be defined as the time in which a subject takes the first dose of IMP for that analysis period. The end of the

analysis period will be the last measurement taken prior to the start of the next analysis period or the end of the study.

Measurements taken on or after the initiation of IMP in Period 1, and before dosing with IMP for Period 2, or through the end of the study if Period 2 dosing is not initiated, are considered Period 1 measurements, and will be assigned to the treatment randomized or received in Period 1, as appropriate. Measurements taken on or after the initiation of IMP in Period 2, and before dosing with IMP for Period 3, or through the end of the study if Period 3 dosing is not initiated, are considered Period 2 measurements, and will be assigned to the treatment randomized or received in Period 2, as appropriate. Measurements taken on or after the initiation of IMP in Period 3, and before dosing with IMP for Period 4, or through the end of the study if Period 4 dosing is not initiated, are considered Period 3 measurements, and will be assigned to the treatment randomized or received in Period 3, as appropriate. A measurement taken after initiation of dosing for Period 4 is considered a Period 4 event and is assigned to the treatment randomized or received in Period 4, as appropriate.

The 12-lead ECG and vital sign measurements performed pre-dose on Day 1 of each period will serve as the period-specific baseline. For safety laboratory tests, C-SSRS, and vital sign measurements (standing heart rate and blood pressure) not performed pre-dose on Day 1, the assessment performed on the check-in day (Day -1) for each period serves as the baseline value for that period. For [redacted] the Predose value for a specific period will serve as the Period Baseline. [redacted]

4.2.2. By-Study Visit Displays

When data are collected serially over time, individual data presentations may include by-study visit displays. Visits will be presented according to the nominal visit as obtained from the CRF or laboratory data. Unscheduled visits will be included in the listings.

5. STATISTICAL ANALYSIS METHODS

5.1. General Considerations

Descriptive statistical methods will be used to summarize the data from this study. No formal hypothesis testing is planned for this trial. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (N), number of observations (n), mean, median, standard deviation (SD), Q1, Q3, minimum, and maximum for continuous data and frequencies and percentages for categorical data. Figure presentations will include appropriate variability indicator such as SD or standard error (SE).

All data collected during the study will be included in data listings. Unless otherwise noted, the data presentations will be sorted first by trial part (A or B), cohort, and subject number. Unless otherwise noted, summary tables will be separated into Part A Cohorts 1 and 2, Part A Food Effects, and Part B.

In Part A, the term "treatment sequence" refers to the sequence of treatment for each individual. "Treatment group" refers to treatment with CVL-354, at different doses, or placebo. Since Part A is a crossover study, subjects will appear in multiple groups. For Part A Cohorts 1 and 2, "Treatment period" refers to Periods 1 through 4 described in Figure 1. For Part A Food Effects, "Treatment period" refers to Period 1 and 2 described in Figure 2.

In Part B, "treatment group" refers to treatment with CVL-354, at different doses, or placebo QD or BID. Doses will be determined based on data from Part A.

For summary presentations, placebo subjects will be combined across cohorts within a given Part.

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

5.2. Populations for Analyses

The analysis sets that are defined for this trial are described in Table 3.

Table 3: Analysis Set Descriptions

Term	Description
All Screened	All participants who consent to participate in the clinical trial
Randomized	All participants who are randomized to IMP
Safety Analysis Set	All randomized participants who receive at least 1 dose of IMP
PK Analysis Set	All participants in the Safety Analysis Set who have at least 1 quantifiable CVL-354 concentration

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

5.3. Statistical Hypotheses

No formal hypothesis testing is planned for this trial.

5.4. Multiplicity Adjustment

All analyses will be conducted without adjustment for multiple comparisons.

5.5. Strata and Covariates

No strata or covariates will be examined.

5.6. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition will be presented for all screened subjects. The number of subjects who were screened, met all eligibility criteria, as well as the number of subjects included in different Analysis sets will be presented. Screen failures and reason for failure will be presented. The number of subjects who completed the study and discontinued from the study will be provided, as well as reason for discontinuation. Additionally, the number of days on study will be summarized. Data will be presented by cohort for Part A Cohorts 1 and 2, sequence for Part A Food Effects, and treatment group for Part B. For Part A Cohorts 1 and 2, a separate presentation by sequence will be provided.

Demographic data and baseline characteristics including age, sex, childbearing potential, ethnicity, height, weight, body mass index (BMI) will be summarized using descriptive statistics with respect to randomized population. Data will be presented by cohort for Part A Cohorts 1 and 2, sequence for Part A Food Effects, and treatment group for Part B. For Part A Cohorts 1 and 2, a separate presentation by dose will be provided.

5.7. Exposure to Treatment

The number of subjects who received IMP, including dose, and the number of subjects who completed dosing through the last visit/date will be summarized. Reason for premature discontinuation of IMP will be summarized. Additionally, for Part B, the duration of exposure to IMP will be summarized.

[redacted]

[redacted]

5.9. Safety Analysis

All safety analyses will be performed on the Safety Analysis Set. Should any subjects receive a treatment other than their randomized treatment, the treatment received will be used in the safety presentation. All analyses will be presented separately by Part. Analyses will be presented by treatment group. For Part A, treatments will be assigned as described in Section 4.2.1.

5.9.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 or later by system organ class, preferred term, and severity. If a subject experiences multiple events that map to a single preferred term, the greatest Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade and strongest investigator assessment of relation to IMP will be assigned to the preferred term for the appropriate summaries. Events with missing severity or relationship, will be classified as outlined in Section 4.1.1.1.

For Part A, all TEAEs will be attributed to a treatment period based on start date as specified in Section 4.2.1. Any TEAE occurring during the washout period will be attributed to the treatment most recently administered.

The occurrence of TEAEs will be summarized by treatment group for Part A and Part B, using preferred terms, system organ class, and severity. Separate summaries of TEAEs, treatment-emergent serious adverse events (TESAEs), TEAEs by severity, TEAEs related to IMP, AESIs, and events leading to the discontinuation of study will be generated by system organ class and preferred terms. For Part B, a separate analysis of AEs leading to the discontinuation of IMP will be provided.

All AEs reported will be listed for individual subjects showing both verbatim and preferred terms and treatment group at onset of the AE. All AEs that occurred prior to the initiation of IMP will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.1.1.2 as required to determine treatment-emergent events.

5.9.2. COVID-19 Coronavirus Infection Testing

Participants must have COVID-19 testing done with a negative test result within a maximum of 5 days prior to, but as close as possible to each admission to the clinic. COVID-19 testing may be performed after admission per the investigator's discretion. An AE will be recorded if the result is positive or indeterminate. Indeterminate tests will be repeated. COVID-19 testing results will be listed.

5.9.3. Concomitant Medications and Non-Drug Therapy/Procedures

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary (Version: Global B3, March 2021 or later). Concomitant medications will be summarized by frequency of classification and preferred term and presented by treatment group.

Prior and concomitant non-drug therapy/procedures will be coded using MedDRA Version 24.0 or higher. Concomitant non-drug therapy/procedures will be summarized by frequency of system organ class and preferred term and presented by treatment group.

5.9.4. Clinical Laboratory Assessments

Descriptive summaries of selected (quantitative) clinical laboratory results will be presented by study day and treatment group. Laboratory values outside the normal range for each parameter will be identified using shift tables. Each subject's hematology, blood chemistry, and quantitative urinalysis values will be flagged as "low" (below the lower limit of normal/LLN), "normal" (within the normal range), or "high" (above the upper limit of normal/ULN) relative to the normal ranges of the central laboratory. Each subject's qualitative urinalysis values will be flagged as "normal" or "abnormal". Shifts from baseline, or period baseline if Part A, to high/normal/low status for hematology and blood chemistry parameters that are not CTCAE graded will be presented to the maximum post-baseline/post-period baseline value and the minimum post-baseline/post-period baseline value for each laboratory test. Shifts from baseline, or period baseline if Part A, to normal/abnormal status for urinalysis parameters that are not CTCAE graded will be presented to the maximum post-baseline/post-period baseline value and the minimum post-baseline/post-period baseline value for each laboratory test. Otherwise, for hematology, blood chemistry, and urinalysis parameters that are CTCAE graded, laboratory toxicities will be programmatically graded by severity using Cerevel's modified CTCAE Version 5.0. Shifts from baseline, or period baseline if Part A, to greatest (worst) treatment-emergent laboratory toxicity will be presented.

The number and percentage of subjects who have post-baseline/post-period baseline elevations in liver transaminase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) or bilirubin abnormalities in relation to fold above the ULN 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/post-period 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 >3 × ULN would be counted once in the ALT >1.5 × ULN category and once in the ALT >3 × ULN category, regardless of how many ALT elevations the subject had that met the >3 × ULN and >1.5 × ULN elevation criteria.

- ALT and/or AST >3 × ULN and total bilirubin >1.5 or 2 × ULN
- AST >1.5, 3, 5, 10, 20 × ULN
- ALT >1.5, 3, 5, 10, 20 × ULN
- Total bilirubin >1, 1.5, 2 × ULN
- Alkaline phosphatase (ALP) >1.5 × ULN

In addition, a Hy's law plot, a shift plot showing liver safety panel tests over time (baseline/period baseline vs. post-baseline/post-period baseline), and distribution plots of ALT, AST, ALP, and bilirubin over time will be produced. 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 and treatment. The distribution plots for AST, ALP, and bilirubin will use the same format as is used for ALT.

5.9.5. Vital Signs

Vital signs include systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature. Supine blood pressure and heart rate measurements will be obtained after at least 3 minutes of rest.

At specified time points (see Schedule of Assessments), the supine measurements will be followed by measurements in the standing position (after standing for at least 3 minutes) to allow for orthostatic assessments. Orthostatic hypotension is defined as symptomatic orthostatic dizziness or a decrease of ≥20 mmHg in systolic blood pressure upon standing compared with the average of the resting blood pressure measurement.

Descriptive summaries of vital signs (body temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, and heart rate; including orthostatic change) and their change from baseline/period-baseline will be presented by visit/study day, time point, position (as applicable), and treatment.

The following out-of-range vital signs will be summarized for analysis records occurring post-baseline:

- Heart Rate – Supine
  - <45 bpm
  - <60 bpm
  - >100 bpm
- Systolic Blood Pressure- Supine
  - ≤90 mmHg
  - ≥140 mmHg
- Diastolic Blood Pressure- Supine
  - ≤60 mmHg
  - ≥90 mmHg
- Respiratory Rate
  - <10 bpm
  - <12 bpm
  - >20 bpm
- Temperature
  - <35.3°C
  - >37.7°C

Vital sign results, including orthostatic changes, will be listed. An additional listing of out-of-range vital signs will also be listed.

5.9.6. Electrocardiograms (ECGs)

5.9.6.1. Continuous Electrocardiogram Recordings (Holter)

Continuous ECGs readings and corresponding changes from period baseline, if Part A, or study baseline, if Part B, will be summarized by time point using descriptive statistics. The results of individual subjects at each timepoint will also be listed.

5.9.6.2. Standard 12-lead Electrocardiograms

ECG parameters and corresponding changes from period baseline, if Part A, or study baseline, if Part B, will be summarized by time point using descriptive statistics. The results of individual subjects at each timepoint will also be listed.

The number and proportion of subjects having a worst post-baseline QTcF values 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.

5.9.7. Suicidal Ideation and Behavior Risk Monitoring

The maximum post-baseline/post-period baseline results from the C-SSRS will be summarized by treatment. 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 for each treatment period.

All C-SSRS elements will be reflected in a listing.

5.10. Pharmacokinetics

The pharmacokinetic analysis is detailed in a separate PK Analysis Plan (Appendix 9.5).

5.11. Protocol Deviations

All protocol deviations will be reviewed by the project team prior to unblinding to identify subjects with important protocol deviations. Summaries of important deviations for the Safety Analysis Set will be presented by category and subcategory of deviation. All deviations from the protocol of the Safety Analysis Set will be listed by category along with a description and any additional comments.

5.12. Timing of Analyses

An interim database lock and analysis once Part A is complete may be conducted. Should the circumstance arise that the safety, tolerability, and pharmacokinetic data summary of completed cohorts are required for regulatory purpose, other interim analyses may also be conducted.

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

6. CHANGES IN THE PLANNED ANALYSES

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

7. REVISION HISTORY

Date	Revision	Rationale

8. REFERENCES

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

US Food and Drug Administration (FDA). Guidance for industry: Drug-induced liver injury: premarketing clinical evaluation; Jul 2009. Accessed 17 Mar 2023. https://www.fda.gov/media/116737/download

US FDA. Guidance for industry: Assessment of abuse potential of drugs; Jan 2017. Accessed 13 Sep 2021. https://www.fda.gov/media/116739/download

9. APPENDICES

9.1. Schedule of Assessments

The Schedules of Assessments, as taken from the protocol, are provided in Table 4 (Part A, SAD Cohorts 1 and 2), Table 5 (Part A, Food Effect Cohort 3), and Table 6 (Part B, MAD Cohorts 1-5).

Table 4: Schedule of Assessments – Part A, Single Ascending Dose (Cohorts 1 and 2)

Trial Periods/Phases	Screening		Treatment (In Clinic)															Follow-up[a]
	Screening[b]	Initial Check-in[b,c]	Subsequent Check-ins[b,c]	Periods 1 to 4[d]													Check-out/ET	
Day	**-30 to -2**	**-1**	**-1**	**1**										**2**		**3**		
Trial Hour				**Predose[e]**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	
Entrance and History																		
Informed consent	X																	
Assign screening number	X																	
Inclusion/exclusion criteria	X	X	X[f]															
Medical and psychiatric history[g]	←----------	----------→		X[g]														
Demography	X																	
History of drug and alcohol use	X																	
Test for alcohol[h]	X	X	X															
Randomization				X[i]														
[redacted]																		
Safety Assessments																		
Height (Screening only) and weight	X	X	X															
Physical/neurological examination[j]	X	X	X														X	
Continuous ECG (telemetry)		X[k]																
Continuous ECG (Holter)				←----------					X[l]							----------→		

Trial Periods/Phases	Screening		Treatment (In Clinic)														Follow-up[a]
	Screening[b]	Initial Check-in[b,c]	Subsequent Check-ins[b,c]	Periods 1 to 4[d]												Check-out/ET	
Day	-30 to -2	-1	-1	1										2		3	
Trial Hour				Predose[e]	0	0.5	1	2	3	4	6	8	12	16	24	36	48	
Standard 12-lead ECG[m]	X	X	X	X		X	X	X		X		X	X		X		X	
Supine heart rate and blood pressure[n]	X	X	X	X		X	X	X		X		X	X		X		X	
Standing heart rate and blood pressure[o]	X	X	X					X		X								
Respiratory rate and temperature	X	X	X	X											X		X	
C-SSRS[p]	X	X	X														X	
Prior/concomitant treatments[q]	←----------																----------→	
Adverse event monitoring[r]			X[r]	X[r]	←----------												----------→	
Laboratory																		
Blood for safety laboratory	X	X	X												X		X	
Urine for safety laboratory	X	X	X												X		X	
Urine drug screening[s]	X	X	X															
Hepatitis B, C, HIV	X																	
FSH[t]	X																	
PK blood sample				X[u]		X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for future biospecimen research[v]		X																
Other																		
Dosing					X													
Telephone contact																		X

Abbreviations: COVID-19=coronavirus disease-2019; C-SSRS=Columbia-Suicide Severity Rating Scale; [redacted] ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating-hormone; IMP=investigational medicinal product; PK=pharmacokinetic; [redacted]

[a] Contact with participant via phone call, internet/web, or other acceptable means of communication to check on their status 14±3 days after their final dose of IMP in the trial.
[b] Participants must have COVID-19 testing done with a negative test result within a maximum of 5 days prior to, but as close as possible to, each admission to the clinic. COVID-19 testing may be performed after admission per the investigator's discretion.
[c] Assessments can be completed at Check-in for all participants in the cohort (sentinel and non-sentinel) during each period. No additional Check-in assessments are required for non-sentinel participants provided that those participants remain domiciled under close observation and the Check-in assessments are performed within 48 hours prior to dosing.
[d] There will be a washout period of at least 5 days between doses.
[e] Predose assessments to be completed within 60 minutes of dosing unless otherwise noted.
[f] Inclusion/exclusion criteria will be assessed at the start of each trial period to ensure ongoing participant eligibility with the exception of age or assessments that are only scheduled during Screening (eg, height).
[g] Medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history. This also applies to replacement participants.
[h] An alcohol test (breathalyzer or blood/urine) is required at Screening and at Check-in for each period. The alcohol test may be conducted at any time during the trial at the discretion of the investigator.
[i] Period 1 only.
[j] Full physical and neurological examinations should be completed at Screening and Check-out of each period (or ET). A limited examination (cardiovascular, pulmonary, and gastrointestinal) should be completed at Check-in to clinic on Day -1 of each period. Symptom driven physical and/or neurological examinations may be done at any time point during the trial at the investigator's discretion.
[k] A one-time baseline report of continuous ECG telemetry will be recorded for each participant by the site for a minimum of 12 hours starting on Day -1 prior to first dose. This baseline report will also be required for replacement participants.
[l] Continuous ECG will be recorded for a minimum of 26 hours, starting at least 2 hours predose and continuing until 24 hours postdose. Electrocardiograms will be extracted from the continuous recording by a central ECG service from the following time points: -45, -30, and -15 minutes predose, and 0.5, 1, 2, 3, 4, 8, 12, and 24 hours postdose. Participants should be resting quietly in a supine position for at least 10 minutes before and 5 minutes after each extraction time point.
[m] Triplicate ECGs will be obtained to confirm eligibility at Screening. Single ECGs will be obtained at all other time points.
[n] Blood pressure and heart rate measurements will be obtained from participants in a supine position after at least 3 minutes of rest.
[o] Orthostatic blood pressure and heart rate measurements will be obtained from participants in the standing position.
[p] The "Baseline/Screening" C-SSRS form will be completed for all participants at Screening to determine eligibility. The "Since Last Visit" C-SSRS form will be completed at Check-in for each period to ensure that the participant continues to qualify for the trial and will also be completed at Check-out (or ET).
[q] Concomitant medications should be recorded from Screening through the participant's last visit/contact.
[r] Adverse events (serious and nonserious) will be recorded from first dose of IMP through the participant's last visit/contact. This also applies to replacement participants.
[s] Additional urine drug screening can be conducted at any time during the trial at the discretion of the investigator.
[t] A confirmatory FSH is required for all post-menopausal women.
[u] Predose PK samples (1 sample and 1 backup sample) will be obtained within 15 minutes prior to dosing.
[v] Future biospecimen research sample is optional and is only to be collected if signed consent is obtained from the participant. Sample can be collected at any time prior to initiation of first dose.

Table 5: Schedule of Assessments – Part A, Food Effect (Cohort 3)

Trial Periods/Phases	Screening		Treatment (In Clinic)														Follow-up[a]
	Screening[b]	Check-in[b]	Periods 1 and 2[c]														
Day	-30 to -2	-1	1											2		3/ET	20
Trial Hour			Predose[d]	0	0.5	1	2	3	4	6	8	12	16	24	36	48	
Entrance and History																	
Informed consent	X																
Assign screening number	X																
Inclusion/exclusion criteria	X	X															
Medical and psychiatric history[e]	←----------→																
Demography	X																
History of drug and alcohol use	X																
Test for alcohol[f]	X	X															
Randomization			X[g]														
Safety Assessments																	
Height (Screening only) and weight	X	X															
Physical/neurological examination[h]	X	X														X	
Standard 12-lead ECG[i]	X	X	X		X	X	X		X		X	X		X		X	
Supine heart rate and blood pressure[j]	X	X	X		X	X	X		X		X	X		X		X	
Standing heart rate and blood pressure[k]	X	X					X										
Respiratory rate and temperature	X	X	X											X		X	

Trial Periods/Phases	Screening		Treatment (In Clinic)														Follow-up[a]
	Screening[b]	Check-in[b]	Periods 1 and 2[c]														
Day	**-30 to -2**	**-1**	**1**											**2**		**3/ET**	**20**
Trial Hour			**Predose[d]**	**0**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	
C-SSRS[l]	X	X														X	
Prior/concomitant treatments[m]	←----------																----------→
Adverse event monitoring[n]			←----------														----------→
Laboratory																	
Blood for safety laboratory	X	X												X		X	
Urine for safety laboratory	X	X												X		X	
Urine drug screening[o]	X	X															
Hepatitis B, C, HIV	X																
FSH[p]	X																
PK blood sample			X[q]		X	X	X	X	X	X	X	X	X	X	X	X	
Blood sample for future biospecimen research[r]		X															
Other																	
Dosing				X[s]													
Telephone contact																	X[a]

Abbreviations: COVID-19=coronavirus disease-2019; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating-hormone; IMP=investigational medicinal product; PK=pharmacokinetic.

[a] Contact with participant via phone call, internet/web, or other acceptable means of communication to check on their status 14±3 days after their final dose of IMP in the trial.

[b] Participants must have COVID-19 testing done with a negative test result within a maximum of 5 days prior to, but as close as possible to, admission to the clinic. COVID-19 testing may be performed after admission per the investigator's discretion.

[c] The treatment phase will comprise 2 periods with a 2-day washout between Periods 1 and 2. Participants will be discharged from the clinic on Period 2 Day 3 (Check-out).

[d] Predose assessments to be completed within 60 minutes of dosing unless otherwise noted.

[e] Medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history.

[f] An alcohol test (breathalyzer or blood/urine) is required at Screening and at Check-in. The alcohol test may be conducted at any time during the trial at the discretion of the investigator.
[g] Period 1 only.
[h] Full physical and neurological examinations should be completed at Screening and Check-out (or ET). A limited examination (cardiovascular, pulmonary, and gastrointestinal) should be completed at Check-in. Symptom driven physical and/or neurological examinations may be done at any time point during the trial at the investigator's discretion.
[i] Triplicate ECGs will be obtained to confirm eligibility at Screening. Single ECGs will be obtained at all other time points.
[j] Blood pressure and heart rate measurements will be obtained from participants in a supine position after at least 3 minutes of rest.
[k] Orthostatic blood pressure and heart rate measurements will be obtained from participants in the standing position.
[l] The "Baseline/Screening" C-SSRS form will be completed for all participants at Screening to determine eligibility. The "Since Last Visit" C-SSRS form will be completed at Check-in to ensure that the participant continues to qualify for the trial and will also be completed at Check-out (or ET).
[m] Concomitant medications should be recorded from Screening through the participant's last visit/contact.
[n] Adverse events (serious and nonserious) will be recorded from first dose of IMP through the participant's last visit/contact.
[o] Additional urine drug screening can be conducted at any time during the trial at the discretion of the investigator.
[p] A confirmatory FSH is required for all post-menopausal women.
[q] Predose PK samples (1 sample and 1 backup sample) will be obtained within 15 minutes prior to dosing.
[r] Future biospecimen research sample is optional and is only to be collected if signed consent is obtained from the participant. Sample can be collected at any time prior to initiation of first dose.
[s] Dose to be administered after a high-fat breakfast during fed period and under fasted conditions during fasted period.

Table 6: Schedule of Assessments – Part B, Multiple Ascending Dose (Cohorts 1 to 5)

Trial Periods/Phases	Screening		Treatment (In Clinic)											Follow-up		
	Screening[a]	Check-in[a]												In Clinic		Contact[b]
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-9**	**10**	**11-13**	**14**	**15/16**	**17/ET**	**29**
Entrance and History																
Informed consent	X															
Assign screening number	X															
Inclusion/exclusion criteria	X	X														
Medical and psychiatric history[c]	←----------															
Demography	X															
History of drug and alcohol use	X															
Test for alcohol[d]	X	X														
Randomization			X													
[redacted]																
Safety Assessments																
Height (Screening only) and weight	X	X													X	
Physical/neurological examination[f]	X	X							X						X	
Continuous ECG (Holter)			X[g]										X[g]			
Standard 12-lead ECG[h]	X	X	X			X			X		X		X		X	
Supine heart rate and blood pressure[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Standing heart rate and blood pressure[j]	X	X	X			X			X				X			
Respiratory rate and temperature	X	X	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X	X	
C-SSRS[l]	X	X		X					X				X		X	
Prior/concomitant treatments[m]	←----------															

Trial Periods/Phases	Screening		Treatment (In Clinic)											Follow-up		
	Screening[a]	Check-in[a]												In Clinic		Contact[b]
Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-9**	**10**	**11-13**	**14**	**15/16**	**17/ET**	**29**
Adverse event monitoring[n]			←----------										----------→			
Laboratory																
Blood for safety laboratory	X	X				X			X		X		X		X	
Urine for safety laboratory	X	X				X			X		X		X		X	
Urine drug screening[o]	X	X														
Hepatitis B, C, HIV	X															
FSH[p]	X															
Serum Cystatin-C[q]	X	X				X			X		X		X		X	
Urine β-2-microglobulin[q,r]		X											X			
PK blood sample[s]			X	X	X		X		X	X		X	X	X	X	
[redacted]																
Urine sample for PK and metabolite scouting		X[u]											X[u]			
Blood sample for future biospecimen research[v]		X														
Other																
Dosing			X	X	X	X	X	X	X	X	X	X	X			
Meals[w]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Telephone contact																X[b]

Abbreviations: COVID-19=coronavirus disease-2019; C-SSRS=Columbia-Suicide Severity Rating Scale; [redacted]; ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating-hormone; IMP=investigational medicinal product; PK=pharmacokinetic; QD=once daily; [redacted].

[a] Participants must have COVID-19 testing done with a negative test result within a maximum of 5 days prior to, but as close as possible to, admission to the clinic. COVID-19 testing may be performed after admission per the investigator's discretion.

[b] Contact with participant via phone call, internet/web, or other acceptable means of communication to check on their status 14±3 days after their final dose of IMP in the trial.

[c] Medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history.

[d] An alcohol test (breathalyzer or blood/urine) is required at Screening and at Check-in. The alcohol test may be conducted at any time during the trial at the discretion of the investigator.

[e] [redacted]
[f] Full physical and neurological examinations should be completed at Screening, Day 7, and Day 17/ET. A limited examination (cardiovascular, pulmonary, and gastrointestinal) should be completed at Check-in. Symptom driven physical and/or neurological examinations may be done at any time during the trial at the investigator's discretion.
[g] Continuous ECG will be recorded for a minimum of 26 hours, starting at least 2 hours predose and continuing until 24 hours postdose. Electrocardiograms will be extracted from the continuous recording by a central ECG service from the following time points on Days 1 and 14: -45, -30, and -15 minutes predose and 0.5, 1, 2, 3, 4, 8, 12, and 24 hours after the morning dose. Participants should be resting quietly in a supine position for at least 10 minutes before and 5 minutes after each extraction time point.
[h] Triplicate ECGs will be obtained to confirm eligibility at Screening. Single ECGs will be obtained at predose for all other time points.
[i] Blood pressure and heart rate measurements will be obtained from participants in a supine position after at least 3 minutes of rest. On Day 1 and on Day 14, blood pressure and heart rate measurements will be obtained at -30 minutes predose and at 0.5, 1, 2, 4, 8, 12, and 24 hours after the morning dose. On Days 4 and 7, blood pressure and heart rate measurements will be obtained at predose and at 2 hours after the morning dose. On all other days, blood pressure and pulse rate measurements will be obtained at predose.
[j] On dosing days, orthostatic blood pressure and heart rate measurements will be obtained at 2 hours after the morning dose with the participants in the standing position.
[k] Respiratory rate and body temperature will be taken at predose on Days 1 through 14.
[l] The "Baseline/Screening" C-SSRS form will be completed for all participants at Screening to determine eligibility. The "Since Last Visit" C-SSRS form will be completed at Check-in to ensure that the participant continues to qualify for the trial and will also be completed on Days 2, 7, 14, and 17/ET.
[m] Concomitant medications should be recorded from Screening through the participant's last visit/contact.
[n] Adverse events (serious and nonserious) should be recorded from first dose of IMP through the participant's last visit/contact.
[o] Additional urine drug screening can be conducted at any time during the trial at the discretion of the investigator.
[p] A confirmatory FSH is required for all post-menopausal women.
[q] Laboratory test not part of eligibility.
[r] The participant should empty their bladder and then drink ~250 mL water. The participant's urine should be collected ~1 hour later.
[s] PK samples (1 sample and 1 backup sample) will be obtained predose (within 15 minutes prior to dosing) and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours following administration of the first dose of IMP on Day 1 and on Day 14 at predose (within 15 minutes prior to dosing) and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after the morning dose. A single predose PK sample will be taken on Days 3, 5, 7, 9, and 11.
[t] [redacted]
[u] Spot urine samples will be collected on Day -1. Cumulative urine samples will be collected on Day 14 (0-24 hour collection).
[v] Future biospecimen research sample is optional and is only to be collected if signed consent is obtained from the participant. Sample can be collected at any time prior to initiation of first dose.
[w] Meals consist of a light breakfast (~0700 hours, 1 hour prior to dosing), lunch (~1200 hours, 4 hours after dosing), and dinner (~1800 hours), and an evening snack (~2130 hours). On days with intensive ECGs (extractions by central ECG service), participants will fast for at least 10 hours prior to dosing and will remain fasting for the first 4 hours following dosing with a small snack given right after the 4-hour time point and lunch right after the 6-hour time point. Participants must abstain from all food and drink (except water) for at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to collection of PK samples on days when intensive sampling will be done (Days 1 and 14).

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

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

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

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

Self-Injurious Behavior Without Suicidal Intent During Treatment

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

Baseline C-SSRS Score

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

Treatment-Emergent Suicide-Related Event

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

Treatment-Emergent Suicidal Ideation Compared to Recent History

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

Treatment-Emergent Serious Suicidal Ideation Compared to Recent History

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

Emergence of Serious Suicidal Ideation Compared to Recent History

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

Emergence of Suicidal Behavior Compared to all Prior History

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

9.3. Programming Conventions

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8.
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.
- Group headers: In the summary tables, the group headers will identify the summary group and the 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 due to missing data.
    - 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. The number of missing observations, if any, will be noted.
    - 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. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by part, subject number, and date, if applicable. If a listing is sorted in a different manner, the listing shells will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
    - Standard deviations will be reported to two decimal places beyond the number of decimal places the original parameter is presented.

- Means, Medians, Q1 and Q3 values will be reported to one decimal place beyond the number of decimal places as the original parameter is presented.
- Calculated percentages will be reported with no decimals.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
- Time will be presented according to the 24-hour clock (HH:MM).

9.4. Abbreviations

Abbreviation	Definition
AE	adverse event
Ae	amount of the dose administered recovered
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
APMP	Abuse Potential Monitoring Plan
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve over the time interval 0 to 24 hours postdose
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{τ}	area under the concentration-time curve over a dosing interval (τ)
BID	twice daily
BMI	body mass index
C_{max}	maximum plasma concentration
CL/F	apparent clearance of drug from plasma
COVID-19	coronavirus disease-2019
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
F	bioavailability
FSH	follicle stimulating-hormone
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product

Abbreviation	Definition
KOR	kappa opioid receptor
LLN	lower limit of normal
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect-level
PK	pharmacokinetic(s)
PTR	peak to trough ratio
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
Rac	accumulation ratio
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SRT	Safety Review Team
$t_{½}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to last quantifiable concentration
ULN	upper limit of normal
[redacted]	[redacted]
V_z/F	apparent volume of distribution during the terminal phase
WHO	World Health Organization

9.5. Pharmacokinetic Analysis Plan

PHARMACOKINETIC ANALYSIS PLAN

A Phase 1, Double-Blind (Investigator and Participant), First-in-Human Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of CVL-354 in Healthy Participants

Pharmacokinetic Analysis Plan Status: Final v1

Pharmacokinetic Analysis Plan Date: 10 February 2023

Sponsor Reference Number: CVL-354-1001

Labcorp Study Number: 8473318

Sponsor:
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[redacted]
Labcorp Drug Development
[redacted]

1 PHARMACOKINETIC ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page, the Pharmacokinetic Analysis Plan (PKAP) is considered final, the signatories agree to the pharmacokinetic (PK) analyses to be performed for this study. Once the PKAP has been signed, the PK analyses based upon this document can proceed. Any modifications to the PKAP made after signing may result in a work-scope change.

Labcorp approval:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 23 Feb 2023 | 2:04:30 PM EST
[redacted]

[redacted] PharmD, PhD
[redacted]
Labcorp Drug Development

Date

Sponsor approval:

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 23 Feb 2023 | 2:02:52 PM EST
[redacted]

[redacted], PhD
[redacted]
Cerevel Therapeutics, LLC

Date

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 23 Feb 2023 | 3:32:30 PM EST
[redacted]

[redacted], PhD
[redacted]
Cerevel Therapeutics, LLC

Date

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3 ABBREVIATIONS

$\%AUC_{extrap}$	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
%Fluctuation	percentage fluctuation at steady state
Ae	amount of the dose administered recovered
Ae_{t1-t2}	amount of the dose administered recovered in urine over the time interval t1 to t2 at steady state
ANOVA	analysis of variance
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve over the time interval 0 to 24 hours postdose
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{τ}	area under the concentration-time curve over a dosing interval (τ)
BID	twice daily
BLQ	below the limit of quantification
C_{avg}	average plasma concentration
CI	confidence interval
CL/F	apparent clearance of drug from plasma
CL_R	renal clearance
C_{max}	maximum plasma concentration
CSR	clinical study report
C_{trough}	trough plasma concentration
CV	coefficient of variation
$DAUC_{24}$	area under the concentration-time curve over a dosing interval (τ) normalized by dose administered
$DAUC_{inf}$	area under the concentration-time curve from time zero extrapolated to infinity normalized by dose administered
$DAUC_{last}$	area under the concentration-time curve from time zero to the time of the last quantifiable concentration normalized by dose administered
$DAUC_{\tau}$	area under the concentration-time curve over a dosing interval (τ) normalized by dose administered
DC_{max}	maximum plasma concentration normalized by dose administered
fe	percentage of the dose administered recovered
fe_{t1-t2}	percentage of the dose administered recovered in urine over the time interval t1 to t2 at steady state
GLSM	geometric least squares mean
IMP	investigational medicinal product

KOR	Kappa opioid receptor
λ_z	apparent terminal elimination rate constant
λ_z Lower	start of exponential fit
λ_z N	number of data points included in the log-linear regression
λ_z Span Ratio	time period over which apparent terminal elimination rate constant was determined as a ratio of apparent terminal half-life
λ_z Upper	end of exponential fit
LC/MS/MS	liquid chromatography with tandem mass spectrometry
ln	natural log
LR	linearity ratio
LSM	least squares mean
MAD	multiple ascending dose
max	maximum
MDD	major depressive disorder
min	minimum
MOR	mu opioid receptors
N	number of participants
n	number of observations
NA	not applicable
NC	not calculated
NOAEL	no observed adverse effect level
PK	pharmacokinetic(s)
PKAP	pharmacokinetic analysis plan
PTR	peak to trough ratio
QD	once daily
R	randomization
Rac	accumulation ratio
Rac, AUC_τ	accumulation ratio based on area under the concentration-time curve over a dosing interval (τ)
Rac, C_{max}	accumulation ratio based on maximum plasma concentration during the dosing interval
SAD	single ascending dose
Seq	sequence
SD	standard deviation
SOP	Standard Operating Procedures
SRT	Safety Review Team
TBD	to be determined
t_{last}	time of the last quantifiable concentration

T_{max}	time to maximum plasma concentration
$t_{1/2}$	apparent terminal elimination half-life
V_z/F	apparent volume of distribution during the terminal phase

4 INTRODUCTION

This PKAP has been developed after review of the Clinical Study Protocol CVL-354-1001 version 3.0, dated 25 May Sep2022 (1). This PKAP describes the planned analysis of the PK data from this study.

The intent of this document is to provide guidance for the PK and statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between the Sponsor and Labcorp Drug Development (hereafter, referred to as Labcorp) Clinical Pharmacology Services. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. When the PKAP is agreed upon and finalized, it will serve as guidance for this study's PK report.

This PKAP supersedes the PK considerations identified in the protocol. If additional analyses are required to supplement the planned analyses described in this PKAP, they may be performed and identified in the PK report. Any substantial deviations from this PKAP will be agreed upon between the Sponsor and Labcorp Clinical Pharmacology Services and identified in the PK report.

4.1 Background

Kappa opioid receptor (KOR) activation is implicated in reduced activity of the reward (mesolimbic) pathway. Recent evidence suggests that selective antagonism of KORs may provide therapeutic benefit in treating major depressive disorder (MDD). CVL-354 is a brain-penetrant, potent KOR antagonist with >10-fold pharmacological selectivity over mu opioid receptors (MORs) that is being developed for treatment of MDD. Nonclinical data generated to date support development of CVL-354 for treatment of MDD.

The aim of this 2-part, first-in-human trial is to investigate the safety, tolerability, and pharmacokinetics (PK) of CVL-354, following single ascending dose (SAD) and multiple ascending dose (MAD) oral administration in healthy participants.

5 STUDY OBJECTIVES

The scope of this PKAP and the PK report will address a component of the following secondary objectives from the study protocol:

Part A (Single Ascending Dose [SAD])

- To evaluate the plasma pharmacokinetics of CVL-354 following single ascending doses administered orally to healthy participants
    - Pharmacokinetics parameters of CVL-354 following single oral doses:
        - C_{max}
        - T_{max}
        - AUC_{24}
        - AUC_{last}
        - AUC_{inf}
        - CL/F
        - V_Z/F

        - $t_{1/2}$
- To evaluate the effect of food following single doses of CVL-354 administered orally to healthy participants
    - Pharmacokinetics parameters of CVL-354 following single oral doses:
        - C_{max}
        - T_{max}
        - AUC_{24}
        - AUC_{last}
        - AUC_{inf}
        - CL/F
        - V_Z/F
        - $t_{1/2}$

Part B (Multiple Ascending Dose [MAD])

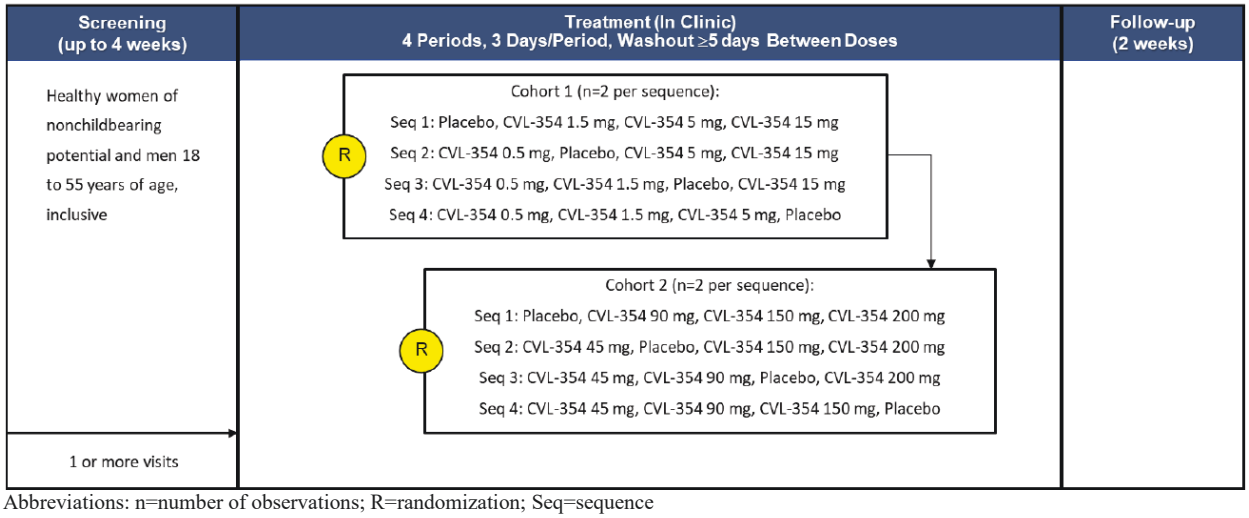
- To evaluate the plasma pharmacokinetics of CVL-354 following multiple ascending doses administered orally to healthy participants
    - Pharmacokinetics parameters of CVL-354 on Days 1 and 14:
        - C_{max}
        - T_{max}
        - C_{trough}
        - AUC_{τ}
        - CL/F (Day 14 only)
        - V_Z/F (Day 14 only)
        - PTR (Peak-to-trough ratio) (Day 14 only)
        - Rac, Cmax (Day 14 only)
        - Rac, AUC (Day 14 only)
        - $t_{1/2}$ (Day 14 only)
        - A_e (Day 14 only)
        - CL_R (renal clearance; Day 14 only)

6 STUDY DESIGN

This is a Phase 1, double-blind (investigator and participant), randomized, placebo-controlled, single-center trial that will be conducted in 2 parts to evaluate safety, tolerability, and PK of CVL-354 following single and multiple doses in healthy participants.

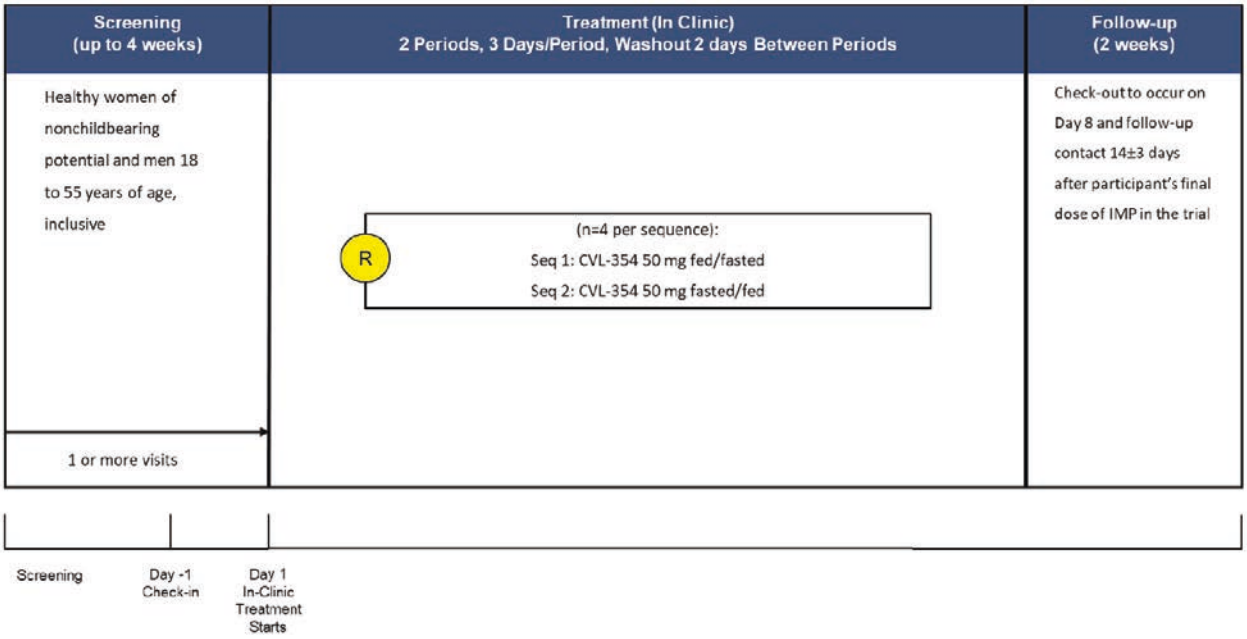
Information regarding the study design is detailed in the CVL-354-1001 Protocol version 3.0 (1).

Figure 1: Study Design Schematics
Part A (SAD, Cohorts 1 and 2)



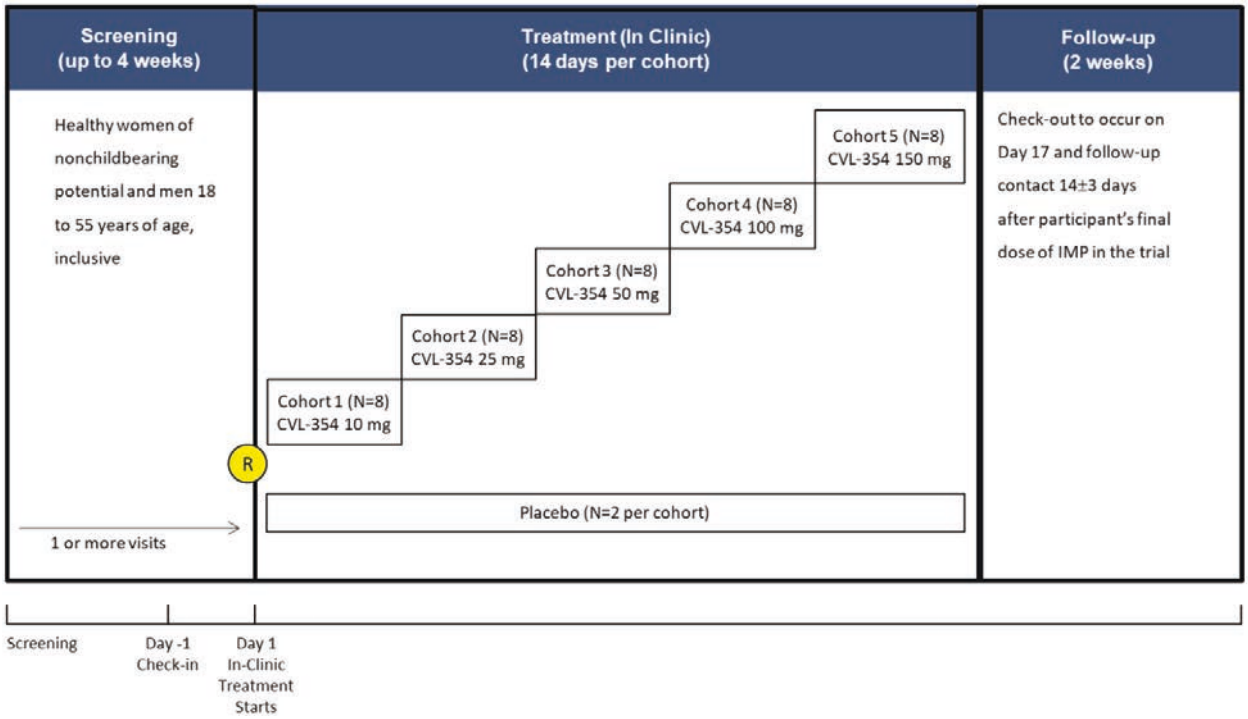
Abbreviations: n=number of observations; R=randomization; Seq=sequence

Part A (Food Effect, Cohort 3)



Abbreviations: IMP=investigational medicinal product; n=number of observations; R=randomization; Seq=sequence

Part B (MAD, Cohorts 1-5)



Abbreviations: IMP=investigational medicinal product; N=number of participants; R=randomization.

6.1 SAD and Food Effect– Part A

6.1.1 SAD (Cohorts 1 and 2)

Dose escalation will proceed according to a double-blind (investigator and participant), 4-period crossover, single ascending dose methodology. Up to 2 cohorts of participants may be evaluated.

Cohorts 1 and 2 will be dosed in a sequential manner for up to 4 periods each. Progression to each dose level will occur following evaluation of all available cumulative safety, tolerability, PK, and other emergent data from the previous cohorts and periods. The current trial may evaluate up to 8 different dose levels in Cohorts 1 and 2; however, some doses may be repeated, if required. The starting dose for Part A will be 0.5 mg. Each dosing period will be separated by a washout period of at least 5 days.

Cohorts 1 and 2 will comprise of approximately 8 participants (3:1 ratio of CVL-354 to placebo within each treatment period). All participants will receive single oral doses of CVL-354 or placebo during each period.

Doses, in general, will be escalated in Cohort 1 and Cohort 2 until the maximum tolerated dose is achieved or the CVL-354 exposures (C_{max} and AUC_{24}) reach, or are projected to reach, the predefined human exposure limits established based on the no observed adverse effect level (NOAEL) exposures [redacted]. Dose escalation may also be stopped if it is determined that sufficient exposures are achieved,

based on estimated target occupancy. Based on emergent data, the actual doses may change; however, new doses will not exceed half-log increments (3.3-fold) from previous dose. Smaller increments (eg, ≤ 2-fold) will be evaluated as exposures approach the proposed stopping criteria.

Table 1: SAD Planned Dosing Levels

Cohort[a]	N[b]	Period 1	Period 2	Period 3	Period 4
Cohort 1	2	Placebo	1.5 mg	5 mg	10 mg
	2	0.5 mg	Placebo	5 mg	10 mg
	2	0.5 mg	1.5 mg	Placebo	10 mg
	2	0.5 mg	1.5 mg	5 mg	Placebo
Cohort 2	2	Placebo	40 mg	80 mg	100 mg
	2	20 mg	Placebo	80 mg	100 mg
	2	20 mg	40 mg	Placebo	100 mg
	2	20 mg	40 mg	80 mg	Placebo

[a] Doses/treatments may be modified based on emergent safety, tolerability, and pharmacokinetic data or repeated to confirm safety/tolerability.
[b] N= Number of participants. Approximately 8 participants (3:1 ratio of CVL-354 to placebo within each treatment period). Sentinel dosing for each dosing period (n=2; 1 CVL-354 and 1 placebo) will be employed to ensure safety and tolerability before initiation of the rest of the cohort.

6.1.2 Food Effect Evaluation (Cohort 3)

Cohort 3 will be scheduled after completion of single dose escalation to evaluate the effect of food on CVL-354 exposures after a single 50 mg dose. The selected dose is 4-fold lower than the top single CVL-354 200 mg dose that is considered safe and tolerated. For evaluation of food effect, a 2-period crossover design will be utilized, with approximately 8 participants randomized to 1 of 2 sequences (fed/fasted or fasted/fed). The duration of each period will be 3 days, with a 2-day washout between Period 1 and Period 2.

6.2 MAD – Part B

The safety and PK of double-blind (investigator and participant), multiple-dose administration of CVL-354 will be evaluated in Part B of the trial after completion of dose escalation in Part A. Part B may overlap with Part A, Cohort 3 (evaluation of food effect on CVL-354 exposures).

Up to 5 sequential cohorts of 10 participants each will be evaluated in Part B. Participants will receive oral doses of either CVL-354 or placebo for up to 14 days. Eligible participants will be admitted to the clinic on Day -1 and will be randomized in a 4:1 ratio (8 participants active treatment: 2 participants placebo). Cohorts will be initiated in a sequential manner after review of all available safety, tolerability, and PK data (at least up to Day 15) from previous cohorts.

Each dose of CVL-354 will be administered once daily (QD) throughout Part B of the trial based on data obtained during Part A of the trial.

The starting dose for Part B will be 10 mg QD. In Part A, a single oral CVL-354 dose of 200 mg was deemed to be safe and well tolerated. The exposures from daily doses of 10 mg QD are expected to be well below the highest exposures investigated in the SAD part [redacted] During Part B, all preceding doses should be deemed safe and tolerated before progressing to higher

doses. Similar to Part A, dose increments in Part B will not exceed half-log increments (3.3-fold) early in escalation and smaller escalation steps (≤2-fold) will be implemented at doses closer to stopping criteria.

6.3 PK Stopping Criteria – Part A and Part B

- **SAD**: If, based on the observed data, the group mean C_{max} or AUC_{24} (based on total plasma concentrations) of the next planned dose is projected to exceed the exposure limits [redacted] that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

- **MAD:** If, based on the observed data, the group mean steady state (Day 14) C_{max} or AUC_{24} (based on total plasma concentrations) of the next planned dose is projected to exceed the maximum exposure in SAD [redacted], that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next dose will occur if the last dose was tolerated and after satisfactory review of the available safety, tolerability, and PK data from a minimum of 6 participants (including at least 1 placebo participant) within a treatment period.

The dose increments will be based on observed exposures and forward predictions. The size of the exposure increments may be changed (not exceeding 3.3-fold [half-log] increments) as the trial progresses, dependent upon emerging PK, safety, and tolerability data. Any decision to change the size of the exposure increment will be made jointly by the investigator and the trial team and after careful evaluation of all available data.

6.4 Dose Administration

- All doses in Parts A, except for dosing under "fed" conditions, will be administered under fasted conditions following an overnight fast of at least 10 hours. Participants will continue to fast for 4 hours following dosing on Day 1.
- For dosing under "fed" conditions during food evaluation, following an overnight fast of at least 10 hours, participants will start breakfast approximately 25 minutes prior to administration of IMP. The IMP will then be administered within approximately 5 minutes of completion of the meal.
- For Part B, on days with intensive PK sampling (Day 1 and Day 14), the IMP will be administered under fasted conditions following an overnight fast of at least 10 hours. Participants will continue to fast for 4 hours following dosing on these intensive PK sampling days. On other days, each dose of IMP will be administered at approximately the same time each morning at least 1 hour following the morning meal.
- Each dose will be administered with 240 mL of water.

6.5 PK Sample Collections

Blood and urine (MAD part only) samples will be obtained during the study for measurement of CVL-354 concentrations in plasma and urine. For PK assessments, there will be an acceptable blood collection window of ±10% of the nominal time point (eg, within 6 minutes of a 60-minute sample).

SAD and Food effect

Serial PK blood samples (1 sample and 1 backup sample) will be collected during the SAD portion for each participant receiving drug and placebo at predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose. Predose PK samples (1 sample and 1 backup sample) will be obtained within 15 minutes prior to dosing.

MAD

PK blood samples (1 sample and 1 backup sample) will be obtained predose (within 15 minutes prior to dosing) and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours following administration of the first dose of IMP on Day 1 and on Day 14 at predose (within 15 minutes prior to dosing) and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours after the morning dose. A single predose PK sample will be taken on Days 3, 5, 7, 9, and 11.

Cumulative pharmacokinetic urine samples will be collected during the MAD study for each participant receiving drug and placebo on Day 14 (0-24 hour) postdose.

6.6 PK Sample Bioanalysis

Plasma and urine samples will be stored and shipped to Q2 Solutions who will perform bioanalysis of CVL-354 using a validated LC/MS/MS method to determine plasma and urine concentrations. The details of the bioanalysis method will be described in the bioanalysis plan prior to the analysis. Further instructions and details on the processing, collection, and handling of samples will be provided in separately defined Laboratory Manual.

7 ANALYSIS SETS

7.1 Safety Analysis Set

All randomized participants who receive at least 1 dose of IMP.

7.2 Pharmacokinetics Analysis Set

All participants in the Safety Analysis Set who have at least 1 quantifiable CVL-354 concentration.

8 PHARMACOKINETIC ANALYSIS

8.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma and urine concentrations of CVL-354 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or higher):

Part A* (SAD and Food Effect)

Parameter	Units[a]	Definition
AUC_{last}	h*ng/mL	area under the concentration-time curve from time zero to the time of the last quantifiable concentration[b]
AUC_{24}	h*ng/mL	area under the concentration-time curve over the time interval 0 to 24 hours postdose[b]
AUC_{inf}	h*ng/mL	area under the concentration-time curve from time zero extrapolated to infinity[b, c]
$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
C_{max}	ng/mL	maximum plasma concentration
T_{max}	h	time to maximum plasma concentration
t_{last}	h	time of the last quantifiable concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent clearance of drug from plasma
V_z/F	L	apparent volume of distribution during the terminal phase
$DAUC_{last}$	h*ng/mL/mg	AUC_{last} normalized by dose administered[d]
$DAUC_{24}$	h*ng/mL/mg	AUC_{τ} normalized by dose administered[d]
$DAUC_{inf}$	h*ng/mL/mg	AUC_{inf} normalized by dose administered[d]
DC_{max}	ng/mL/mg	C_{max} normalized by dose administered[d]

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
[c] Based on the last observed quantifiable concentration.
[d] Calculated by dividing the parameter by the dose (mg).
** Concentration-time profile following each discrete single dose in Part A Profile Day 1, including all periods of the food effect evaluation.*

Part B*

Parameter	Units[a]	Definition
AUC_{last}	h*ng/mL	area under the concentration-time curve from time zero to the time of the last quantifiable concentration[b]
AUC_{24}	h*ng/mL	area under the concentration-time curve over the time interval 0 to 24 hours postdose (Day 1 only)[b]
AUC_{inf}	h*ng/mL	area under the concentration-time curve from time zero extrapolated to infinity (Day 1 only)[b, e]

$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity (Day 1 only)
AUC_{τ}	h*ng/mL	area under the concentration-time curve over a dosing interval (τ) (Day 14 only)[b,d]
C_{max}	ng/mL	maximum plasma concentration
C_{trough}	ng/mL	trough plasma concentration; observed at the end of the dosing interval
%Fluctuation	%	percentage fluctuation at steady state, equivalent to peak-to-trough ratio (PTR) in the protocol
T_{max}	h	time to maximum plasma concentration
t_{last}	h	time of the last quantifiable concentration
$t_{1/2}$	h	apparent terminal elimination half-life (Day 14 only)
CL/F	L/h	apparent clearance of drug from plasma (Day 14 only)
V_z/F	L	apparent volume of distribution during the terminal phase (Day 14 only)
Rac, AUC_{τ}	NA	accumulation ratio based on AUC_{τ} (Day 14 only)
Rac, C_{max}	NA	accumulation ratio based on C_{max} during the dosing interval (Day 14 only)
LR	NA	linearity ratio (Day 14 only)
Ae_{t1-t2}	mg	amount of the dose administered recovered in urine over a dosing interval (t1 to t2) at steady state (Day 14 only)
Cum Ae_{t1-t2}	mg	cumulative amount of the dose administered recovered in urine over a dosing interval (t1 to t2) at steady state (Day 14 only)
fe_{t1-t2}	%	percentage of the dose administered recovered in urine over a dosing interval (t1 to t2) at steady state (Day 14 only)
Cum fe_{t1-t2}	%	cumulative percentage of the dose administered recovered in urine over a dosing interval (t1 to t2) at steady state (Day 14 only)
CL_R	L/h	renal clearance of drug from plasma (Day 14 only)
$DAUC_{\tau}$	h*ng/mL/mg	AUC_{τ} normalized by dose administered[c]
$DAUC_{last}$	h*ng/mL/mg	AUC_{last} normalized by dose administered[c]
DC_{max}	ng/mL/mg	C_{max} normalized by dose administered[c]

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
[c] Calculated by dividing the parameter by the dose administered (mg).
[d] The dosing interval τ throughout part B will be 24 hours .
[e] Based on the last observed quantifiable concentration.
* Concentration-time profile following multiple dosing on Profile Day 1 and Day 14.
NA = not applicable

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, C_{trough}, t_{last}, and T_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, T_{max} will be assigned to the first occurrence of C_{max}.

Predose (trough) plasma concentrations on dosing days 3, 5, 7, 9 and 11 will be listed.

The accumulation ratio(s) (R_{ac}, AUC and R_{ac}, C_{max}) will be calculated as follows:

R_{ac}, AUC = AUC_{τ} Profile Day 14 / AUC_{24} Profile Day 1

R_{ac}, C_{max} = C_{max} Profile Day 14 / C_{max} Profile Day 1

The linearity ratio (LR) will be calculated as ratio of AUC_{τ} following multiple dosing (Day 14) to AUC_{inf} following a single dose (Day 1):

LR = AUC_{τ} Profile Day 14 / AUC_{inf} Profile Day 1

8.1.1 Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{max}, and the adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is ≥0.7. Parameters requiring λ_z for their calculation (eg, AUC_{inf}, $t_{1/2}$, CL/F (Profile Day 1 only), and V_z/F) will only be calculated if the R^2-adj value of the regression line is ≥0.7.

The following regression-related diagnostic PK parameters will be determined where possible:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj	NA	adjusted coefficient for determination of exponential fit

NA = not applicable

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the clinical study report (CSR).

8.1.2 Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

If the extrapolated area is >20%, AUC_{inf} (and derived parameters) may be excluded from the summary statistics and statistical analysis at the discretion of the sponsor or pharmacokineticist.

For evaluation of food effect, if AUC_{inf} cannot be determined reliably for all participants, an alternative AUC measure, such as AUC to a fixed timepoint, may be used in the statistical analysis of food effect.

If the τ PK blood sample is collected slightly early (ie, the 24-hour), the actual sampling time of the τ sample may be used for the calculation of AUC_τ. However, the AUC_τ parameter will be calculated if the τ sample is within 60 minutes of the nominal sampling time.

8.1.3 Calculation of Urinary Parameters

The amount of the dose administered recovered (Ae) in urine as CVL-354 for each urine collection interval (t_1-t_2) will be calculated as the product of urine analyte concentration and urine volume. Where only urine sample weight is supplied, a specific gravity of 1 g/mL will be assumed, and it will be considered equivalent to urine volume.

A total cumulative $Ae_{0\text{-}x\ h}$ will be calculated by summing the $Ae_{t1\text{-}t2}$ values over the 0-x h interval, where x = the end of the dosing interval.

The percentage of the dose administered recovered over the time interval t1 to t2 ($fe_{t1\text{-}t2}$) as CVL-354 will be calculated for each urine collection interval (equivalent to a dosing interval) as follows:

$$fe_{t1\text{-}t2} = (Ae_{t1\text{-}t2} / \text{dose}) \times 100\%$$

Cumulative $fe_{0\text{-}x\ h}$ will be calculated by summing the $fe_{t1\text{-}t2}$ values over the 0-x h period in the same manner as cumulative $Ae_{0\text{-}x\ h}$.

Renal clearance (CL_R) will be calculated over 0-t2 according to the following formula, where cumulative Ae is calculable over the dosing interval (0-t2 equivalent to τ):

$$CL_R = Ae_{0\text{-}t2} / AUC_\tau$$

8.1.4 Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma concentration is missing, it will be set to 0 by default within Phoenix WinNonlin for the first dosing day of all parts of the study (Study Profile Day 1).
- For multiple dose part of the study (Study Profile Day 14), if the analyte concentration at τ (24 hours postdose) is missing, this may be substituted with the predose concentration. Similarly, if the predose concentration is missing then this may be substituted with the concentration at τ.

Urine concentrations that are BLQ will be set to 0 for the calculation of $Ae_{t1\text{-}t2}$.

8.1.5 Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value on the first dosing day of all parts of the study (Study Profile Day 1) will be considered anomalous and set to missing for the PK analysis. This will be set to 0 by default in Phoenix WinNonlin.

For Cohort 3 of Part A, if the predose concentration is >5% of C_{max} in the second treatment period, all PK concentration and parameter data will be excluded from the summary statistics and statistical analysis for that period.

8.2 Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates from the nominal time by more than ±10%, the plasma concentration will be flagged and excluded from the concentration summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For plasma concentration data, the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.

- Arithmetic mean or median values that are BLQ will be presented as 0.
- Concentrations will be reported to the level of precision in which they were received from the analytical laboratory.

For PK parameters, the following rule will apply:

- Geometric mean and coefficient of variation will not be calculated for t_{last} or T_{max}.

8.2.1 Presentation of Urine Drug Concentration Data

Urine drug concentrations will be listed only to the level of precision in which they were received from the analytical laboratory.

8.2.2 Presentation of Pharmacokinetic Parameters

For the calculation of summary statistics of PK parameters, all not calculated (NC) values in a data series will be set to missing.

Individual PK parameters will be presented to three significant figures. For the calculation of summary statistics, data will be handled and presented as described in section 9.1.

9 STATISTICAL METHODOLOGY

9.1 General

All PK concentrations and parameters will be listed.

Summary tables by treatment will be provided for all concentrations and PK parameters.

Summary statistics will only be presented for data where detailed in this PKAP. Summary statistics will include the arithmetic mean, standard deviation (SD), geometric mean, coefficient of variation (CV) of geometric mean, median, minimum (min), maximum (max), and number of observations (n) for concentrations and all PK parameters (except t_{last} or $T_{max,}$ where geometric mean and CV of geometric mean will not be calculated). Summary statistics will be calculated for concentration and PK parameter data for participants included in the PK analysis set and will be stratified by treatment.

Summary tables, mean (±SD) figures, and overlaying individual figures will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales.

For the calculation of summary statistics for plasma concentrations, data will be used as received from the bioanalytical laboratory. For calculation of summary statistics for PK parameters, unrounded data will be used. Statistics will be reported to three significant figures with the exception of N and n which will be presented to the nearest integer. Individual PK parameters will be presented to three significant figures.

The full battery of summary statistics will only be calculated if there are at least three values in the data series. Zeros are considered to be values. If there are fewer than three values in the data

series, only min, max, and n will be presented. The other summary statistics will be denoted as NC. If the value of the arithmetic mean and/or median is BLQ, these will be presented as zero.

All statistical summaries and figures for concentration and PK parameter data will be performed using SAS software Version 9.4 or higher.

9.2 Statistical Evaluation of Dose Proportionality and Food Effect

A dose-normalized plot will be produced to investigate the dose proportionality of AUC_{last}, AUC_{24}, AUC_{inf} and C_{max} for Part A and Part B (Day 1 and Day 14). A statistical analysis will be conducted to investigate the food effect on the treatment by comparing Test treatment (fed) to Reference treatment (fasted).

For Food effect:

The ln-transformed[2] $AUC_{inf,}$ AUC_{last}, AUC_{24} and C_{max} for CVL-354 will be analyzed using a linear mixed model.[3] The model will include planned treatment sequence, period, and actual treatment (i.e., fast/fed status) as fixed effects, and participant within planned treatment sequence as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the fed and fasted treatments, and corresponding 90% CI will be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90%.

Additionally, the pooled estimate (across treatments) of the within-subject CV will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;
 by parcat1n parcat1 pkday paramn param;
 class trtan aperiod trtseqp usubjid;
 model lpk = trtan aperiod trtseqp / cl residual ddfm = kr2;
 lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
 random intercept / subject = usubjid(trtseqp);
 ods output lsmeans = <data out>;
 ods output diffs = <data out>;
 ods output covparms = <data out>;
run;
```

10 PHARMACOKINETIC REPORT

10.1 Interim PK Analyses

An interim PK analysis is planned for Part A after each period (1-4) for cohorts 1 and 2 to assess drug exposures. Cohort 3 of Part A will be used to study food effect. Part B will evaluate oral doses of either CVL-354 or placebo for up to 14 days that will be administered QD throughout Part B of the trial based on data obtained during Part A. The interim analysis consists of only group summary using descriptive statistics. Individual level data will be kept strictly confidential and will not be accessible to any study personnel except Bioanalytical laboratory personnel, Labcorp PK analysts, and Cerevel Clinical Pharmacology personnel pre-specified in the Cerevel Study Blind Protection Plan. It is critical to maintain the integrity of blind for the study. Additional interim PK analyses may be performed based on the results of the interim analyses. Interim PK reports will be completed after each interim analysis in support of dose escalation.

10.2 Final Report

The PK report for the analysis of CVL-354 in plasma and urine will contain a summary of the methodology, results, and conclusions. Prior to issuing a final report, Labcorp Clinical Pharmacology Services will provide the draft report to the Sponsor for review and comment. The report will include, but will not necessarily be limited to the following:

- Any changes from the planned analyses indicated in the PKAP
- The dates on which the study protocol are approved and the final report is issued

The report will be finalized after incorporation of Sponsor comments, as applicable. Unless otherwise specified, one electronic copy of the report will be sent to the Sponsor. The report will be finalized after approval from Sponsor or 6 months after issuing of draft report.

11 REGULATORY REQUIREMENTS

This pharmacokinetic analysis and report will be conducted in accordance with the protocol, this PKAP, Labcorp Standard Operating Procedures (SOPs), and other applicable regulatory requirements.

12 REFERENCES

1. A Phase 1, Double-blind (Investigator and Participant), First-in-Human Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of CVL-354 in Healthy Participants, Study Protocol version 3.0 (25 May 2022), Cerevel Therapeutics, LLC, Sponsor Reference No. CVL-354-1001
2. Keene ON. The log transformation is special. Stat Med. 1995;14(8):811819.
3. Brown H, Prescott R. Applied Mixed Models in Medicine. Chichester: John Wiley & Sons, 1999.

13 TABLES, FIGURES, AND LISTINGS

Shells are provided in a separate document to present examples of data presentation.

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