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

NCT Number: NCT05138653

Document Dates: Protocol Version 3: 25-May-2022

CLINICAL PROTOCOL

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: CVL-354-1001

Compound Number: 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

Legal Registered Address: 222 Jacobs Street, Suite 200, Cambridge, MA 02141 United States

Regulatory Agency Identifier Number

Regulatory Agency File	Identifying #
IND:	155,364

CONFIDENTIAL – PROPRIETARY INFORMATION

Version 3.0: 25 May 2022
Version 2.0: 16 Sep 2021
Version 1.0: 07 Jun 2021

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

SPONSOR SIGNATORIES:

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PROTOCOL VERSION 3.0 SUMMARY OF CHANGES TABLE

Document History	
Document:	**Date (Day-Month-Year)**
Version 3.0	25 May 2022
Version 2.0	16 Sep 2021
Original Protocol Version 1.0	07 Jun 2021

Amendment: Protocol Version 3.0 (25 May 2022)

Overall Rationale for the Amendment: The overall rationale for the amendment is to provide information on anticipated dose levels for the multiple ascending dose (MAD) part of the trial based on the results from the single ascending dose (SAD) evaluation.

Section # and Name[a]	**Description of Change**	**Brief Rationale**
Sponsor Signatories	Updated sponsor signatory	Change in internal responsibilities
1.1 Synopsis 4.1 Overall Design	Relocated text about double-blind design to clarify descriptions specific to SAD and MAD design, due to inclusion of food effect evaluation in Part A (for which IMP assignment is not blinded).	Moved to descriptions specific to SAD and MAD design, due to inclusion of food effect evaluation in Part A (for which IMP assignment is not blinded)
1.1 Synopsis 4.1.1 Single Ascending Dose and Food Effect - Part A	Added descriptions on Part A design aspects regarding SAD evaluation for Cohorts 1 and 2 and food effect evaluation for Cohort 3	Previous protocol version noted that additional dose levels or food effect would be explored in Cohort 3. Based on outcome of SAD evaluation (Part A Cohorts 1 and 2), Cohort 3 will be used for evaluation of food effect only.
1.1 Synopsis 2.3 Benefit/Risk Assessment 4.1 Overall Design 4.1.2 Multiple Ascending Dose - Part B	Revised text regarding sequential conduct of Parts A and B	Dose escalation was completed in Part A SAD evaluation (Cohorts 1 and 2), enabling determination of dosing paradigm for Part B MAD evaluation and rescheduling of food effect evaluation in Part A (Cohort 3) to allow overlap with Part B conduct

Section # and Name[a]	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design 4.1.1.2 Food Effect Evaluation (Cohort 3) 4.2 Scientific Rationale for Trial Design 6.1 Trial Treatments Administered 6.3.1 Participant Assignment to Treatment	Added dose selected for food effect evaluation	Provide doses based on data from Part A dose escalation
1.1 Synopsis 1.3 Schedule of Assessments 4.1.1.1 Single Ascending Dose (Cohorts 1 and 2)	Reworded content about sentinel and non-sentinel participants, including language about check-in assessments	To incorporate content from clarification memo issued by sponsor to site
1.1 Synopsis 1.3 Schedule of Assessments 4.1.2 Multiple Ascending Dose - Part B 4.4 Guidance for Dose Escalation/Stopping Rules	Deleted content regarding BID dosing, including footnotes in both Schedule of Assessment tables for Part B	To confirm that QD dosing was established for Part B based on results from Part A
1.1 Synopsis 4.1.2 Multiple Ascending Dose - Part B	Added starting dose for Part B, details regarding exposure in Part A, and details on IMP formulations to be used in Part B	To incorporate sponsor decision based on results from Part A dose escalation
1.1 Synopsis 4.1.3 Other Design Considerations	Revised to note respective in-clinic periods for SAD and food effect cohorts	To reflect differences between SAD and food effect design aspects
1.1 Synopsis	Revised disclosure statement	To reflect changes to trial design
1.1 Synopsis 9.2 Sample Size Determination	Specified that sample size for Part A includes food effect cohort	To reflect inclusion of food effect evaluation, as previous text referred to SAD only
1.1 Synopsis 9.4.3 Pharmacokinetic Analyses 9.4.4 [redacted]	Added Q1 and Q3 to list of descriptive statistics	To correct inadvertent omission in previous protocol version
1.1 Synopsis 9.4.1 General Considerations	Noted that separate analyses will be performed for each part of the trial (Part A SAD, Part A food effect, Part B MAD)	To clarify planned statistical analyses
1.1 Synopsis 9.4.3 Safety Analyses	Added text regarding safety analyses in synopsis Clarified how safety endpoints will be summarized	To correct inadvertent omission in previous protocol version

Section # and Name[a]	Description of Change	Brief Rationale
1.1 Synopsis 9.4.3 Pharmacokinetic Analyses	Added content regarding analysis of food effect	To reflect inclusion of food effect in trial design
1.2 Schema	Part A: Updated doses for Cohorts 1 and 2 Removed Cohort 3 from Part A figure and created new figure specific to Cohort 3	 To provide actual doses from Part A SAD portion To reflect changes to trial design
1.2 Schema	Added dose for food effect evaluation and anticipated doses for Part B	To provide anticipated doses based on results from Part A dose escalation
1.3 Schedule of Assessments	Part A (Cohorts 1 and 2): Removed Cohort 3 from table title	To reflect change to Part A design, resulting in dose escalation for Cohorts 1 and 2 only
1.3 Schedule of Assessments	Created new table for Part A Cohort 3	To provide Schedule of Assessments specific to food effect cohort
1.3 Schedule of Assessments	Schedule of Assessments – Part B, Multiple Ascending Dose (Cohorts 1 to 5): Modified table footnote for orthostatic assessments	To clarify that the 2-hour post-dose time point was applicable to dosing days
1.3 Schedule of Assessments	Schedule of Assessments – Part B, Multiple Ascending Dose (Cohorts 1 to 5): Added serum cystatin-C and urine β-2-microglobulin as additional safety laboratory tests	To permit appropriate evaluation of renal function following multiple doses
2.2.2 Nonclinical Pharmacokinetics and Metabolism	Deleted sentence about projected plasma clearance of CVL-354	To reflect changes to other sections, based on availability of emergent data from SAD evaluation
[redacted]	[redacted]	[redacted]
2.2.5 Emergent Clinical Data	New section	To provide preliminary safety and PK data from Part A dose escalation cohorts
2.3 Benefit/Risk Assessment	Added statement on benefit/risk assessment from clinical data	To reflect sponsor consideration of emergent data from Part A dose escalation cohorts

Section # and Name[a]	Description of Change	Brief Rationale
4.1.1.1 Single Ascending Dose (Cohorts 1 and 2)	Created new subsection specific to Part A SAD cohorts (Cohorts 1 and 2)	To organize content relevant to trial design for SAD evaluation (Cohorts 1 and 2)
4.1.1.1 Single Ascending Dose (Cohorts 1 and 2)	Added statement referring to section where actual doses administered to Cohorts 1 and 2 were added (Section 2.2.5)	To aid the reader in locating the information
4.1.1.2 Food Effect Evaluation (Cohort 3)	Created new subsection specific to Part A food effect cohort (Cohort 3)	To organize content relevant to trial design for food effect evaluation (Cohort 3)
4.1.4 Definition of Completed Participant	Added text for Part A to distinguish definition of completed participant for dose escalation vs food effect	To reflect differences between SAD and food effect design
4.2 Scientific Rationale for Trial Design	Revised content specific to Part A dose escalation and food effect cohorts	To reflect differences and provide additional details on relevant trial design aspects
4.2 Scientific Rationale for Trial Design	Expanded on previous text regarding food effect evaluation	To provide additional details
4.2 Scientific Rationale for Trial Design	Added text regarding addition of serum cystatin-C and urine β-2-microglobulin laboratory tests	To provide rationale for additional tests in the trial
4.3 Dosing Rationale	Revised dosing rationale to provide content on the basis of observed PK in humans rather than predicted PK, including dose projected to provide 90% KOR occupancy in humans, maximum dose in Part A, projected exposures at maximum dose, and proposed doses for Part B (with associated projected exposures, RO, and exposure margins)	To reflect changes due to results obtained during Part A dose escalation
4.4 Guidance for Dose Escalation/Stopping Rules	Clarified that if, based on observed data, the next planned dose is projected to exceed the maximum exposures in Part A, that dose will not be explored.	To reflect results from Part A of the trial
5.1 Inclusion Criteria	Specified the use of condoms as a contraception requirement for sexually active men with a pregnant or nonpregnant partner of childbearing potential	To clarify contraception requirements in the trial
5.3.1 Meals and Dietary Restrictions	Added statement that actual start and stop times for breakfast and IMP administration will be recorded	To provide details for recording of relevant data
5.3.1 Meals and Dietary Restrictions	Added statement that no water is permitted for at least 2 hours postdose	To avoid potential abdominal distension

Section # and Name[a]	Description of Change	Brief Rationale
6.1 Trial Treatments Administered	CVL-354 Solution: Added unit dose strength Added actual doses for Part A Cohorts 1 and 2 and starting dose for Part B Cohort 1	To align with current sponsor standards To reflect results obtained during Part A dose escalation
6.1 Trial Treatments Administered	CVL-354 Capsules: Completed corresponding rows of table, including anticipated dosage levels for Part A Cohort 3 and Part B Cohorts 2-5	To provide information on capsule IMP, including anticipated doses based on results obtained during Part A dose escalation
6.1 Trial Treatments Administered	Placebo: Provided corresponding information regarding capsule dosage form	To provide information on capsule IMP
6.1 Trial Treatments Administered	Overall: Revised presentation	To align with current sponsor standards
6.2 Preparation, Handling, Storage, and Accountability	Deleted mention of "suspension"	For consistency with revisions in Section 6.1 (Table 10)
6.3.1 Participant Assignment to Treatment	Added content on randomization to treatment sequence for food effect cohort	To provide relevant details
6.3.1 Participant Assignment to Treatment	For text about mirror randomization number, specified that Part A applies to Cohorts 1 and 2	To provide relevant details
6.3.2 Blinding	Added sentence that treatment assignment will not be blinded for food effect portion	To provide relevant details
6.3.2 Blinding	Removed text regarding documentation of unblinding in eCRF	To incorporate updated sponsor standard language
8.3.3 Vital Sign Measurements	Revised definition of orthostatic hypotension, including calculation relative to supine assessments	To correct errors from previous protocol version
10.2 Appendix 2: Clinical Laboratory Tests	Added a row for "Additional Required Tests" and added serum cystatin-C and urine β-2-microglobulin as additional safety laboratory tests to be taken	To permit appropriate evaluation of renal function following multiple doses
10.6 Appendix 6: Kidney Safety for First-in-Human Trial 11 References	Added a new appendix with guidance regarding the monitoring of kidney function Added supporting references	To provide additional safety monitoring in this first-in-human trial

Section # and Name[a]	Description of Change	Brief Rationale
Overall	Minor grammatical and wording corrections/clarifications made throughout protocol	To correct minor errors from the previous version of the protocol

Abbreviations: BID=twice daily; eCRF=electronic case report form; IMP=investigational medicinal product; KOR=kappa opioid receptor; MAD=multiple ascending dose; [redacted]; PK=pharmacokinetic; QD=once daily; RO=receptor occupancy; SAD=single ascending dose.

[a] Numbering (eg, section numbers and numbered lists) refers to current version of the protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Sponsor Name: Cerevel Therapeutics, LLC

Name of Investigational Medicinal Product: CVL-354

Protocol 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

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

IND Number: 155,364

Trial Phase: 1

Treatment/Indication: Major depressive disorder

Rationale: 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 [redacted] 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.

Objectives and Endpoints

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 ○ $t_{1/2}$
• 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 ○ $t_{1/2}$

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; $t_{1/2}$=apparent terminal half-life; SAD=single ascending dose; T_{max}=time to maximum plasma concentration; V_z/F=apparent volume of distribution during terminal phase.

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) ○ $t_{1/2}$ (Day 14 only) ○ Ae (amount eliminated unchanged in urine at steady state on Day 14) ○ Renal clearance (Day 14 only)

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; MAD=multiple ascending dose; PTR=peak-to-trough ratio; Rac=accumulation ratio; $t_{1/2}$=apparent terminal half-life; T_{max}=time to maximum plasma concentration; V_z/F=apparent volume of distribution during terminal phase.

Overall Design:

This is a Phase 1, 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.

Part B of the trial will start after completion of single dose escalation in Part A (Cohorts 1 and 2). The evaluation of food effect for Part A (Cohort 3) may be conducted in parallel with Part B, using a CVL-354 dose of 50 mg. Single doses of CVL-354 up to 200 mg are considered to be safe and well tolerated based on review of data from Part A Cohorts 1 and 2.

Part A (Single Ascending Dose and Food Effect)

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 will be evaluated.

Cohorts 1 and 2 will be dosed in a sequential manner for up to 4 periods each (see schema in Section 1.2). 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. The proposed doses in Part A for Cohorts 1 and 2 are presented in the schema provided in Section 1.2. 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.

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.

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).

A schematic of the trial design is provided in Section 1.2.

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 adverse event (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.

Other Design Considerations

Participants will be admitted to the trial site on Day -1 and remain at the clinic through Day 3 of each period (Part A, Cohorts 1 and 2), through Day 3 of Period 2 (Part A, Cohort 3), or through Day 17 (Part B).

Dose-escalation decisions for Part A and Part B will be made by the SRT, comprising sponsor personnel (or designee/supporting personnel) and site investigator or physician designee.

If a participant discontinues before completing all periods within a cohort or withdraws for reasons unrelated to the safety of the IMP, the participant may be replaced at the investigator's and sponsor's discretion. In Part A, if a participant discontinues from the trial, the replacement participant will complete the rest of original treatment sequence of discontinued participant.

Disclosure Statement: This is a 2-part single dose (4-way crossover, Part A ascending dose;) and multiple ascending dose (Part B) trial that is blinded to the investigator and participants. The food effect evaluation in Part A is an open-label, 2-way crossover design.

Number of Participants:

- Part A (SAD, food effect): 8 participants per cohort for a total of approximately 16 participants if 2 cohorts complete single ascending dose evaluation. The food effect cohort will comprise approximately 8 participants, for a total of approximately 24 participants in Part A.
- Part B (MAD): 10 participants per cohort (8 CVL-354, 2 placebo) for a total of approximately 50 participants if 5 cohorts complete.

In the event of higher than anticipated early terminations due to coronavirus disease-2019 (COVID-19) or other reasons, Cerevel may extend enrollment in order to achieve trial objectives.

Key Entry Criteria:

- Healthy women of nonchildbearing potential and men, ages 18 to 55 years, inclusive

Intervention Groups, Trial Treatment, and Duration:

Part A (SAD, food effect) – In Cohorts 1 and 2, all participants will receive treatment with up to 3 single oral doses of CVL-354 and/or 1 single oral dose of placebo in a 4-period crossover design. The starting dose of CVL-354 will be 0.5 mg. Participants will be randomized to 1 of 4 treatment sequences for Cohorts 1 and 2.

Cohort 3 will be used to evaluate food effect, with participants randomized to a treatment sequence (fed/fasted or fasted/fed).

Total trial duration per participant during dose escalation will be approximately up to 100 days and include the following: a 4-week Screening Period, a Treatment Period (in-clinic) comprising up to 4 periods of 3 days each, at least 5 days washout between doses, and a follow-up contact 14 days after the final dose of IMP.

For the food effect evaluation, total trial duration per participant will be approximately 50 days and include the following: a 4-week Screening Period, a Treatment Period (in-clinic) comprising 2 periods of 3 days each, a 2-day washout between periods, and a follow-up contact 14 days after the final dose of IMP.

Part B (MAD) – All participants will be randomized in a 4:1 ratio to receive treatment with multiple oral doses of CVL-354 (dose and regimen to be determined) or placebo. Total trial duration per participant will be approximately up to 58 days and include the following: a 4-week

Screening Period, a Treatment Period (in-clinic) of up to 14 days, follow-up (in clinic) for 3 days, and a follow-up contact 14 days after the final dose of IMP.

Statistical Methods:

Sample Size Estimation:

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 due to COVID-19 or other factors, Cerevel may extend enrollment in order to achieve trial objectives.

Statistical Methods:

Descriptive statistical methods will be used to summarize the data from this trial. All available data for randomized participants will be listed by participant. Separate analyses will be performed for each part of the trial (Part A SAD, Part A food effect, Part B MAD).

All PK exposure parameters (eg, C_{max}, AUC) will be summarized by dose, where applicable, using descriptive statistics including the arithmetic mean, median, standard deviation, coefficient of variation, minimum and maximum values, Q1, Q3, and geometric mean.

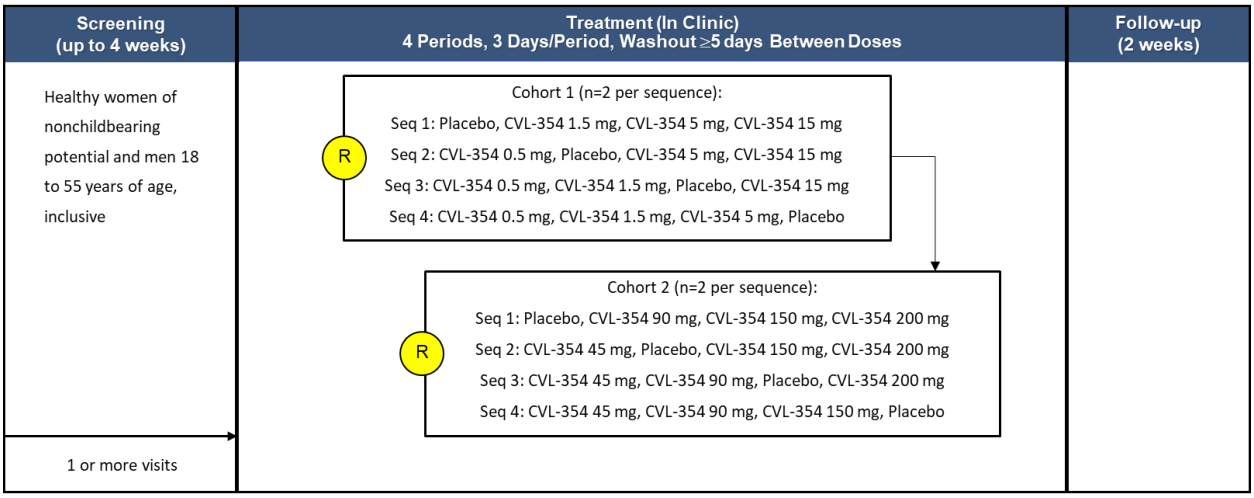
For food effect assessment, the single dose of CVL-354 administered in fasted state is the reference treatment and the single dose of CVL-354 administered in fed state is the test treatment.

Treatment-emergent adverse events, including AEs potentially related to abuse, will be coded according to the Medical Dictionary for Regulatory Activities and summarized by treatment, system organ class, and preferred term. Further summaries will be done by seriousness, severity, relationship to IMP, and dose at the time of onset. Other safety endpoints will be summarized with descriptive statistics by treatment and timepoint, including vital sign measurements, ECG, clinical laboratory assessments and suicidality monitored during the trial using Columbia-Suicide Severity Rating Scale.

1.2. Schema

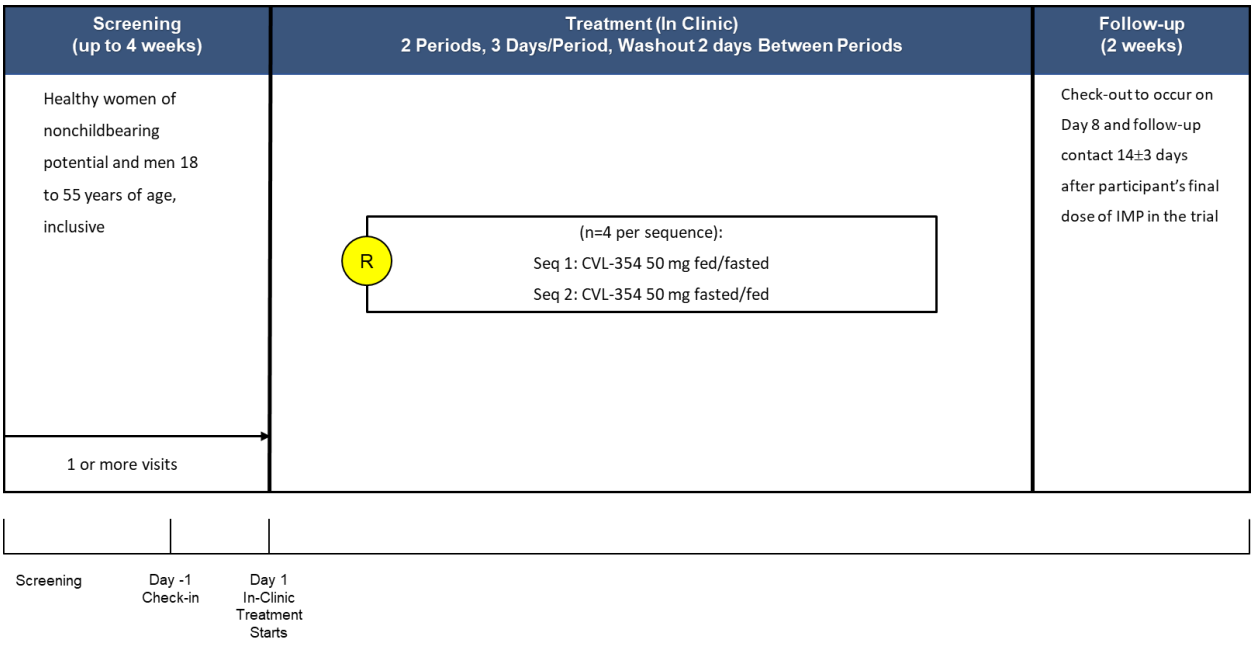
The trial schematics for the single ascending dose (Part A, Cohorts 1 and 2), food effect (Part A, Cohort 3), and multiple ascending dose (Part B, Cohorts 1-5) cohorts are provided in Figure 1, Figure 2, and Figure 3, respectively. Part B may be run in parallel with Part A Cohort 3.

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



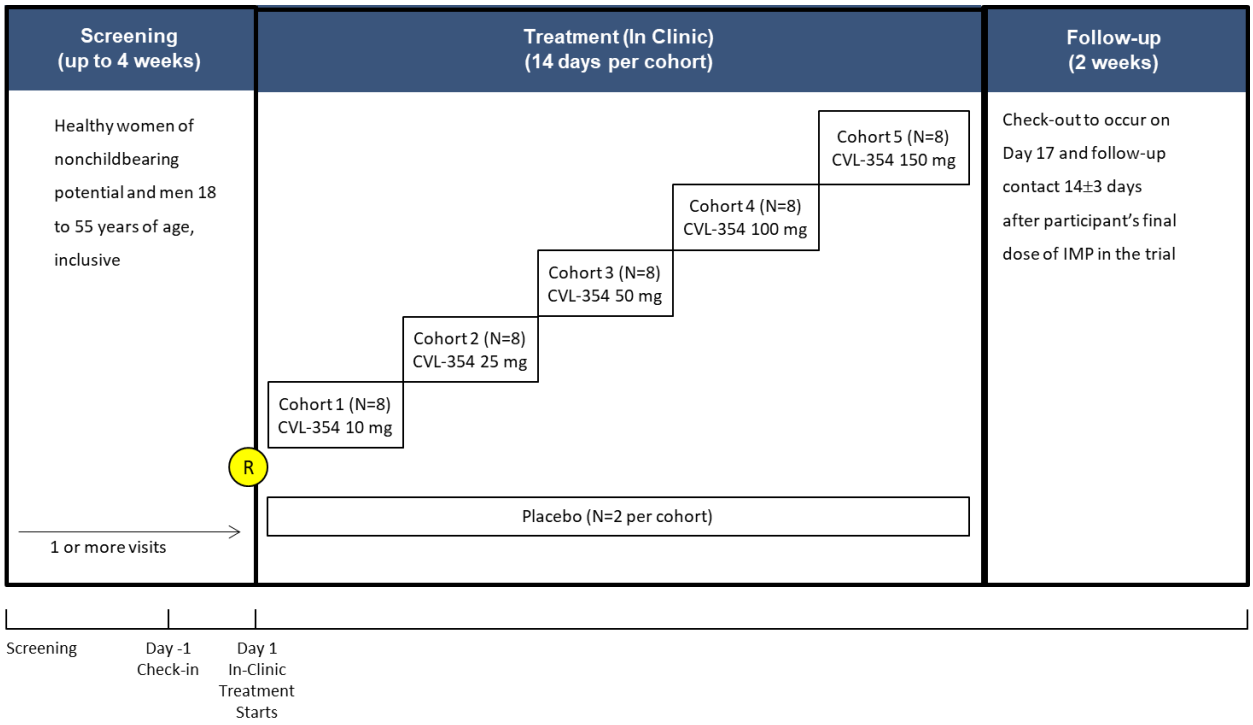
Abbreviations: IMP=investigational medicinal product; R=randomization; Seq=sequence.
For each period, Check-in is on Day -1 and Check-out is on Day 3.
Follow-up consists of a contact to check on status 14±3 days after a participant's final dose of IMP in the trial.
Doses/treatment may be modified based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

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.

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.

1.3. Schedule of Assessments

The Schedules of Assessments are provided in Table 1 (Part A, SAD Cohorts 1 and 2), Table 2 (Part A, Food Effect Cohort 3), and Table 3 (Part B, MAD Cohorts 1-5).

For Part B, a detailed schedule of assessments for Days 1 and 14 is provided in Table 4 .

Table 1: 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]																		
[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)				←----------													----------→	
Standard 12-lead ECG[m]	X	X	X	X		X	X	X		X		X	X		X		X	

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	
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]-5; 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 2: 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. Further details on fed and fasting conditions are provided in Section 5.3.1.

Table 3: 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]-5; 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. See Table 4 for details on Day 1 and Day 14 assessments. 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).

Table 4: Schedule of Assessments – Part B, Multiple Ascending Dose (Detailed Assessments on Days 1 and 14)

Assessment	Predose (minutes)	Post Morning Dose (hours)										
		0.5	1	2	3	4	6	8	12	16	24	36/48/72
Continuous ECG (Holter)[a]	X (-45, -30, and -15 minutes)	X	X	X	X	X		X	X		X	
Standard 12-lead ECG	X (-15 minutes)	X	X	X		X		X	X		X	
Supine HR and BP[b]	X (-30 minutes)	X	X	X		X		X	X		X	
RR and temperature	X											
Standing HR and BP[c]				X								
PK[d]	X (-15 minutes)	X	X	X	X	X	X	X	X	X	X	X[e]
[redacted]												

Abbreviations: BP=blood pressure; [redacted]; ECG=electrocardiogram; HR=heart rate; PK=pharmacokinetic; QD=once daily; RR=respiratory rate; [redacted]

Note: When multiple assessments are planned for the same time points, the preferred order assessment is as reflected in the table (ie, ECG, followed by HR and BP, etc).

[a] ECGs for exposure-response modeling analysis will be recorded for a minimum of 26 hours from 2 hours predose until 24 hours postdose. Participants should be resting quietly in a supine position for at least 10 minutes before the nominal ECG extraction time points and 5 minutes after each extraction time point, without any significant environmental distractions (noise, loud music, TV, computer or phone use, etc). Holter leads will be checked for proper connectivity prior to each time point. For time points with multiple assessments, ECGs will be obtained, then vital signs, followed by PK samples.

[b] BP and HR measurements will be obtained from participants after at least 3 minutes of rest.

[c] Orthostatic BP and HR measurements will be obtained from participants in the standing position.

[d] One sample and 1 backup sample at time points indicated.

[e] These samples will be obtained after the morning dose on Day 14 only.

2. INTRODUCTION

2.1. Trial Rationale

Major depressive disorder (MDD) is a debilitating and chronic illness characterized by a broad spectrum of emotional and physical symptoms. Despite the availability of numerous treatments (eg, pharmacotherapy, cognitive behavioral psychotherapy, electroconvulsive therapy), approximately 30% of patients remain untreated, only 40% to 70% of patients respond to their treatment, and 10% to 30% of patients are treatment-resistant (Jaffe et al, 2019; Hasin et al, 2018; Khan and Brown, 2015; Al-Harbi, 2012). In treatment-responsive patients, high rates of relapse and recurrence have been reported (Bai et al, 2020; Rush et al, 2006). Moreover, remission rates are low (approximately ≤50%) across clinical trials evaluating antidepressants (Oluboka et al, 2018; Machado et al, 2006; Thase et al, 2005) and partial response is common (Trivedi et al, 2006). Incomplete (inadequate) response to treatment for MDD is associated with an increased risk of relapse (Mulder et al, 2009; Möller, 2008), impaired social and occupational functioning (Jaffe et al, 2019; Judd et al, 2002) and consequently, an increased economic burden (Gauthier et al, 2019; Jaffe et al, 2019; Sobocki et al, 2006; McIntyre and O'Donovan, 2004). Thus, novel antidepressant therapies that can achieve consistent and more favorable short- and long-term outcomes represent an unmet medical need in patients with MDD.

Kappa opioid receptor (KOR) activation is implicated in reduced activity of the reward (mesolimbic) pathway, negative mood states, and dysphoria. Recent evidence suggests that selective antagonism of KORs may provide therapeutic benefit in treating MDD (Jacobson et al, 2020a). CVL-354 is a brain-penetrant potent KOR antagonist with >10-fold pharmacological selectivity over mu opioid receptors (MORs), which is being developed for treatment of MDD. Nonclinical pharmacology and safety data generated to date support 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.

2.2. Background

A growing body of data suggests that antagonism of KORs is a promising approach to addressing mood disorders (Carlezon and Krystal, 2016). KORs are highly expressed in brain regions associated with anhedonia, depression (nucleus accumbens) and anxiety (amygdala) (Cahill et al, 2014; Naganawa et al, 2016). As regulators of key circuits involved in reward and mood, KORs present a unique therapeutic target to intervene in MDD (Jacobson et al, 2020a). Nonclinical studies have demonstrated that activation of KORs results in 1) reduced dopaminergic tone in the nucleus accumbens and 2) induction of negative mood states (Carlezon et al, 2006). In humans, KOR agonism led to dose-dependent dysphoric and psychotomimetic effects (Pfeiffer et al, 1986).

KOR antagonism is a well-known target for treatment of MDD and there have been efforts at development of therapeutic agents for this mechanism of action. In an example of polypharmacy

therapy, ALKS-5461, a combination of buprenorphine (MOR partial agonist and KOR antagonist) and samidorphan (MOR antagonist), has been evaluated for efficacy as adjunctive treatment of MDD in adults with inadequate response to antidepressants (Zajecka et al, 2019).

[redacted]

CVL-354 has been evaluated in a standard battery of genetic toxicity studies, safety pharmacology (neurofunctional, pulmonary, and cardiovascular) studies, and single- and repeat-dose [redacted] toxicity studies up to 3 months in duration. The route of these studies was by oral gavage since oral is the intended clinical route of administration. The results of nonclinical pharmacology, PK, and toxicology studies are summarized in the following subsections. Additional details regarding nonclinical data for CVL-354 are provided in the Investigator's Brochure.

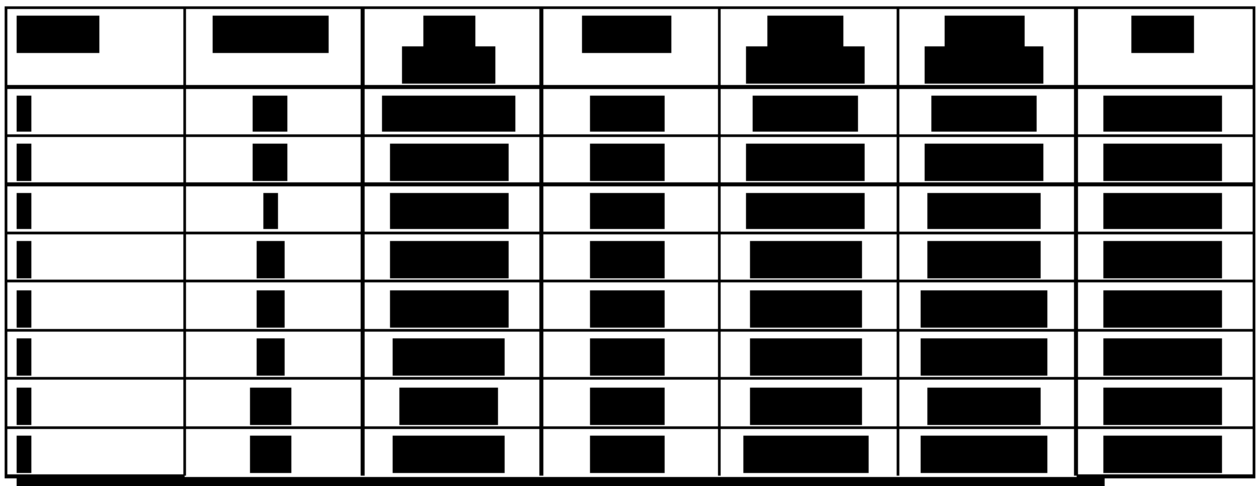
[redacted]

[redacted]

the corresponding stopping exposure criteria in humans are [redacted]

[redacted]

[redacted]



[redacted]

[redacted]

3. OBJECTIVES AND ENDPOINTS

The primary and secondary objectives and corresponding endpoints are summarized in Table 6 (SAD portion) and Table 7 (MAD portion).

Additional exploratory endpoints may be evaluated during the trial, including food effect in the SAD portion, [redacted] in the MAD portion, and the [redacted] in the SAD and MAD portions. Banked biospecimens will be collected from consenting participants for potential exploratory research. Plasma and urine samples will also be obtained for metabolite scouting.

Table 6: Objectives and Endpoints - Part A (SAD)

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 ○ $t_{1/2}$

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; $t_{1/2}$=apparent terminal half-life; SAD=single ascending dose; T_{max}=time to maximum plasma concentration; V_z/F=apparent volume of distribution during terminal phase.

Table 7: Objectives and Endpoints - Part B (MAD)

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} ○ AUCτ ○ 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) ○ $t_{1/2}$ (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; MAD=multiple ascending dose; PTR=peak-to-trough ratio; Rac=accumulation ratio; $t_{1/2}$=apparent terminal half-life; T_{max}=time to maximum plasma concentration; V_z/F=apparent volume of distribution during terminal phase.

4. TRIAL DESIGN

4.1. Overall Design

This is a Phase 1, 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. The single ascending dose and food effect portion (Part A) are described in Section 4.1.1 and the multiple ascending dose portion (Part B) is described in Section 4.1.2.

Part B of the trial will start after completion of single dose escalation in Part A (Cohorts 1 and 2). The evaluation of food effect for Part A (Cohort 3) may be conducted in parallel with Part B, using a CVL-354 dose of 50 mg. Single doses of CVL-354 up to 200 mg are considered to be safe and well tolerated based on review of data from Part A Cohorts 1 and 2.

4.1.1. Single Ascending Dose and Food Effect- Part A

4.1.1.1. Single Ascending Dose (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 will be evaluated.

Cohorts 1 and 2 will be dosed in a sequential manner for up to 4 periods each (see schema in Section 1.2). 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. The proposed doses in Part A for Cohorts 1 and 2 are presented in Table 8. Based on emergent data, the actual doses may change (from those presented in Table 8); 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 an SRT meeting.

Actual doses administered to Cohorts 1 and 2 at the time of the protocol amendment (Version 3.0) are provided in Section 2.2.5.

Table 8: Example Dosing Paradigms for CVL-354 Single Ascending Dose in Cohorts 1 and 2

Cohort	N	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

Doses/treatment may be modified based on emergent safety, tolerability, and pharmacokinetic data.
Doses may be repeated to confirm safety/tolerability.

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.

4.1.1.2. 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 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). Details of fasted and fed conditions are provided in Section 5.3.1. 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.

4.1.2. Multiple Ascending Dose - 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).

A schematic of the trial design is provided in Section 1.2.

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] 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.

4.1.3. Other Design Considerations

Participants will be admitted to the trial site on Day -1 and remain at the clinic through Day 3 of each period (Part A, Cohorts 1 and 2), through Day 3 of Period 2 (Part A, Cohort 3), or through Day 17 (Part B).

Dose-escalation decisions for Part A and Part B will be made by the SRT, comprising sponsor personnel (or designee/supporting personnel) and site investigator or physician designee, as described in Section 4.4.

If a participant discontinues before completing all periods within a cohort or withdraws for reasons unrelated to the safety of the IMP, the participant may be replaced at the investigator's and sponsor's discretion. In Part A, if a participant discontinues from the trial, the replacement participant will complete the rest of original treatment sequence of the discontinued participant.

Trial procedures and their timing are summarized in the Schedules of Assessments for Parts A and B (Section 1.3).

4.1.4. Definition of Completed Participant

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, Cohorts 1 and 2], Day 3 in Period 2 [Part A, Cohort 3]), or Day 17 [Part B]), as shown in the Schedule of Assessments in Section 1.3.

A participant who completed all procedures except the follow-up contact would therefore not be considered an early termination participant.

4.2. Scientific Rationale for Trial Design

This trial will investigate the effect of SAD and MAD of CVL-354 in healthy participants to evaluate the safety, tolerability, and PK of CVL-354 in humans. This information is critical for providing appropriate dosing and safety monitoring plans for next stages of CVL-354 development. Safety assessments such as ECGs (including baseline telemetry in SAD dose escalation cohorts), vital sign measurements, and clinical laboratory tests are well established and appropriate to the trial design.

The sequential cohort, crossover design for the single ascending dose evaluation in Part A (Cohorts 1 and 2), crossover design for food effect evaluation in Part A (Cohort 3), and sequential cohort design for the multiple ascending dose portion (Part B), are standard designs that are widely used for such trials. A sentinel cohort of participants at each dose in Part A (Cohorts 1 and 2 only), ensures that the dose is safe and tolerated prior to dosing the rest of the participants in the cohort.

This trial will also investigate the effect of food on CVL-354 exposures after a single 50 mg dose, a dose that is approximately 2-fold higher than the projected efficacious dose. Any food effect observed at this dose may be extrapolated to lower doses. Moreover, a CVL-354 dose of 50 mg is 4-fold lower than the top dose of 200 mg evaluated in the SAD part of the trial. [redacted]

Dosing for 14 days in Part B ensures achievement of PK steady state and also evaluation of longer-term effects of CVL-354 exposure on safety/tolerability parameters in a controlled, inpatient setting. This information is critical to identification of a tolerated dose and implementation of appropriate safety monitoring procedures in later stages of development. [redacted] In addition, an Abuse Potential Monitoring Plan (APMP) has been developed for this trial (see Section 8.4.6).

The Columbia-Suicide Severity Rating Scale (C-SSRS) is commonly used for stringent monitoring of suicidality in clinical trials of neurological compounds (Posner et al, 2011).

4.3. Dosing Rationale

[redacted]

Predicted human CVL-354 exposures in plasma and projected KOR occupancy in human brain were used to set the starting doses in conjunction with NOAEL exposures. As mentioned

previously, other KOR antagonists (aticaprant, BTRX-335140) have been previously dosed safely to KOR receptor occupancies of ≥90%. Therefore, a starting dose of 0.5 mg CVL-354 has been selected for Part A based on projected KOR and MOR occupancy calculations and exposure margins for C_{max} and AUC estimates. Moreover, the starting dose of 0.5 mg is also <1/1900 of the human equivalent dose (HED; 60 kg human) based on the NOAEL doses in dogs (15 mg/kg BID) and rats (100 mg/kg/day) according to Food and Drug Administration guidance for HED calculation (FDA Guidance for Industry, 2005).

The maximum single dose administered in Part A of this trial is 200 mg. [redacted] A previous single ascending dose trial with aticaprant safely escalated to doses approximately 6-fold higher than the target efficacious dose (Lowe et al, 2014).

The starting dose for Part B will be 10 mg QD [redacted]. The starting dose for MAD was selected such that total CVL-354 doses (140 mg over 14 days) would not exceed the maximum single dose deemed safe and tolerated in the SAD part (200 mg). [redacted] The starting dose of 10 mg QD is projected to result in steady-state exposures that are [redacted] lower than the exposure limiting criteria. The proposed top dose of 150 mg QD in Part B is selected, based on data from Part A cohorts, such that the projected steady state C_{max} and AUC_{24} do not exceed the values investigated in Part A and deemed safe and tolerated by the SRT. The projected CVL-354 exposures at the 150 mg QD are projected to be [redacted] lower than the NOAEL exposures in the 3-month [redacted] study.

[redacted]

[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[redacted]

a [redacted]

[b] [redacted]

Dose escalation will be guided by safety, tolerability, and observed/predicted exposures. Based on the observed CVL-354 PK, the escalation scheme for remaining doses may be adjusted upward or downward or repeated, but the increment of C_{max} and AUC will be targeted to a) not to exceed half-log increments and b) not exceed the predefined human exposure limits or the maximum exposures from Part A (whichever is lower). Smaller increments (~2-fold) will be implemented as exposures approach the limiting criteria. The decision to alter the escalation scheme will be made jointly between the investigator and sponsor, as noted in Section 4.4.

Across both parts, all available cumulative data from previous cohorts/doses will be used to inform subsequent doses. Overall, the proposed dose range of CVL-354 in this first-in-human trial is anticipated to attain sufficient range of plasma concentrations with sufficient margins above the projected therapeutic dose range and understand the impact of CVL-354 on safety/tolerability.

4.4. Guidance for Dose Escalation/Stopping Rules

Dose-escalation stopping rules will be used to determine whether the maximum tolerated dose (MTD) has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. Standard safety laboratory assessments, vital signs, safety ECGs, and AE monitoring before and after dosing will provide relevant safety data to guide the dose-escalation decision. The exposure (AUC_{24} and C_{max}) of CVL-354 will also be considered for dose escalation.

An SRT will be established for this trial, which will include representatives from the sponsor (or external designee/supporting personnel) and site investigator or physician designee. The sponsor trial team may not overrule the investigator's decision to stop dose escalation. The SRT will review safety, tolerability, and preliminary PK data after every dose prior to initiation of subsequent doses. Further details will be provided in the SRT charter. Possible actions following SRT review include, but are not limited to, the following:

- Continuing dose escalation, as planned
- Administration of an intermediate dose between the current and next planned dose
- Repeat administration of the current dose
- Administration of a lower dose than the existing dose levels
- Stopping further dose escalation
- Trial termination

The SRT may consider stopping further dose escalation in Parts A and B of the trial if any one of the following criteria is met:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar drug-related Grade 2 AEs or adverse events of special interest (AESIs)

  - Abnormal laboratory test results or other safety assessments (eg, ECG, vital sign measurements) that are clinically significant would meet the definition of an AE as defined in Section 10.3.1 (Table 14). Guidelines for grading of AE severity are provided in Section 10.3.3 (Appendix 3).

- If 2 or more participants receiving active drug at a given dose level develop drug-related Grade 3 AEs or AESIs
- Any drug-related Grade 4 AE or drug-related serious adverse event (SAE) that occurs in a participant receiving active treatment
- Other findings that, at the discretion of the sponsor trial team and investigator, indicate that dose escalation should be halted, or it is determined (by sponsor and investigator) that the limit of safety and/or tolerability has been reached.

In the case of an SAE occurring during active treatment, the investigator will contact the medical monitor and notify the sponsor of the event as soon as possible. Dosing will be paused for all participants, until causality is assessed by the investigator and the sponsor. If the SAE is determined (by SRT) to be either drug-related or relationship is unknown, dosing at the current dose level will be stopped, and further dose escalation will be terminated. If the SAE is determined to be not drug-related by the investigator and the sponsor, then the trial may resume at the current dose level.

In addition, the dose escalation will be terminated based on the following PK criteria:

- 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 exposures in SAD (Part A), 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.

4.5. End of Trial Definition

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

5. TRIAL POPULATION

Healthy women of nonchildbearing potential and men 18 to 55 years of age, inclusive, will be enrolled into this trial.

5.1. Inclusion Criteria

Individuals are eligible for participation in this trial only if all of the following criteria apply:

1.	Women of nonchildbearing potential and men 18 to 55 years, inclusive, at the time of signing the ICF. The criteria for determination of childbearing potential are provided in Section 10.4.1.3.
2.	Overtly healthy as determined by medical evaluation, including medical and psychiatric history, physical and neurological examinations, ECG, vital sign measurements, and laboratory test results, as evaluated by the investigator.
3.	Body mass index of 18.5 to 30.0 kg/m2, inclusive, and total body weight >50 kg (110 lb) at Screening.
4.	Sexually active men with a pregnant or nonpregnant partner of childbearing potential must agree to comply with the following contraception requirements during the trial and for 14 days after the last dose of IMP: • Use acceptable (at minimum) or highly effective contraception as defined in Section 10.4.1.2 and Section 10.4.1.1, respectively, or remain abstinent. • Use condoms. In addition, male participants should not donate sperm for a minimum of 14 days following the last dose of IMP.
5.	Capable of giving signed informed consent as described in Section 10.1.3 (Appendix 1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
6.	Ability, in the opinion of the investigator, to understand the nature of the trial and comply with protocol requirements, including the prescribed dosage regimens, scheduled visits, laboratory tests, and other trial procedures.

Abbreviations: ECG=electrocardiogram; ICF=informed consent form; IMP=investigational medicinal product.

5.2. Exclusion Criteria

Individuals are not eligible for participation in this trial if any of the following criteria apply:

Medical History and Concurrent Conditions	
1.	Current or past history of significant cardiovascular, pulmonary, gastrointestinal, renal, hepatic, metabolic, genitourinary, endocrine (including diabetes mellitus), malignancy (except for basal cell carcinoma of the skin and cervical carcinoma in situ, at the discretion of the investigator), hematological, immunological, neurological, or psychiatric disease that, in the opinion of the investigator or medical monitor, could compromise either participant safety or the results of the trial.

2.	"Yes" responses for any of the following items on the C-SSRS (within the individual's lifetime): • Suicidal Ideation Item 3 (Active Suicidal Ideation with Any Methods [Not Plan] without Intent to Act) • Suicidal Ideation Item 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) • Suicidal Ideation Item 5 (Active Suicidal Ideation with Specific Plan and Intent) • Any of the Suicidal Behavior items (Actual Attempt, Interrupted Attempt, Aborted Attempt, Preparatory Acts or Behavior) "Yes" responses for any of the following items on the C-SSRS (within past 12 months): • Suicidal Ideation Item 1 (Wish to be Dead) • Suicidal Ideation Item 2 (Non-Specific Active Suicidal Thoughts) Serious risk of suicide in the opinion of the investigator is also exclusionary.
3.	History of substance or alcohol-use disorder (excluding nicotine or caffeine) as per DSM-5 criteria within 12 months prior to signing the ICF.
4.	Any condition that could possibly affect drug absorption, including, but not limited to, complicated appendectomy or cholecystectomy, bowel resections, bariatric weight loss surgery, gastric banding, or gastrectomy.
5.	Receipt of SARS-CoV2 vaccination or booster as follows: • mRNA: within 14 days prior to dosing • Non-mRNA: within 28 days prior to dosing In addition, participants who plan to receive SARS-CoV2 vaccination or booster while participating in the trial or for at least 14 days after the last dose of IMP will be excluded.
6.	Have recently been diagnosed with symptomatic COVID-19 or test positive for COVID-19 within 30 days prior to signing the ICF.
Prior or Concomitant Therapies	
7.	Use of prohibited medication prior to randomization or likely to require prohibited concomitant therapy (eg, prescription and over-the-counter medications, herbal medications, vitamins, and supplements) during the trial (see Section 6.5).
Laboratory Test Results	
8.	Either of the following: • History of HIV, hepatitis B, or hepatitis C infection • Positive result for HIV, hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody
9.	Positive drug screen (including nicotine) or a positive test for alcohol (note: individuals who test positive for nicotine or alcohol may be rescreened).
10.	Any of the following clinical laboratory test results (and confirmed by a single repeat measurement, if deemed necessary): • AST or ALT ≥1.5 × ULN • Total bilirubin ≥1.5 × ULN. Individuals with a history or suspicion of Gilbert's syndrome may be eligible provided the direct bilirubin is <ULN.

11.	Estimated glomerular filtration rate at Screening <90 mL/min/1.73 m2, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al, 2009).
Other Exclusionary Assessments	
12.	12-lead ECG demonstrating any of the following at Screening or initial Check-in (Day -1): • QTcF interval >450 ms • QRS interval >120 ms • PR interval >220 ms Note: at Screening, eligibility will be determined based on the average of a centrally read triplicate set of ECGs. At initial Check-in (Day -1), a single ECG will be obtained. If any of the above criteria are not met at subsequent Check-ins, consult the medical monitor to determine whether the participant remains eligible to continue in the trial.
13.	Blood pressure measurements demonstrating any of the following at Screening or Check-in (Day -1 of each period): • Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg ○ Blood pressure will be measured after at least 3 minutes in supine position. At Screening, the average of 2 measurements will be used to determine eligibility and a single measurement at each Check-in. • Orthostatic hypotension, 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) • Symptomatic orthostatic dizziness
14.	Heart rate <45 bpm or >100 bpm based on vital signs assessment (rather than ECG). Heart rate will be measured in a supine position after at least 3 minutes of rest. The average of 2 measurements taken 1-2 minutes apart will be used to determine eligibility at Screening and a single measurement at each Check-in.
15.	Any other abnormal safety findings unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the participant or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. Tests with abnormal results may be repeated to ensure the reproducibility of the result before excluding a potential participant based on criteria provided in the protocol.
Lifestyle or Other Miscellaneous Exclusions	
16.	Refusal to abstain from grapefruit-containing foods or beverages or Seville orange-containing foods or beverages from 7 days prior to Day -1 through Check-out from the clinic for each treatment period.
17.	Current use of tobacco or nicotine-containing products (cigarettes, cigars, chewing tobacco, snuff, e-cigarettes, etc).
18.	History of chronic consumption of >400 mg/day of caffeine-containing drinks or food (eg, >4 cups [8 ounces] of brewed coffee, 9 cans [12 oz] of diet cola, 12 cans [12 oz] of cola, 8.5 cups of brewed black tea, 2 energy shot drinks).
19.	Refusal to adhere to lifestyle considerations as defined in Section 5.3.
20.	Considering or scheduled to undergo any surgical procedure during the trial.
21.	Any other condition that would preclude IMP administration or trial participation (eg, difficulty swallowing, poor venous access).

22.	Known allergy or hypersensitivity to the IMP, closely related compounds, or any of their specified ingredients.
23.	Donated more than 500 mL of blood in the 2 months prior to signing the ICF.
24.	Current enrollment or past participation within 30 days or 5 half-lives (whichever is longer) prior to signing the ICF in any other clinical trial involving an IMP.
25.	Employee of the investigator, clinic, or sponsor with direct involvement in the proposed trial or other trials under the direction of the investigator or clinic, as well as family members of the employee or investigator.
26.	Anyone who should not participate in the trial in the opinion of the sponsor, investigator, or medical monitor.
27.	Part B only: anyone who participated in Part A of the trial.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; COVID-19=coronavirus disease-2019; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ECG=electrocardiogram; ICF=informed consent form; IMP=investigational medicinal product; mRNA=messenger ribonucleic acid; QTcF=QT interval corrected for heart rate using Fridericia's formula; SARS-CoV2=severe acute respiratory syndrome coronavirus 2; ULN=upper limit of normal.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants are required to abstain from consumption of caffeine-containing foods or caffeinated beverages (eg, coffee, tea, cola, energy drinks), grapefruit-containing foods or beverages, and Seville orange-containing foods or beverages from 7 days prior to Day -1 through Check-out from the clinic for each treatment period.

On days with intensive ECGs (extractions by central ECG service) and PK collection (Day 1 in Part A, Days 1 and 14 in Part B), participants will fast for at least 10 hours prior to dosing and 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. Water is permitted until 1 hour prior to IMP administration and can be consumed ad libitum after dosing.

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).

The following guidelines apply for dosing under "fed" conditions during food effect evaluation:

- Following an overnight fast of at least 10 hours, participants should start breakfast approximately 25 minutes prior to administration of IMP.
- The entire breakfast will be consumed approximately over a 20-minute period with the IMP administered within approximately 5 minutes of completion of the meal. Actual start and stop times for breakfast and IMP administration time will be recorded.

- There are no water restrictions prior to dosing for participants dosed under fed conditions. The IMP should be administered with 240 mL of ambient temperature water.
- No water is permitted for at least 2 hours postdose. No food will be allowed for at least 4 hours postdose.
- The breakfast will be a high calorie/high fat meal (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) consisting of 2 eggs fried in butter, 2 strips of bacon or 50 g of meat or sausage, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk.

5.3.2. Alcohol and Tobacco Restrictions

Participants will abstain from alcohol for at least 24 hours prior to each admission to the clinic until each Check-out. Participants may undergo an alcohol breath test or blood/urine alcohol test at the discretion of the investigator.

Use of tobacco or nicotine-containing products (cigarettes [including e-cigarettes], cigars, chewing tobacco, snuff, etc) is prohibited within 28 days prior to signing the informed consent form (ICF) and during the trial. Vaping is not permitted during the trial.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the trial (eg, walking, watching television, reading).

5.3.4. Effects on Ability to Drive and Use Machinery

The effect of CVL-354 on the ability to drive and use machines has not been systematically evaluated.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) at screening may be rescreened once at the discretion of the investigator and after consultation with the sponsor unless screen failure is due to a positive urine drug screen for illicit substances. Rescreened participants will be assigned a new participant number.

6. TRIAL TREATMENTS

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

6.1. Trial Treatments Administered

A summary of the IMP to be administered during this trial is presented in Table 10.

Table 10: Investigational Medicinal Product Administered

IMP	**CVL-354 Solution (Extemporaneous)**	**CVL-354 Capsules**	**Placebo**
Type	Drug	Drug	Drug
Dose Formulation	Oral solution	Capsule	Matching oral solution vehicle (without active pharmaceutical ingredient) Matching capsule filled with silicified microcrystalline cellulose
Unit Dose Strength(s)	0.5 mg/10 mL – 500 mg/10 mL	5 mg, 25 mg, 100 mg	Not applicable
Dosage Level(s)	Part A Cohort 1 0.5, 1.5 mg, 5 mg, or 15 mg Part A Cohort 2 45 mg, 90 mg, 150 mg, or 200 mg Part B Cohort 1 10 mg QD	Part A Cohort 3 50 mg Part B Cohorts 2-5 25 mg QD, 50 mg QD, 100 mg QD, or 150 mg QD	Not applicable
Route of Administration	Oral	Oral	Oral
Sourcing	CVL-354 capsules will be provided by Cerevel. The CVL-354 oral solution preparation will be supplied by Cerevel and the solution will be prepared by the pharmacy of the trial site.		
Packaging and Labeling	Capsule IMP provided by Cerevel will be in 60 cc HDPE bottles and should be stored in accordance with the drug label. The CVL-354 API for oral solution provided by Cerevel and oral solution will be supplied in amber-glass bottles. The bottles will be labeled according to local regulatory requirements and language. Oral solution will be prepared before dosing by the pharmacy of the trial site.		

Abbreviations: API=active pharmaceutical ingredient; HDPE=high-density polyethylene; IMP=investigational medicinal product; QD=once daily.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit (original shipment and/or moving of IMP supply from 1 office or facility to another within the site's network) for all IMP received and any discrepancies are reported and resolved before use of the IMP.

CVL-354 and placebo oral dosing solution will be prepared by site staff and details of the dose preparation requirements will be provided by Cerevel in a separate extemporaneous dispensing record. Prepared doses will be provided in unit dose containers and labeled in accordance with appropriate regulations and the investigator's site labeling requirements.

Only participants enrolled in the trial may receive IMP and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the preparation, handling, storage, accountability, and disposition of IMP are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Participant 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.

Further instructions on replacement participants are available in the Operations Manual.

6.3.2. 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.

6.4. Trial Treatment Compliance

The time and dose of each IMP administration, along with information on any missed or inappropriately administered dose, will be recorded in source documents and the eCRF. Compliance will be ensured by a hand and mouth check during the oral dosing administration.

6.5. Prior and Concomitant Therapy

All prescription and over-the-counter medications are prohibited from 28 days prior to first dose of IMP through the end of the trial (as defined Section 4.5) with the exception of acetaminophen (maximum total daily dose of 1 g) and topical steroid use as needed for treatment of an AE. Use of herbal medications, vitamins, and supplements is also prohibited during the trial.

The investigator will record all medications and therapies taken by the participant for treatment of an AE until the end of the trial. The following information will be recorded in the eCRF: medication, indication, dose, frequency, route, start date, and end date.

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

6.6. Dose Modification

Guidance for dose escalation/stopping rules is provided in Section 4.4.

The decision to proceed to the next dose level of CVL-354 in successive cohorts/periods will be made by the SRT based on a full review of the safety, tolerability, and preliminary PK data obtained from the completed prior doses.

If ongoing data surveillance during the treatment interval reveals consistent notable AEs or safety concerns at a dose, which are determined to be attributable to the drug treatment, continued dosing within the cohort will be temporarily halted and no participants will be dosed until full safety review can take place to determine if dose modification or termination of the cohort are appropriate.

6.7. Intervention after the End of the Trial

There will be no provision of CVL-354 for participants after they complete or discontinue treatment in this trial.

7. DISCONTINUATION OF TRIAL TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Trial Treatment

After treatment assignment, a participant may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a participant or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. If IMP is permanently discontinued, the participant will be encouraged to remain in the trial for the evaluations at safety follow-up. See the Schedule of Assessments (Section 1.3) for data to be collected at the time of discontinuation of IMP and follow-up and for any further evaluations that need to be completed.

The IMP may be discontinued for any of the following reasons listed below:

- Adverse event
- Protocol deviation
- Noncompliance with study schedule
- Withdrawal by participant
- Physician decision

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

7.2. Discontinuation of Trial

7.2.1. Discontinuation of Entire Trial

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

7.2.2. Discontinuation of Individual Site

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

7.2.3. Individual Participant Discontinuation From the Trial

All participants have the right to withdraw their consent from further participation in the trial at any time without prejudice. Participants cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a participant's participation in the trial at any time if medically necessary.

At the time of discontinuing from the trial, if possible, an early termination visit should be conducted. See the Schedule of Assessments (Section 1.3) for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the IMP and from the trial at that time.

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

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

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a participant's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the participant and the integrity of the trial. A participant may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should determine if the participant can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only participants who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.3. Procedures to Encourage Continued Trial Participation

In all cases of impending consent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) with the participant their options of continuing in the trial. The

investigator should ensure understanding and documentation of the reasons for the participant's desire to withdraw consent.

7.4. Lost 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.

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

- The site personnel must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the trial.

8. TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the Schedule of Assessments (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue trial intervention.

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

8.1. Screening and Baseline Assessments

All screening evaluations must be completed and reviewed to confirm that potential 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.

[redacted]

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Assessments (Section 1.3).

- If the initiation of assessment (eg, vital sign measurement) is within 10% before or after the nominal time point (eg, 6 minutes before or 6 minutes after a 60-minute sample) and within ±6 minute window for early time points (0.5 hour and 1 hour), this will not be considered a protocol deviation, as long as the exact time of sampling is captured in the source documents.
- For the assessments described below, when multiple procedures are scheduled on the same visit, the following chronology of events should be adhered to, where possible:
  - ECGs
  - Vital sign measurements
  - Blood specimen collection
  - C-SSRS
  - Physical and neurological examinations
  - Other procedures (eg, concomitant medications, AEs) may be obtained as convenient relative to the procedures listed above before or after blood specimen collection

During the MAD portion of the trial, the preferred order of assessments on intensive PK sampling days (Days 1 and 14) is provided in Table 4.

8.3.1. Height and Weight

Height will be measured at Screening only, with a stadiometer, measuring stick, or tape.

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

- Scales should be calibrated and reliable; scales should be at zero just prior to each participant's weigh-in session
- A participant should void prior to being weighed, if possible, and be minimally clothed (ie, no shoes or heavy overgarments)
- Weight should be recorded before a participant's meal

8.3.2. 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 limited 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.

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

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

8.3.3. Vital Sign Measurements

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 [Section 1.3]), 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).

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

Further details on taking vital sign measurements are provided in the appropriate trial specific manuals.

8.3.4. Electrocardiograms

This section describes the procedures for continuous ECG recordings and standard 12-lead ECGs.

8.3.4.1. 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 (Section 1.3). Electrocardiograms will be extracted from the continuous recording by a central ECG service (note: these data are not required for dose escalation decision-making). Participants should be resting quietly in a supine position for at least 10 minutes before the nominal ECG extraction time points and 5 minutes after each extraction time point without any significant environmental distractions (noise, loud music, TV, computer or phone use, etc). Holter leads will be checked for proper connectivity prior to each time point.

Procedures to limit the sources of electrocardiographic variability will be used throughout the trial and will include the following: staff training to ensure proper recording technique, standardized lead placement including ink marks on the skin to allow for exact duplication of lead position, shaving lead placement sites prior to lead placement and controlling the timing of ECG assessments relative to phlebotomy, sleep, activity, and meals.

Instructions regarding the collection and transfer of continuous ECG data are detailed in a separate manual.

8.3.4.2. Standard 12-Lead Electrocardiograms

Electrocardiogram recordings will be obtained after the participant has been supine and at rest for approximately 3 minutes. Additional 12-lead ECGs may be obtained at the investigator's discretion and should always be obtained in the event of an early termination. The ECG results will be evaluated at the investigational site to determine the participant's eligibility, to monitor safety during the trial and dose escalation decisions. The principal investigator (or qualified designee) will review, sign, and date each ECG reading, noting whether or not any abnormal results are of clinical significance. The ECG will be repeated if any results are considered to be clinically significant. Any clinically relevant changes occurring during the trial will be recorded in the AE section of the eCRF. Additional guidance on collection of ECGs will be provided in the Operations Manual.

At Screening, triplicate 12-lead ECGs are required to assess participant eligibility. A triplicate set of ECGs is 3 consecutive ECGs collected 1 to 2 minutes apart over a 5-minute period. If, during screening, according to the investigator's judgment, any abnormal ECG finding is deemed medically significant (impacting the safety of the participant or the interpretation of the trial results) or meets an exclusion criterion (see Section 5.2), the participant should be excluded from the trial. The central ECG service will provide the QTcF corrections and average of the 3 ECGs performed.

At all other specified time points in the Schedule of Assessments (Section 1.3) where an ECG recording must be performed, only a single ECG is required.

Exclusion criteria for screening do not apply as mandatory discontinuation criteria for participants who are already randomized. A repeat ECG should be performed in case of any clinically significant abnormality that is identified in a randomized participant during the

treatment period and, in these cases, the medical monitor should be consulted on the appropriateness of the participant continuing in the trial.

8.3.5. Clinical Safety Laboratory Assessments

See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the medical monitor notified.

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the Schedule of Assessments.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Suicidality will be monitored during the trial using the C-SSRS. This semi-structured interview was originally developed to evaluate the link between antidepressants and suicidal behavior and ideation in youth and adverse events from pediatric clinical trials (Posner et al, 2011). It was designed to quantify the severity of suicidal ideation and behavior. Trial personnel administering the C-SSRS must have completed the appropriate training and have valid certification. 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 exclusion criteria based on the C-SSRS are provided in Section 5.2.

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.

8.4. Adverse Events and Serious Adverse Events

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or trial procedures, or that caused the participant to discontinue IMP (see Section 7)

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be recorded from the first dose of IMP until follow-up contact at the time points specified in the Schedules of Assessments (Section 1.3).

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.4.4. Regulatory Reporting Requirements for SAEs/AESIs

Prompt notification by the investigator to the sponsor regarding an SAE/AESI is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor will

comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

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

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review, acknowledge, and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

8.4.5. Pregnancy

Details of all pregnancies in female partners of male participants will be collected after the start of IMP and until the final contact.

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

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

8.4.6. Adverse Events of Special Interest

All AESIs should be reported according to the procedures and timelines for SAEs (see Section 10.3.4). Detailed narratives will be written for any participant who develops an AESI.

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 Guidance for Industry, 2017).

8.5. Treatment of 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.

There is no specific antidote for overdose with CVL-354. In the event of an overdose, treatment should consist of general supportive measures. The investigator should complete the following:

1. Contact the medical monitor immediately
2. Closely monitor the participant for any AE/SAE and clinically significant vital signs, ECG, or laboratory abnormalities. Additional safety procedures may need to be performed at the investigator's discretion.
3. Document the quantity of the excess dose as well as the duration of the overdose (if multiple time points) in the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

This section includes descriptions of the blood and urine samples obtained for PK assessments, including metabolite scouting.

All PK samples should be obtained at the exact nominal time relative to dosing. Samples obtained within 10% of the nominal time point (eg, within 6 minutes of a 60-minute sample) will not be considered a protocol deviation, as long as the exact time of sampling is captured in the source documents.

Plasma and urine samples 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. Plasma samples from this trial may be stored up to 1 year after completion of the clinical study report (CSR).

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.

Plasma concentration data from this trial combined with other data may also be used to build and/or update a population PK model for CVL-354 for the purpose of further characterizing the PK or PK/pharmacodynamic behavior of the compound. Any population PK assessment will be described in a separate report.

Statistical analyses of PK parameters are briefly described in Section 9.4.3.

8.6.1. Blood for Pharmacokinetic Analysis of CVL-354

During each PK sampling time point, a 4 mL blood sample will be collected into appropriately labeled tubes at the times specified in Section 1.3 (Schedule of Assessments). The blood samples will be used to provide approximately 2 × 1 mL plasma samples (1 primary and 1 backup) for quantitation of CVL-354 in plasma.

The PK backup samples may also be used for exploratory metabolite scouting work.

8.6.2. Urine for Analysis of CVL-354 (MAD Portion Only)

On Day 14 in the MAD portion of the trial, urine will be collected at times specified in Section 1.3 (Schedule of Assessments). Full 0-24 hour urine samples will be collected, and corresponding total urine volume will be recorded. The samples will be split into 2 aliquots. Amount of parent excreted into the 24-hour cumulative urine samples will be determined for renal clearance calculation.

The urine samples collected for analysis of CVL-354 may also be used for exploratory urine metabolite scouting work.

8.7. Pharmacodynamic Assessments

Pharmacodynamics are not evaluated in this trial.

8.8. Pharmacogenomics

Pharmacogenomics are not evaluated in this trial.

[redacted]

8.10. Future Biospecimen Research

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite

variation patterns of participants who respond well and those who respond poorly to treatment may help to better define the most appropriate group of participants in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them at Cerevel makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, pharmacodynamics, tolerability, or safety not anticipated prior to the beginning of this trial.

Future biospecimen research samples will be collected from participants who provide additional consent specifically for this sample collection. Research performed on these samples may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial). The objective of collecting these specimens is to explore and identify biomarkers that inform the scientific understanding of diseases or their therapeutic treatments.

8.11. Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

No formal hypothesis testing is planned for this trial.

9.2. Sample Size Determination

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 due to COVID-19 or other factors, Cerevel may extend enrollment in order to achieve trial objectives.

9.3. Populations for Analyses

The analysis sets that are defined for this trial are described in Table 11.

Table 11: 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.

9.4. Statistical Analyses

9.4.1. General Considerations

The key analyses for the primary and secondary endpoints are described in this section. Full details of these analyses will be included in the statistical analysis plan (SAP), which will be developed and finalized before database lock. Descriptive statistical methods will be used to summarize the data from this trial. All available data for randomized participants will be listed by participant. Separate analyses will be performed for each part of the trial (Part A SAD, Part A food effect, Part B MAD).

9.4.2. Safety Analyses

Treatment-emergent adverse events, including AEs potentially related to abuse, will be coded according to MedDRA and summarized by treatment, system organ class, and preferred term. Further summaries will be done by seriousness, severity, relationship to IMP, and dose at the time of onset.

Other safety endpoints will be summarized with descriptive statistics by treatment and timepoint, including vital sign measurements, ECG, clinical laboratory assessments and suicidality monitored during the trial using C-SSRS.

9.4.3. Pharmacokinetic Analyses

All PK exposure parameters (eg, C_{max}, AUC) will be summarized by dose, where applicable, using descriptive statistics including the arithmetic mean, median, standard deviation, coefficient of variation, minimum and maximum values, Q1, Q3, and geometric mean.

For food effect assessment, the single dose of CVL-354 administered in fasted state is the reference treatment and the single dose of CVL-354 administered in fed state is the test treatment. Natural log-transformed dose-normalized AUC_{inf}, AUC_{last}, and C_{max} (for CVL-354) will be analyzed using a mixed effect model with sequence, period, and fast/fed status as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (test-reference) and corresponding 90% CIs will be obtained from the model. Then they will be exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CIs for the ratios.

Additional detail on the PK analysis will be provided in the SAP.

[redacted]

9.4.5. Interim Analyses

No interim analyses are planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical trials (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the participant and answer all questions regarding the trial.

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

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

Participants must be reconsented to the most current version of the ICF(s) during their participation in the trial.

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

10.1.4. Data Protection

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

The participant must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant and outlined in the ICF.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Trial Data

Cerevel fulfills its commitment to publicly disclose clinical trial results through posting trial results on ClinicalTrials.gov, the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

In all cases, trial results are reported by Cerevel in an objective, accurate, balanced, and complete manner and are reported regardless of trial outcome or the country in which the trial was conducted.

Clinical trial US Basic Results are posted on Clinicaltrials.gov for all Cerevel-sponsored interventional trials conducted in participants that evaluate the safety and/or efficacy of a Cerevel product, regardless of the geographical location in which the trial is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.5 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

Cerevel posts European Union (EU) Basic Results on EudraCT for all Cerevel-sponsored interventional trials that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date as defined in Section 4.5 for trials in adult populations or within 6 months of the primary completion date for trials in pediatric populations.

10.1.6. Data Quality Assurance

All participant data relating to the trial will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

The investigator must permit trial-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for the longest of the following periods:

- At least 2 years after the date on which approval to market the drug is obtained (or if IMP developments is discontinued, the date regulatory authorities were notified of discontinuation)
- At least 3 years after the sponsor notified the investigator that the final report has been filed with regulatory authorities
- A longer period if required by local regulations or institutional policies

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

10.1.7. Source Documents

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

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request

previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

10.1.8. Trial and Site Closure

The sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further trial treatment development

10.1.9. Publication Policy

The results of this trial may be published or presented at scientific meetings at the sponsor's discretion.

The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter trials only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 12 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

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.

Table 12: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	Platelet count RBC count Hemoglobin Hematocrit Prothrombin time and INR MCH MCHC MCV	WBC count with differential (absolute and %): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Chemistry	BUN Creatinine Glucose Albumin Cholesterol (total, HDL, LDL) Triglycerides Uric acid Potassium Sodium Calcium Bicarbonate Chloride Magnesium Phosphorus	ALT AST Alkaline phosphatase GGT CPK Total bilirubin and direct bilirubin Total protein
Routine Urinalysis	Urine dipstick with reflex to microscopy if positive finding Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick	
Additional Required Tests	Serum Cystatin-C Urine β-2-microglobulin	
Other Screening Tests	A confirmatory FSH is required for post-menopausal women. Breathalyzer or blood/urine test for alcohol and urine drug screen (including cotinine) Serology (HIV, HBsAg, HBcAb, Hepatitis C Ab) SARS-CoV2 testing Thyroid-stimulating hormone with reflex to free T4 if abnormal	

Abbreviations: Ab=antibody; Ag=antigen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CPK=creatine phosphokinase; FSH=follicle stimulating-hormone; GGT=gamma glutamyl transferase; HBc=hepatitis B core; HBsAg=hepatitis B surface; HDL=high-density lipoprotein; INR=international normalized ratio; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SARS-CoV2=severe acute respiratory syndrome coronavirus 2; T4=thyroxine; WBC=white blood cell.

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

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

10.3.1. Definition of AE

Table 13: Definition of AE

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

Table 14: Events Meeting the AE Definition

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after trial treatment administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical manifestations of a suspected drug-drug interaction. • Signs, symptoms, or the clinical manifestations of a suspected overdose of either trial treatment or a concomitant medication.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

Table 15: Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose in the view of either the investigator or sponsor, results in any of the following outcomes:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a

complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias.

10.3.3. Recording and Follow-Up of AEs and/or SAEs/AESIs

Table 16: Recording and Follow-Up of AEs and/or SAEs/AESIs

AE and SAE/AESI Recording

• When an AE/SAE/AESI occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.
• The investigator will then record all relevant AE/SAE/AESI information in the eCRF.
  ○ Nonserious AEs must be recorded on the AE eCRF with the current status noted. All nonserious events (that are not considered AESIs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).
  ○ If updated information (eg, resolved status) on SAE/AESI status becomes available after a participant's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor according to the appropriate reporting procedures.
  ○ The investigator will follow SAEs/AESIs until the events are resolved, stabilized, or the participant is lost to follow-up or has died. Resolution means that the participant has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the participant's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the participant is lost to follow-up, or has died.
  ○ Any new SAEs/AESIs reported to the investigator that occur after the last scheduled contact and are determined by the investigator to be related to the use of the IMP, should be reported to the sponsor. This may include SAEs/AESIs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs/AESIs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the participant is lost to follow-up or has died.
• It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE/AESI eCRF page.
• There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

Assessment of Severity

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE v5.0; https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)

Adverse events not listed by the NCI-CTCAE will be graded according to the criteria defined below.

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the participant.

Note: An instrumental activity of daily living refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE/AESI.
- The investigator will assess the relationship as either of the following:
  - **Related**: An AE will be considered "related" to the use of the IMP if there is evidence to suggest a reasonable possibility of a causal relationship between the IMP and the AE.
  - **Not Related**: An AE will be considered "not related" to the use of the IMP if there is no plausible causal relationship between the IMP and the AE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE/AESI, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/AESI and has provided an assessment of causality.
- There may be situations in which an SAE/AESI has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE/AESI data to the sponsor or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE/AESI follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Table 17: Follow-Up of AEs and SAEs/AESIs

Follow-Up of AEs and SAEs/AESIs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE/AESI as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE/AESI data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs and AESIs

Table 18: SAE/AESI Reporting to the Sponsor or Designee via an Electronic Data Collection Tool

SAE/AESI Reporting to the Sponsor or Designee via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE/AESI to the sponsor or designee will be the electronic data collection tool. • The site will enter the SAE/AESI data as soon as it becomes available within 24 hours of awareness. • If the electronic data collection tool is unavailable, then the site will use the paper SAE/AESI form (see next section). • After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE/AESI from a trial participant or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken off-line, then the site can report this information on the paper SAE/AESI form (see next section) or to the sponsor or designee by telephone.

Table 19: SAE/AESI Reporting to the Sponsor or Designee via Paper Form (if needed)

SAE/AESI Reporting to the Sponsor or Designee via Paper Form
• If the electronic data collection tool is unavailable, then the site will use the paper SAE/AESI form. The SAE or AESI paper form should be used to electronically transmit this information to the sponsor or designee. • Contacts for electronic transmission of the paper SAE/AESI form are provided in the Operations Manual. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE or AESI data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the appropriate SAE or AESI form within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

10.4.1.1. Highly Effective Form of Contraception (Failure Rate <1%)

A highly effective form of contraception (failure rate of <1%) is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

10.4.1.2. Acceptable Birth Control Methods (Failure Rate >1% per Year)

Acceptable birth control methods that result in a failure rate of more than 1% per year include the following:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide*
- Cap, diaphragm or sponge with spermicide*

*A combination of male condom with a cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered acceptable but is not a highly effective birth control method.

10.4.1.3. Contraception and Pregnancy Avoidance Procedures

The following definitions apply for contraception and pregnancy avoidance procedures:

A woman is considered a woman of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral oophorectomy, and complete salpingectomy.

In this trial, postmenopausal state is defined as no menses for at least 12 consecutive months without an alternative medical cause in addition to an FSH level >40 IU/mL.

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

10.4.2. Collection of Pregnancy Information

10.4.2.1. Male Participants With Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this trial. This applies only to male participants who receive IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 12 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5. Appendix 5: Future Biospecimen Research

Use/Analysis of Deoxyribonucleic Acid

- Genetic variation may impact a participant's response to trial treatment, susceptibility to, and severity and progression of disease. Variable response to trial treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.
- DNA samples will be used for research related to CVL-354 or major depressive disorder and related diseases. They may also be used to develop tests/assays including diagnostic tests related to CVL-354 and/or interventions of this drug class and major depressive disorder. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- There are no planned analyses of DNA samples. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-trial assessment of genetic factors involved in the response to CVL-354 or IMPs of this class to understand trial disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate trial summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on CVL-354 or trial treatments of this class or major depressive disorder continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Kidney Safety for First-in-Human Trial

10.6.1. Elevations in Serum Creatinine

Serum creatinine (SCr) level may be affected by age, muscle mass, diet, activity, and tubular transporter activity, and SCr elevations can occur without impacting overall kidney function. Nonetheless, kidney function is closely monitored using blood urea nitrogen (BUN), serum creatinine, and urinalysis.

Table 20: Monitoring of Abnormal Kidney Function Tests

Lab Result	Action
Serum creatinine > ULN	Repeat for confirmation approximately 1 hour after drinking a large glass (~250 mL) of water
Urinalysis (UA) • ≥ +1 protein • + glucose • Active urine sediments (eg, hematuria, pyuria, casts [WBC, RBC, tubular epithelial, or granular])	Repeat for confirmation approximately 1 hour after drinking a large glass (~250 mL) of water

Abbreviations: RBC=red blood cell; ULN=upper limit of normal; WBC=white blood cell.

Contact the medical monitor if the repeat confirmation SCr >1.2× ULN or urine continues to have proteinuria, glucosuria, or active urine sediments.

10.6.2. Potential Cases of Acute Kidney Injury

Abnormal values in SCr that meet the KDIGO 2012 (KDIGO, 2012) criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury (AKI) and should be regarded as important medical events.

- Increase in SCr ≥0.3 mg/dL (26.5 mmol/L) within 48 hours
- Increase in SCr ≥50% from baseline
- Urine volume output <0.5 mL/kg/h for 6 hours

The baseline is defined as the most recent SCr prior to randomization/dosing.

10.6.2.1. Marked Elevations in Serum Creatinine

For increases of SCr ≥50% relative to the participant baseline:

- Temporarily withhold IMP until a repeat SCr as soon as practically feasible, preferably within 24 hours of awareness.
- If the second measurement of SCr is still ≥50% from the participant baseline, IMP should be permanently discontinued.
- Adequate, immediate, supportive measures should be taken if AKI is suspected.

10.6.2.2. Evaluation of Potential Cases of AKI

Participants suspected of having potential AKI should promptly (as soon as practically feasible, preferably within 24 hours of awareness) have an evaluation, which includes a detailed medical history, physical examination, and laboratory tests.

Laboratory tests include, at a minimum:

- Serum:
  - BUN, creatinine, sodium, potassium, chloride, bicarbonate, phosphorus, and calcium
  - Creatine kinase and cystatin-C
- Urine: Dipstick, microscopic examination, indices, and β-2-microglobulin.

Consider consultation with a nephrologist.

Close daily observation of the participant and assessment of kidney function should be continued until the SCr elevations and the associated abnormal UA results return to baseline or normalize.

10.6.2.3. Stopping Criteria for the Cohort

Further dosing with IMP will be stopped for the cohort if ≥2 healthy participants within a given dose level meet the criteria established in Section 10.6.2.1 and permanently discontinued IMP.

10.6.2.4. Stopping Criteria for Dose Escalation

Serum creatinine may be potentially impacted by OCT2, MATE1, and MATE2K transporter inhibition by test drugs. Serum cystatin-C, which is not affected by the above transporters, may be used to monitor renal function. If ≥2 healthy participants within the same dosing level/cohort have a decline in eGFR cystatin-C ≥25% from baseline using the CKD-EPI 2012 formula for cystatin-C (Inker et al, 2012), then dose escalation stops.

10.7. Appendix 7: Abbreviations

Abbreviation	Definition
ACLS	Advanced Cardiovascular Life Support
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
APMP	Abuse Potential Monitoring Plan
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BUN	blood urea nitrogen
C_{avg}	average plasma concentration
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease-2019
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DAMGO	[D-Ala2, N-MePhe4, Gly-ol] enkephalin
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EU	European Union
F	bioavailability
f_a	fraction absorbed
f_h	fraction escaping hepatic metabolism
f_m	fraction metabolized
FSH	follicle stimulating-hormone
f_u	fraction unbound
GCP	Good Clinical Practice
HED	human equivalent dose
ICF	informed consent form
ICH	International Council for Harmonisation
ID_{50}	dose required for 50% inhibition

Abbreviation	Definition
IMP	investigational medicinal product
KDIGO	Kidney Disease: Improving Global Outcomes
IRB	Institutional Review Board
K_i	inhibition constant
KOR	kappa opioid receptor
MAD	multiple ascending dose
MATE	multidrug and toxin extrusion protein
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MOR	mu opioid receptor
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
OCT	organic cation transporter
PK	pharmacokinetic(s)
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SRT	Safety Review Team
$t_{1/2}$	apparent terminal half-life
T_{max}	time of maximum observed concentration
UA	urinalysis
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
[redacted]	[redacted]

10.8. Appendix 8: Protocol Amendment History

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

Amendment: Protocol Version 2.0 (16 Sep 2021)

[redacted]

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints	Added AEs potentially related to abuse to TEAE endpoint (SAD and MAD tables) Added clarification that the following PK endpoints are for Day 14: CL/F; V_Z/F; PTR; Rac, C_{max}; Rac, AUC; $t_{1/2}$; and renal clearance (MAD table)	To align with addition of such events to Section 8.4.6 (Adverse Events of Special Interest) Data required for calculation of these endpoints are only collected at steady state
1.1 Synopsis 4.2 Scientific Rationale for Trial Design	Deletion of parallel-group language (MAD)	Internal consistency about sequential dosing of cohorts
1.2 Schema 4.1.1 Single Ascending Dose - Part A	Figure 1 and Table 6: Revised CVL-354 dosing paradigms for Cohort 2	To align with proposed doses as presented in Table 7
1.2 Schema	Figure 1: Randomization symbol (R) moved from beginning of Treatment Phase to text boxes for each cohort Figure 1, Figure 2: Changed text boxes for cohorts in Treatment Phase from parallel to staggered	To reflect randomization to sequence rather than to cohort To more accurately depict sequential dosing of cohorts
1.3 Schedule of Assessments	Table 1 (SAD), Table 2 (MAD): Revised tables to indicate that medical occurrences before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history and that AEs will be recorded from the first dose of IMP SAD: Changed limited physical and neurological examinations to full examinations at each Check-out (or ET) MAD: Changed limited physical and neurological examinations to full examinations on Day 7 and Day 17/ET	To clarify recording timeframes relative to informed consent and first dose of IMP, including for replacement participants To provide additional opportunities to potentially identify AEs related to the gastrointestinal or central nervous systems, reflecting the addition of such events to Section 8.4.6 (Adverse Events of Special Interest)

Section # and Name	Description of Change	Brief Rationale
	Table 1 (SAD): Changed "Check-in Period 1" to "Initial Check-in" and "Check-in Periods 2-4" to "Subsequent Check-ins" Moved Randomization from Initial Check-in (Day -1) to Predose and added footnote that it is applicable to Period 1 only	To clarify procedures for replacement participants, including recording of medical and/or psychiatric history and AEs To allow for completion of all assessments required for determination of eligibility
	Table 2 (MAD): Day 2: Added C-SSRS Day 1: Removed blood sample for safety laboratory Day 10: Added footnote to respiratory rate and temperature	To obtain additional data for monitoring of suicidal ideation and behavior To correct errors in the previous version of the protocol
	Table 2, Table 3 (MAD): Revised tables to reflect addition of [redacted] on Day 1	[redacted]
	[redacted]	[redacted]
4.2 Scientific Rationale for Trial Design	Added a statement referring to development of an APMP for the trial	To enhance understanding of the safety profile of CVL-354 and to provide guidance to site personnel for identification and reporting of AEs potentially related to abuse
4.4 Guidance for Dose Escalation/Stopping Rules	Revised and reorganized content to summarize potential SRT actions following review of data and to further define criteria for which the SRT may consider stopping further dose escalation Added a paragraph that summarizes the process and the potential impact on dose escalation if an SAE were to occur during active treatment	To clarify actions and more specifically define AEs or other abnormalities that would be considered in the determination of MTD

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion Criterion #11: Added "at Screening" to criterion for estimated glomerular filtration rate	To clarify timeframe for determination of eligibility
	Exclusion Criterion #13: Moved symptomatic orthostatic dizziness text to a separate bullet within the criterion	To separate the text from the bullet that defines orthostatic hypotension
5.2 Exclusion Criteria 5.3.1 Meals and Dietary Restrictions	Exclusion Criterion #16: Increased duration of abstention from 48 hours prior to Day -1 to 7 days prior to Day -1 Increased duration of abstention from 48 hours prior to Day -1 to 7 days prior to Day -1	To ensure minimal to no interaction with IMP
5.4 Screen Failures	Deleted language about SAEs	To align with changes to language about AE recording starting from first dose of IMP
6.3.1 Participant Assignment to Treatment	Revised language to specify that replacement participants in Part A (SAD) will be randomized to the same sequence and replacement participants in Part B (MAD) will be randomized to the same treatment	To reflect differences in trial design between SAD (randomization to sequence) and MAD (randomization to treatment)
6.3.2 Blinding	Added instructions in the event of emergency unblinding	To clarify unblinding procedures in case of emergency
8.4.1 Time Period and Frequency for Collecting AE and SAE/AESI Information	Clarified that AEs will be recorded from the first dose of IMP and medical occurrences that begin before the start of IMP dosing but after obtaining informed consent will be recorded as medical and/or psychiatric history	To confirm timeframes for medical history and AE recording relative to informed consent and first dose of IMP
8.4.6 Adverse Events of Special Interest	Detailed narratives, rather than brief narratives, will be written for any participant who develops an AESI Revised AESI definitions as follows: Added Grade 2 moderate AEs related to the gastrointestinal system Added Grade 2 moderate AEs related to the central nervous system Added AEs potentially related to abuse (followed by summary of key aspects of the APMP)	To enhance understanding of the safety profile of CVL-354 and to provide guidance to site personnel for identification and reporting of AEs potentially related to abuse
8.6 Pharmacokinetics	Added a sentence regarding possible retention of samples for evaluation of bioanalytical methods and metabolites for up to 1 year after CSR completion	Updated as per sponsor's policy on PK sample management

Section # and Name	Description of Change	Brief Rationale
9.4.2 Safety Analyses	Added AEs potentially related to abuse	To align with addition of such events to Section 8.4.6 (Adverse Events of Special Interest)
10.3.3 Recording and Follow-Up of AEs and/or SAEs/AESIs	Deleted the following language: ...that are identified at any time during the trial... ...having been identified throughout the trial...	To align with changes to language about AE recording starting from first dose of IMP
10.3.3 Recording and Follow-Up of AEs and/or SAEs/AESIs 10.3.4 Reporting of SAEs and AESIs	Addition of "AESI" or "AESIs" to section headings and throughout tables within the respective sections	To correct inadvertent omission in the previous version of the protocol
11 REFERENCES	Added new reference: FDA Guidance for Industry, 2017	To reflect inclusion of citation in content regarding abuse potential monitoring added to Section 8.4.6 (Adverse Events of Special Interest)
Overall	General grammatical and wording corrections/clarifications made throughout protocol	To correct minor errors from the previous version of the protocol

Abbreviations: AE=adverse event; AESI=adverse event of special interest; APMP=Abuse Potential Monitoring Plan; AUC=area under the concentration-time curve; CL/F=apparent clearance of drug from plasma; C_{max}=maximum plasma concentration; CSR=clinical study report; C-SSRS=Columbia-Suicide Severity Rating Scale; [redacted]; ET=Early Termination; IMP=investigational medicinal product; MAD=multiple ascending dose; MTD=maximum tolerated dose; PK=pharmacokinetic; PTR=peak-to-trough ratio; R=randomization; Rac=accumulation ratio; SAD=single ascending dose; SAE=serious adverse event; SRT=Safety Review Team; $t_{1/2}$= apparent terminal half-life; TEAE=treatment-emergent adverse event; V_Z/F= apparent volume of distribution during terminal phase.

11. REFERENCES

Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6:369-88.

Bai S, Guo W, Feng Y, et al. Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2020;91(1):21-32.

[redacted]

Cahill CM, Taylor AM, Cook C, Ong E, Morón JA, Evans CJ. Does the kappa opioid receptor system contribute to pain aversion?. Front Pharmacol. 2014;5:253.

Carlezon WA Jr, Béguin C, DiNieri JA, et al. Depressive-like effects of the kappa-opioid receptor agonist salvinorin A on behavior and neurochemistry in rats. J Pharmacol Exp Ther. 2006;316(1):440-7.

Carlezon WA Jr, Krystal AD. Kappa-opioid antagonists for psychiatric disorders: from bench to clinical trials. Depress Anxiety. 2016;33(10):895-906.

[redacted]

FDA. Guidance for industry: assessment of abuse potential of drugs. 2017. Accessed September 13, 2021. Available from: https://www.fda.gov/media/116739/download

FDA. Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. 2005. Accessed March 11, 2021. Available from: https://www.fda.gov/media/72309/download

Gauthier G, Mucha L, Shi S, Guerin A. Economic burden of relapse/recurrence in patients with major depressive disorder. J Drug Assess. 2019;8(1):97-103.

[redacted]

Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry. 2018;75(4):336-46.

Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20-9.

Jaffe DH, Rive B, Denee TR. The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study. BMC Psychiatry. 2019;19(1):247.

Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatr Clin North Am. 2002;25(4):685-98.

Khan A, Brown WA. Antidepressants versus placebo in major depression: an overview. World Psychiatry. 2015;14(3):294-300.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1-138.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Lowe SL, Wong CJ, Witcher J, et al. Safety, tolerability, and pharmacokinetic evaluation of single- and multiple-ascending doses of a novel kappa opioid receptor antagonist LY2456302 and drug interaction with ethanol in healthy subjects. J Clin Pharmacol. 2014;54(9):968-78.

Machado M, Iskedjian M, Ruiz I, Einarson TR. Remission, dropouts, and adverse drug reaction rates in major depressive disorder: a meta-analysis of head-to-head trials. Curr Med Res Opin. 2006;22(9):1825-37.

McIntyre RS, O'Donovan C. The human cost of not achieving full remission in depression. Can J Psychiatry. 2004;49(3)(suppl 1):S10-S16.

Möller HJ. Outcomes in major depressive disorder: the evolving concept of remission and its implications for treatment. World J Biol Psychiatry. 2008;9(2):102-14.

[redacted]

Mulder RT, Frampton CM, Luty SE, Joyce PR. Eighteen months of drug treatment for depression: predicting relapse and recovery. J Affect Disord. 2009;114(1-3):263-70.

Naganawa M, Dickinson GL, Zheng MQ, et al. Receptor occupancy of the κ-opioid antagonist LY2456302 measured with positron emission tomography and the novel radiotracer ^{11}C-LY2795050. J Pharmacol Exp Ther. 2016;356(2):260-6.

[redacted]

Oluboka OJ, Katzman MA, Habert J, et al. Functional recovery in major depressive disorder: providing early optimal treatment for the individual patient. Int J Neuropsychopharmacol. 2018;21(2):128-44.

Pfeiffer A, Brantl V, Herz A, Emrich HM. Psychotomimesis mediated by kappa opiate receptors. Science. 1986;233(4765):774-6.

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.

[redacted]

Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163(11):1905-17.

[redacted]

Sobocki P, Jönsson B, Angst J, Rehnberg C. Cost of depression in Europe. J Ment Health Policy Econ. 2006;9(2):87-98.

[redacted]

Thase ME, Haight BR, Richard N, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. J Clin Psychiatry. 2005;66(8):974-81.

Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163(1):28-40.

Zajecka JM, Stanford AD, Memisoglu A, Martin WF, Pathak S. Buprenorphine/samidorphan combination for the adjunctive treatment of major depressive disorder: results of a phase III clinical trial (FORWARD-3). Neuropsychiatr Dis Treat. 2019;15:795-808.

CLINICAL PROTOCOL PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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: CVL-354-1001

Compound Number: CVL-354

Trial Phase: 1

Sponsor Name: Cerevel Therapeutics, LLC

Legal Registered Address: 222 Jacobs Street, Suite 200, Cambridge, MA 02141 United States

Version 3.0: 25 May 2022

I, the undersigned principal investigator, have read and understand the protocol and agree that it contains the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

Principal Investigator Printed Name

Principal Investigator Signature

Date (DD MMM YYYY)