PROTOCOL

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects

Short Title: Phase 1 SAD/MAD Study of CVN766

Sponsor:	Cerevance Gamma, Inc. One Marina Park Drive, Suite 1410 Boston, MA 02210
Study Number:	CVN766-101
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Compound:	CVN766
Protocol Version:	1.0
Date:	24 September 2021

NCT Number: NCT05105243
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	TBD
Medical Monitor (carries overall responsibility for the conduct of the study)	TBD
Responsible Medical Officer (medical advice on protocol and compound)	[redacted], MD

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations

SIGNATURES

Approved by:

Signature [redacted] Date 24-SEP-2021

[redacted] MD

Medical Monitor

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation, E6 GCP: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 9.9 of this protocol
- Terms outlined in the Clinical Study Site Agreement
- Appendix B – Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

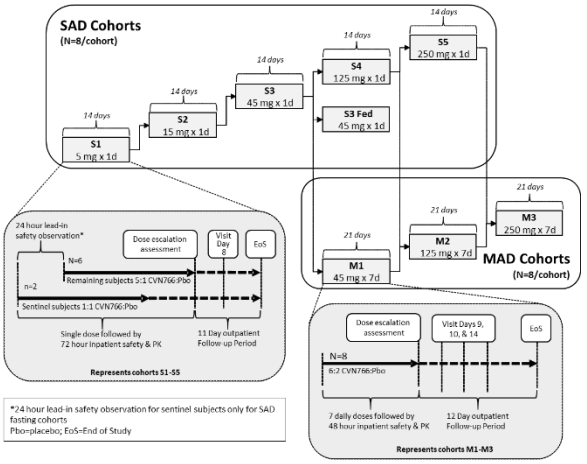
TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance, Inc.	**Compound:** CVN766 	
Title of Protocol: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects	**IND No.:**	**EudraCT No.:** Not Applicable
Study Number: CVN766-101	**Phase:** 1	

Study Design:

This is a Phase 1, randomized, double-blind, placebo-controlled, single- and multiple-dose ascending study in healthy subjects with concurrent PK sampling from blood plasma, urine, and cerebrospinal fluid. The overall study design is outlined below:

Part 1: Single-Dose Regimen and Fasted-Fed Crossover

For the single-dose regimen, approximately 40 healthy male or female subjects will be enrolled in 1 of 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. Each cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a single oral dose of CVN766 suspension, and 2 subjects will receive a matching placebo suspension under overnight fasted conditions. Subjects will remain fasted for 4 hours post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 or placebo to the remainder of subjects within the cohort. After blinded review by the Safety Review Group (SRG) of 24-hour, post-dose safety and tolerability data from the sentinel group, the remaining 6 subjects of each cohort may be dosed provided that the adverse event (AE) profile in the first 2 subjects is considered acceptable. To accommodate the lumbar puncture in the S3 fasted cohort, after the sentinel group, the remaining 6 subjects dosing may be staggered every two days. The planned dose levels will be 5, 15, 45, 125, and 250 mg CVN766. The SRG will review all available blinded safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and pharmacokinetic (PK) data after each cohort and before subsequent dose escalation. Each following dose level may be higher, lower, or remain the same as the preceding cohort, dependent on the recommendation of the SRG.

Additional cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. For example, if cohort S5 is well-tolerated, additional cohorts with higher dose levels may be considered. Such additional cohorts will follow the same schedule of events as for cohorts S1 through S5. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

To assess the effect of food on CVN766 bioavailability in suspension formulation, the single-dose administration

will be repeated in a single cohort (S3) after ingestion of a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the S3 cohort dose level has been assessed, the S3 cohort subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives, has lapsed based on preliminary PK data, whichever is longer). They will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish the entire content of their breakfast within 25 minutes and will receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

Subjects for all cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments. On Day 1, subjects will undergo safety monitoring and PK sampling from blood plasma through 72 hours post-dose and, for cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. The total confinement period will be 4 nights, unless extended at the discretion of the Investigator, e.g., for monitoring and/or management of AEs. Follow-up assessments will occur on approximately Days 8 and 14 and +21 and +28 for cohort S3.

A summary of the single-dose regimen visit schedule is presented below:

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK, Safety and Lumbar Puncture Site Assessments (S3 fasted)	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. S3 subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required at Day -1.

(b) CSF collection will apply only to cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary, to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal, clinically significant (CS) findings were observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 healthy male and female subjects age 18 to 50 years old will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. The dose levels planned to be studied in the multiple-dose regimen are 45, 125, and 250 mg CVN766 for multiple-dose cohorts M1 through M3, respectively. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily oral dose of CVN766, and 2 subjects will receive a matching placebo for 7 days. Dosing will be administered in the fasting state; this can be changed by the SRG if exposure is found to be higher in the fed state. The planned dosing duration for the multiple-dose cohorts is 7 days. However, the duration may be increased to ≤14 days at the discretion of the SRG if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. For each dose on intensive PK sampling days (first and last days of dosing, e.g., Days 1 and 7), subjects will remain fasted for 4 hours post-dose. On other dosing days (Days 2-6), subjects will remain fasted for 1-hour post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 (minimally including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of dose level may be modified by the SRG after the available blinded safety, tolerability, clinical laboratory results,

and PK data in the preceding multiple-dose and corresponding single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in cohort M1 only, from urine through 24 hours post-dose. In cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7), subjects will additionally undergo PK sampling from CSF via lumbar puncture at 3 hours post-dose. If needed to resolve questions arising from prior cohorts' data, subjects in cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., $t_{½}$). The total confinement period will be 9 nights unless extended for additional dosing days or management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose.

A summary of the multiple-dose regimen visit schedule is presented below:

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g., Days 8-9)	3 days ±0 after last dose (e.g., Day 10) & 7 days ± 1 after last dose (e.g., Day 14)	14 days ±2 after last dose (e.g., Day 21)

(a) CSF sampling will occur on Day 7 in cohorts M1 and M2. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or, if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal, clinically significant (CS) findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in cohort M1.

Safety Review Group (SRG)

The SRG will be comprised of the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for ongoing review of safety, tolerability, and clinical laboratory results, and available PK data and deciding:

1. Expand each single-dose cohort from the sentinel cohort to the entire cohort (based on a review of at least 24 hours post-dose safety data from each of the sentinel subjects),
2. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data including at least 72 hours post-dose safety data and clinical laboratory results from each of the subjects in the current cohort),
3. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data including at least 48 hours post 7th dose safety

data from each of the subjects in the current cohort),

4. Add additional dose cohort(s) in either the single- or multiple-dose studies,
5. Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days,

In addition, if 2 or more subjects in a single cohort experience the same type of serious or medically significant event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

Primary Objective:

To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects, and to determine the recommended phase 2 dose (RP2D).

Secondary Objectives:

- To characterize the single-dose PK profile of CVN766 in plasma and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma and CSF
- To assess the effect of food on the bioavailability of CVN766

Exploratory Objectives:

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

[redacted]

Subject Population: Healthy male and female subjects 18 to 50 years old

Number of Subjects:	**Number of Sites:**
Each dose cohort: 8 subjects (6 active:2 placebo) Estimated total: 64 subjects (5 single-dose cohorts, 3 multiple-dose cohorts)	1 (Australia)
Dose Level(s): Planned single-dose levels are placebo, 5 mg, 15 mg, 45 mg, 125 mg, and 250 mg CVN766. Planned multiple dose levels are placebo, 45 mg, 125 mg, and 250 mg CVN766.	**Route of Administration:** Oral
Duration of Treatment: Single or daily oral doses for up to 7 days (+7 days as necessary to reach steady-state and as required by Safety Review Group).	**Period of Evaluation:** Screening Period: up to 28 days Treatment Period: 1-7 days (+7 days, as necessary). Food Effect washout period (for select cohort only): at least 14 days Follow-up Period: approximately 14 days Total Duration: • Single-dose cohorts: approximately 6 weeks • Food effect cohort: approximately 8 weeks • Multiple-dose cohorts: approximately 7 weeks

Main Criteria for Inclusion:

Healthy male and female subjects who are 18 to 55 years of age, inclusive and have a body mass index (BMI) between 18.0 and 32.0 kg/m^2 inclusive at Screening.

A complete list of inclusion criteria is provided in Section 7.1.

Main Criteria for Exclusion:

Subjects have a known hypersensitivity to any component of the formulation of CVN766. Subjects have evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, allergic skin rash, psychiatric disorder, or other abnormality that may impact the ability of the subject to participate or potentially confound the study results. Any finding in the subject's medical history, physical examination, or safety laboratory tests gives reasonable suspicion of a condition that might interfere with the conduct or interpretation of the study.

A complete list of exclusion criteria is provided in Section 7.2.

In addition, subjects may not use any excluded medications, supplements, or food products. Concomitant medications and dietary products to be excluded are listed in Table 3.

Main Criteria for Evaluation and Analyses:

- Safety:

Safety parameters will include AEs, clinical laboratory results, vital signs, physical examinations, electrocardiogram (ECG). AEs will be collected from signing the informed consent form (ICF) up until dosing on Day 1 as pretreatment events (PTEs), and any event that occurs from dosing until 14 days after the last dose will be captured as an AE. Vital signs will be recorded at Screening, Inpatient Check-in (Day -1), and throughout the dosing period. Vital signs will include tympanic body temperature measurement, blood pressure, respiration rate, and pulse (beats per minute [bpm]). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day -1) 15 minutes apart. Heart rate and blood pressure will be measured after at least 5 minutes supine and again at 2 minutes after standing for all scheduled timepoints.

Standard 12-lead ECGs will be recorded at Screening, Inpatient Check-in (Day -1), and periodically throughout the dosing period. Triplicate ECGs will be taken at each timepoint.

A complete list of safety assessments is provided in Section 9.1, and the full Schedule of Study Procedures is provided in Appendix A.

- PK:

The plasma PK parameters are used as PK endpoints to determine drug exposure at each dose and facilitate dose escalations.

Plasma samples will be collected for the determination of concentrations of CVN766 throughout the study as prescribed in the Schedule of Study Procedures (Appendix A). Cerebrospinal fluid (CSF) samples will be collected for the determination of concentrations of CVN766 as described in Section 9.6 and the Schedule of Study Procedures (Appendix A). PK sampling timepoints may be modified or added based on emerging PK data to most appropriately characterize the PK profile of CVN766 as determined by the SRG.

PK parameters of CVN766 will be derived using noncompartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma: C_{max}, AUC from time 0 to the last quantifiable concentration (AUC_t), AUC from time 0 to infinity (AUC_∞), AUC from time 0 to 24 hours (AUC_{24}), time to reach C_{max} (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2z}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F). Multiple-dose PK will also include AUC over the dosing interval (AUC_{tau}), apparent clearance at steady state (CL/F_{ss}), apparent volume of distribution at steady state (Vz/F_{ss}), steady-state nadir concentrations, and accumulation ratios

The PK parameters to be determined from concentrations of CVN766 in CSF will include plasma: CSF ratio by time point. - Pharmacogenomics:

One 6 mL whole blood sample will be collected at pre-dose on Day 1 for pharmacogenomic analysis; this will only be collected once per subject. Two 2.5 mL whole blood samples will be collected at pre-dose on Day 1 and at multiple timepoints post-dose for ribonucleic acid (RNA) pharmacogenomic analysis. The pre-dose RNA blood samples should be collected under fasted conditions and prior to any other blood collection. The samples will be stored for no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from Cerevance. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personal identifying

information, but key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; eligible subjects sign the ICF, which outlines the retention of pharmacogenomic and genotyping analysis in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of this gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

- Endpoints:

The primary endpoints of this study will be the following: percentage of subjects who experience at least one treatment-emergent adverse event (TEAE); percentage of subjects with abnormal and CS safety laboratory, vital signs, or ECG test results at least once post-dose.

The secondary endpoints will be the following plasma PK parameters of CVN766: C_{max}, AUC_{24}, AUC_{∞}, $t_{1/2z}$, AUC from time 0 to end of the dosing interval, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}.

The additional endpoints may include the following plasma PK parameters of CVN766: t_{max}, CL/F, V_z/F, CL/F_{ss}, Vz/F_{ss}, and plasma: CSF ratio.

Exploratory endpoints may include characterization of metabolic enzyme and transporter polymorphisms and/or

[redacted]

Statistical Considerations:

Safety:

AEs will be presented in listings, and TEAEs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be recorded at baseline and post-dose, and changes from baseline will be summarized using shift tables. Individual vital signs will be recorded and observed values and changes from baseline will be summarized. Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and observed values and changes from baseline will be summarized. All summaries will be performed by placebo, each CVN766 dose level (fasted and fed separately), and CVN766 single-dose overall, and separately CVN766 multiple-dose cohorts overall. Placebo data will be pooled across single-dose cohorts and separately pooled across multiple-dose cohorts. Physical exam findings will be presented in data listings.

PK Measures:

Concentrations of CVN766 in plasma and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma and CSF concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically.

PK parameters of CVN766 will be summarized by dose using descriptive statistics. Dose proportionality will be assessed graphically and using a power model.

The concentrations of CVN766 in plasma and CSF will be compared.

Sample Size Justification:

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) is considered sufficient for evaluating the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

3.0 STUDY REFERENCE INFORMATION

3.1 List of Abbreviations

λ_z	terminal elimination rate constant
AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUCτ	area under the plasma concentration-time curve over the dosing interval (τ)
BMI	body mass index
CL/F	apparent clearance after extravascular administration
CL/F_{ss}	apparent clearance after extravascular administration at steady state
[redacted]	[redacted]
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	follicle-stimulating hormone
FT4	free T4
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human-equivalent dose
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
K_2EDTA	dipotassium ethylenediamine tetraacetic acid
LFT	liver function test
MAD	multiple-ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
MRSD	maximum recommended starting dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
Ox1R	orexin 1 receptor
Ox2R	orexin 2 receptor
PK	pharmacokinetic
PRL	prolactin
PT	preferred term
PTE	pretreatment event
QTcB	QT interval with Bazett's correction method
QTcF	QT interval with Fridericia's correction method
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAD	single-ascending dose
SAP	statistical analysis plan
SOC	system organ class
SRG	Safety Review Group
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution after extravascular administration
V_z/F_{ss}	apparent volume of distribution after extravascular administration at steady state
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

The neuropeptide orexin, also known as hypocretin, is produced exclusively in the orexigenic neurons in the hypothalamus. There are two forms of orexin, Orexin-A and orexin-B that are alternatively spliced from the same gene, HCRT. There are two orexin receptors, orexin 1 receptor (Ox1R) and orexin 2 receptors (Ox2R), both of which are G-protein coupled receptors. Both orexin-A and orexin-B can bind to either receptor and in each case, agonist binding results in an increase in intracellular calcium levels. However, while orexin-A is equipotent at both receptors, orexin-B shows a 10-fold selectivity for Ox2R.

Ox1R is selectively expressed in key brain areas relating to psychiatric disorders. Ox1R-expressing neurons in the bed nucleus of the stria terminalis, amygdala, locus coeruleus, raphe nucleus, and the ventral tegmental area are important in regulating emotions of stress, anxiety, motivation, and reward. CVN766 is a potent and highly selective small-molecule Ox1R antagonist with no significant off-target activity. Nonclinical PK and toxicology studies with CVN766 and other Ox1R antagonists have established their pharmacological characteristics and probable safety profile.

Ox2R is expressed in some overlapping areas, including the raphe nucleus, ventral tegmental area, but also areas important to arousal and sleep regulation, including the tuberomammillary nucleus.

The widely used sleep aid suvorexant (Belsomra®), approved for use in Australia, is a dual Ox1R and Ox2R antagonist, but its sleep-inducing effects are generally attributed to its activity on Ox2R. A second dual Ox1R and Ox2R antagonist, lemborexant, appeared safe and effective in clinical studies, has been approved in many countries worldwide, and has been submitted for marketing authorization in Australia.

Clinical effects to be expected of a selective Ox1R antagonist remain uncertain. CVN766 has not yet been studied in humans. Other selective Ox1R antagonists have reported early-stage human clinical trials, notably JNJ-61393215 (ClinicalTrials.gov Identifier: NCT04080752; Salvadore *et al.*, 2020) and ACT-539313 (NCT01954589; Kaufmann *et al.*, 2020; Kaufmann et al., 2021). Both drugs were well tolerated and deemed safe for investigational use, the most common AEs being somnolence and mild headache.

4.2 Rationale for the Proposed Study

CVN766 is a highly selective orexin-1 receptor (Ox1R) antagonist and may have utility as treatment for psychiatric disorders including schizophrenia, panic disorder and anxiety, and addiction. Its safety and PK profile have been preliminarily established in nonclinical toxicology studies. The present study will be the first conducted in humans with CVN766 and will examine the compound's safety, tolerability, and PK in healthy subjects.

Nonclinical pharmacology, toxicity, and pharmacokinetic (PK) studies support the proposed escalating single- and multiple-dose study of CVN766 in healthy subjects with a starting dose of 5 mg. Section 6.2 outlines the justification for the planned dose ranges.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects.

5.1.2 Secondary Objectives

- To characterize the single-dose PK profile of CVN766 in plasma, and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma, and CSF
- To assess the effect of food on the bioavailability of CVN766 in the current formulation

5.1.3 Exploratory Objectives

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints of this study will be the following:

- Percentage of subjects who experience at least one treatment-emergent adverse event (TEAE)
- Percentage of subjects with abnormal and clinically significant (CS) safety laboratory test results at least once post-dose
- Percentage of subjects with abnormal and CS electrocardiogram (ECG) test results at least once post-dose
- Percentage of subjects with abnormal and CS vital sign measurements at least once post-dose

5.2.2 Secondary Endpoints

- Single-dose plasma PK parameters of CVN766 including time to maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to 24 (AUC_{24}) and time 0 to infinity ($AUC\infty$), and terminal elimination half-life (t1/2z)

- Multiple-dose plasma PK parameters of CVN766 including C_{max}, AUC from time 0 to the end of dosing interval, t1/2z, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}
- Single-dose and multiple-dose CSF concentrations and CSF: plasma ratios of CVN766

5.2.3 Additional Endpoints

- Change from baseline in safety laboratory and ECG test results and vital signs
- Additional plasma PK parameters of CVN766 ie, ,CL/F and V_z/F

[redacted]

- Characterization of metabolic enzyme and transporter polymorphisms

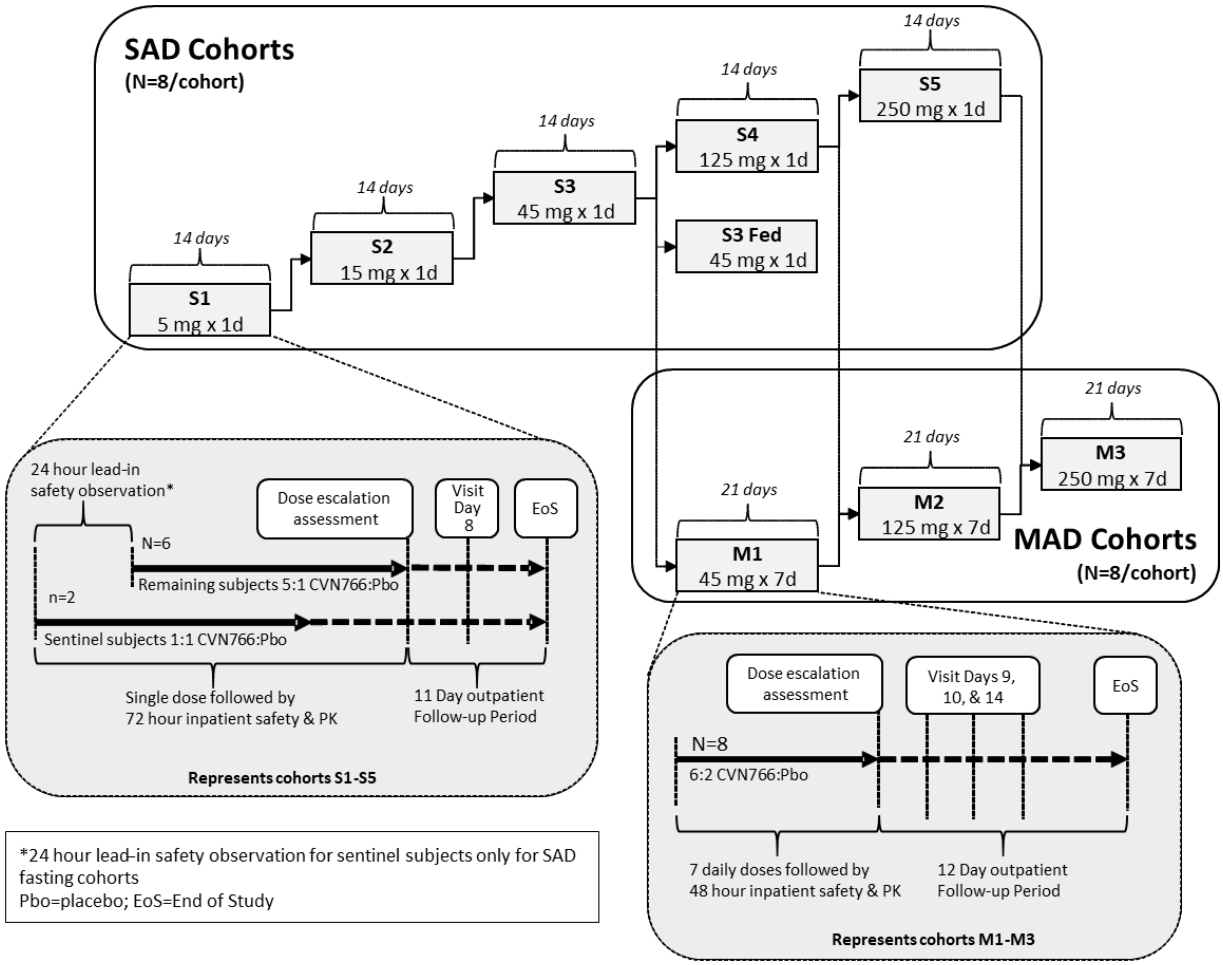
[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled, single- and multi-dose ascending study in healthy subjects. Figure 1 provides a schematic illustration of the study.

Figure 1 CVN766-101 Study Schematic



6.1.1 Part 1: Single-Dose Regimen and Fasted-Fed Crossover

Approximately 40 subjects will be enrolled in 1 of the 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. Dose escalation will only occur after a fully blinded review of all available safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and available PK data, including at least a 72-hour follow-up of the most recent cohort.

The planned dose levels are provided in Table 5. Each cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a single dose of CVN766 and 2 subjects will receive a matching placebo under overnight fasted conditions.

Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 to the remainder of subjects within the cohort. After blinded review of 24-hour post-dose safety and tolerability data, the remaining 6 subjects of each cohort may be dosed provided that the adverse event (AE) profile of CVN766 in the first 2 subjects is considered acceptable.

Subjects for all cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments at least 72 hours after dosing. On Day 1, subjects will undergo safety monitoring (including labs, physical exam, abbreviated neuro exam, cardia telemetry at 12-hours pre-dose) and PK sampling from blood plasma through 72 hours post-dose. In addition, for cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. For subjects participating in the SAD cohorts, the total confinement period will be 4 nights unless extended for management of AEs at the discretion of the Investigator. Follow-up assessments will occur on approximately Days 8 and 14.

To assess the effect of food on bioavailability of CVN766 in suspension formulation, single-dose administration will be repeated in a single cohort after ingestion of a standardized high-fat high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the S3 cohort dose level has been assessed, the S3 cohort subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives has lapsed based on preliminary PK data, whichever is longer) and will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish the entire content of their breakfast within 25 minutes and will receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

An outline of the single-dose study visit schedule is included in Table 1. A Schedule of Study Procedures is listed in Appendix A.

Table 1 Single-Dose Visit Schedule

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK & Safety Assessments	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. Subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required at Day -1.

(b) CSF collection will apply only to cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

6.1.2 Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 subjects will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. Dosing will be administered in the fasting state; this can be changed by the SRG if exposure is found to be higher in the fed state. The dose levels planned to be studied in the multiple-dose regimen (M1 through M3) are provided in Table 5. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily dose of CVN766, and 2 subjects will receive matching placebo for 7 days. However, the duration may be increased to ≤14 days at the discretion of the safety review group (SRG) if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in cohort M1 only, from urine through 24 hours post-dose. In cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7), subjects will additionally undergo PK sampling from CSF via lumbar puncture at 3 hours post-dose. If needed to resolve questions arising from prior cohorts' data, subjects in cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional plasma PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., t½. The total confinement period will be 9 nights unless extended for additional dosing days or for management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose. A summary of multiple-dose study visits is included in Appendix A.

Table 2 Multiple Dose Visit Schedule

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a,f]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g. Days 8-9)	3 days ±0 after last dose (e.g. Day 10) & 7 days ± 1 after last dose (e.g. Day 14)	14 days ±2 after last dose (e.g. Day 21)

(a) CSF sampling will occur on Day 7 in cohorts M1 and M2. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after the last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in cohort M1.

6.1.3 Dose Escalation

The SRG will be comprised of the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for ongoing review of safety, tolerability, clinical laboratory results, and available PK data and deciding to:

- Expand each single-dose cohort from the sentinel cohort to the full cohort (based on a review of at least 24 hours post-dose safety data from each of the sentinel subjects),
- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data including at least 72 hours post-dose safety data and clinical laboratory results from each of the subjects in the current cohort),
- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data including at least 48 hours post 7th dose safety data from each of the subjects in the current cohort),
- Add additional dose cohort(s) in either the single- or multiple-dose studies,
- Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days

If 2 or more subjects in a single cohort experience the same type of serious or medically adverse event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

For each cohort (including sentinel subjects, where applicable), the SRG will carefully review the available blinded safety, tolerability, clinical laboratory results, and PK data to determine whether dosing should stop or continue (and, if continued, at what dose, including whether to repeat the previous dose), whether additional sequential dosing should be implemented in future cohorts or whether the blind should be broken to identify whether the subjects received CVN766 or placebo. However, precautions must be taken not to unblind the study staff, including the investigator.

If all doses are tolerated, then additional cohorts with higher doses may be considered; if MTD is reached in an earlier cohort, following cohorts may study lower doses. The actual choice of the subsequent dose level will occur after the full review of the available blinded safety, tolerability, clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level. If necessary, additional cohort(s) may be added to fully characterize the safety and tolerability of CVN766.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all available safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 (minimally including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of dose level may be modified by the SRG after review of the available blinded safety, tolerability, and clinical laboratory results and PK data in the preceding multiple-dose and next-higher-dosage single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose

cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

All AEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge, will be evaluated to assess the need for the subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (Section 6.3.1).

Additionally, the SRG may decide not to escalate the dose for a particular cohort but rather administer the same or a lower dose level to the next cohort. Additional/ Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

6.2 Justification for Study Design, Dose, and Endpoints

The study is double-blind and placebo-controlled to avoid subjective bias in the assessment of the safety and tolerability of CVN766. Dose escalation will be predicated on a review of available blinded safety, tolerability, and PK data observations for each prior dose cohort.

The sponsor has selected the starting dose level considering the FDA Guidance for Industry (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 06 July 2005) and providing additional safety factors to the initial calculations based on the principles outlined in the guidance. The toxicity profile of CVN766 after oral dosing was examined in repeat dosing studies in rats and dogs. Scaling based on body surface area was conducted by multiplying the NOAELs for the most sensitive animal species by the appropriate conversion factors. Based on these calculations and applying a 10-fold safety margin below the NOAEL human-equivalent dose (HED), the maximum recommended starting dose (MRSD) for this first-in-human study is 167 mg for a 60 kg subject. The selected starting dose level is 5 mg.

The study's multiple-ascending dose (MAD) portion seeks to prepare for subsequent repeat dosing studies in subjects. Each MAD dose level will have been studied or exceeded in the SAD portion of the study before its use in a MAD cohort.

Nonclinical toxicity study data provide a basis for calculating the maximum exposure level that can be presumed safe. Escalating to the HED of the NOAEL in the most sensitive animal species, the maximum dose for clinical use is 1670 mg/day.

The projected $t_{1/2z}$ in animal species ranged up to 6.5 hours, so sample collection through Inpatient Discharge 72 hours post-dose is expected to correspond to more than 5 half-lives and is anticipated to be adequate to document elimination of CVN766. The study design allows for collecting additional PK samples at later timepoints if preliminary emerging PK results are indicated.

AEs, physical exams, vital signs, ECG findings, and clinical laboratory results are used as safety assessments to determine dose tolerability and dose-limiting effects of CVN766. The plasma PK and CSF parameters and PK endpoints will help elucidate the pharmacology of CVN766.

Samples for DNA analysis will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety of the study medication indicates an adverse change in the risk profile for the compound, such that the SRG or Institutional Review Board (IRB) considers the risk is no longer acceptable for subjects participating in the study.

In addition, if any of the following occur, further dosing will be withheld until the SRG reviews the relevant data, including unblinded data (if deemed necessary by the SRG request), and will decide whether it is safe to suspend dosing or continue dosing at either the planned or alternative dose levels or decides to prematurely terminate the study:

1. Two or more subjects in any single cohort or across more than 1 cohort experience the same type of serious or Medically Significant event as defined by the Investigator
2. Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limits of normal (ULN) in the absence of a concomitant bilirubin increase (see point 3 below)
3. One or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN in the presence of a total bilirubin increase >2 ×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., “Hy’s Law cases”)
4. Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate study performance, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an IRB/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; applicable investigational sites will follow the procedure during the course of termination or study suspension.

7.0 SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days prior to randomization or first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the investigator's opinion, the subject can understand and sign the Informed Consent Form and comply with all protocol requirements.
2. The subject is a healthy male or female adult who is 18 to 55 years of age, inclusive at the time of ICF.
3. Subject weighs at least 45 kg (99 lbs) and has a BMI between 18.0 and 32.0 kg/m^2, inclusive at Screening.
4. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agree to use two forms of adequate contraception* from signing the ICF throughout the study and for 90 days after the last dose.

   *Definitions and acceptable methods of contraception are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities are defined in Section 9.1.14 Pregnancy.

5. A female subject of childbearing potential who complies with contraception requirements* or a female with no childbearing potential, defined as the subject has been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (defined as continuous amenorrhea of at least 2 years and FSH>40 IU/L).

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Subject has received any investigational compound within 30 days prior to the first dose of study medication or within 5 half-lives, whichever is greater.
2. Subject is a study site employee or an immediate family member of a study site employee.
3. Subject has evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, full-body allergic skin rash (including hives), psychiatric disorder, evidence of abnormal liver function test, evidence of abnormal renal function tests or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.

   Note: Healthy volunteers with pre-existing stable disease, defined as diseases not requiring significant change in therapy or hospitalization for worsening disease during the 6 wks before enrolment, may be included at the discretion of the Investigator.

4. There is any finding in the subject’s medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking CVN766 or a similar drug in the same class or that might interfere with the conduct of the study

5. Subject has a known hypersensitivity to any component of the formulation of CVN766.
6. Subject has a positive urine result for drugs of abuse at Screening or Inpatient Check-in (Day -1).
7. Subject has a history of a major psychiatric illness or currently receiving therapy for a psychiatric condition
8. Subject has a history of drug abuse or a history of alcohol abuse (more than 14 units/week) within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
9. Subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table as listed in Table 3: Excluded Medications and Dietary Products.
10. Male subjects who do not agree to all the following rules: when sexually active with a female partner(s) of childbearing potential during the study, and for 90 days after the last dose of study drug: a) must use two acceptable methods of birth control (condom or surgical sterilization combined with highly effective method of contraception for the female partner) and b) refrain from sexual activity with female partners who do not use an acceptable method of birth control. Barrier contraception (condom) must be used by all-male subjects who were not surgically sterilized at least 90 days prior to screening. Male subjects must also agree to refrain from sperm donation during the study and until 90 days after the last dose of the study drug.
11. Female subjects who are pregnant or breastfeeding or plan to become pregnant or donate ova during the study or 30 days after the last dose of the study drug. Women of childbearing potential must agree to practice an acceptable method of birth control (e.g., oral or parenteral contraceptives, intrauterine device, barrier, abstinence).

    *Definitions and acceptable methods of contraception are defined in Section 9.1.13. Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.14 Pregnancy.

12. Subject has previously had a seizure or convulsion (lifetime, with the exception of febrile seizures), including absence seizure.
13. Subject has current o recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (i.e., a history of malabsorption, any surgical intervention known to impact absorption [e.g., bariatric surgery or bowel resection], esophageal reflux, peptic ulcer disease, erosive esophagitis, or frequent [i.e., more than once per week] occurrence of heartburn).
14. Subject has a history of cancer or other malignancy, except for basal cell carcinoma or squamous cell carcinoma that has been in remission for at least 3 years prior to Day 1.
15. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or a human immunodeficiency virus infection at Screening.
16. Subject who regularly use nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum). The

casual users may participate but must agree to refrain from the time of Screening for the duration of the study or a positive urine cotinine test at Inpatient Check-in (Day 1).

17. Subject has poor peripheral venous access (defined as more than three failed attempts to cannulate.
18. Subject has donated or lost 450 mL or more of their blood volume (including plasmapheresis) or had a transfusion of any blood product within 45 days prior to Day 1.
19. Subject has an abnormal (CS) ECG at Screening or Inpatient Check-in (Day -1). Entry of any subject with an abnormal (NCS) ECG must be approved and documented by signature by the Investigator or medically qualified sub-investigator.
20. Subject has a supine blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 40 to 90 mm Hg for diastolic, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).
21. Subject has a resting heart rate outside the range of 40 to 100 bpm, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).
22. Subject has a QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms, confirmed with one repeat testing at the Screening Visit or Inpatient Check-in (Day -1) Visit.
23. Subject has abnormal Screening or Inpatient Check-in (Day -1) laboratory values that suggest a CS underlying disease or subject with the following lab abnormalities: ALT and/or AST >1.5 the ULN, confirmed with one repeat testing.
24. Subject has a risk of suicide according to the investigator's clinical judgment or has made a suicide attempt in the previous 2 years.

7.3 Excluded Medications and Dietary Products

Use of the agents in Table 3 (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 3 Prohibited Medications and Dietary Products

28 days prior to Inpatient Check-in (Day -1)	7 days prior to Inpatient Check-in (Day -1)	72 hours prior to Inpatient Check-in (Day -1)
Prescription medications (including oral contraceptives)	OTC medications, including antacids, proton-pump inhibitors, and H2 receptor antagonists [a]	Products containing caffeine or xanthine (e.g., tea or coffee)
Nicotine-containing products	Vitamin supplements	poppy seeds
Nutraceuticals (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Orexin receptor antagonists including suvorexant (Belsomra®), lemborexant (Dayvigo®), and related compounds	
Immunization/Vaccines [b]	Alcohol-containing products	
Known strong inhibitors/inducers of CYPs 3A4/5 [c]		

CYP= cytochrome P-450, OTC=over the counter.

[a] Occasional use of acetaminophen (~1 g/day) and 400mg ibuprofen TDS when required or other medication as approved by the sponsor's Medical Monitor on a case-by-case basis is allowed except on Day 1

[b] Inclusive of but not limited to H1N1 and flu vaccinations. Subjects who have received the COVID19 Vaccine between -10 and -28 days may participate provided they did not experience any side effects of any description. COVID vaccine doses may be administered 7 days post-study medication dosing.

[c] e.g., chloramphenicol, clarithromycin, ketoconazole.

Subjects must be instructed not to take any medications during study participation, including over-the-counter drug products, without first consulting with the investigator.

7.4 Diet, Fluid, Activity Control

Subjects will be confined to the clinic for each of the dosing days as well as a period of time sufficient to collect additional post-dose PK samples and monitor for safety and tolerability (Day -1 through Day 4 for single-dose cohorts and Day-1 through Day 9 for multiple-dose cohorts). During confinement, subjects will be provided 3 standard meals and a snack per day, each containing approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be similar in nutritional content for each subject in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study. Breakfast will not be provided on dosing days until at least 1 hour after dose administration unless otherwise indicated (i.e., Days 2-6 for MAD cohorts). The meal start and stop times and percentage of the meal consumed will be recorded in the source and appropriate electronic case report form (eCRF) for all meals served on dosing days.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence, followed by the study procedure and then the meal.

Subjects will remain in bed at a semi-supine position for 4 hours following the dose administration, except as necessitated by the occurrence of an AE or study procedures (e.g., obtaining a 12-lead ECG). Subjects must refrain from strenuous exercise from 72 hours before Inpatient Check-in and until check-out.

On the dosing days where extensive PK and/or CSF sampling is indicated (i.e., single-dosing Day 1 and first and last multiple-dose days, e.g., days 1 and 7), CVN766 or placebo suspension will be administered with approximately 240 mL of water after a fast of at least 10 hours. Subjects will continue to fast for an additional 4 hours after dosing and eat lunch following the 4-hour PK blood and CSF collection. Subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration.

For the food effect cohort (S3), single-dose administration will be administered after ingesting a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Subjects will finish the entire content of their breakfast within 25 minutes and will receive an investigational product 30 minutes (±5 minutes) after beginning the meal. The S3 (food effect) cohort meals may be staggered to ensure dosing occurs 30 minutes after the beginning of the meal.

Subjects will also fast for at least 10 hours prior to safety laboratory collection times as indicated. However, consumption of water as desired is permitted during this time, except for dosing days, as indicated above.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, Section 9.1.15.

1. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status) if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 × ULN, or
   – ALT or AST >5 × ULN and persists for more than 2 weeks, or
   – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or
   – ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to reach the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal, and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).
6. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator must discontinue a subject's study participation at any time during the study when the subject meets the study discontinuation criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's involvement be terminated, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures

scheduled for the Early Termination Visit. Discontinued or withdrawn subjects may be replaced at the Sponsor's discretion.

Participants who withdraw from the study prior to dosing may be replaced. If a participant withdraws after the first dose of study medication or placebo, no replacement will occur.

8.0 CLINICAL TRIAL MANAGEMENT

8.1 Study Medication and Materials

This section contains information regarding all medication and materials provided directly by the sponsor and/or sourced by other means required by the study protocol, including important sections describing the management of clinical trial material.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN766 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral suspensions as needed throughout the study.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN766 and Matching Placebo

CVN766 drug substance is supplied as a bulk powder to the clinical site and then compounded into oral suspensions. A matching placebo suspension containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor. See Table 4 for the composition of the drug product and matching placebo suspensions.

The oral suspensions will be labeled with the appropriate study information and caution statements.

Table 4 Composition of CVN766 Oral Suspension and Matching Placebo

Component	CVN766 Oral Suspension (individual dose)					Matching Placebo
CVN766 drug substance	5 mg	15 mg	45 mg	125 mg	250 mg	NA
Commercial suspending vehicle[a]	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL

NA=Not applicable;

[a] An off-the-shelf commercial suspending vehicle will be used, and the details of the vehicle will be provided in the Pharmacy Manual.

8.1.1.2 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or the sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

[redacted]

8.1.2 Drug Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN766 drug substance is stored at room temperature. CVN766 oral suspension and matching placebo should be stored according to instructions in the Pharmacy Manual.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the Investigator and in fed or fasting conditions as outlined in Section 7.4.

The exact time of dose will be recorded in the source documents and on the appropriate eCRF.

The planned dose levels to be studied are provided in Table 5. If the planned highest dose level does not reach the desired exposure, then additional cohorts with higher dose levels may be considered. If all planned dose levels are not tolerated in an earlier cohort, the following cohorts may study lower doses at the discretion of the Investigator and the SRG. The actual choice of the subsequent dose level will occur after a full review of the available blinded safety, tolerability, and clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Table 5 describes the treatment and medication type that would be provided for each cohort.

Table 5 Planned Single and Multiple Dose Levels by Cohort

Single-Dose Cohorts			
Cohort	**Planned Treatment***	**No. of Subjects**	**Medication Type**
S1	CVN766 5 mg	6	oral suspension
	Placebo	2	oral suspension
S2	CVN766 15 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fasted	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fed (Same 8 subjects as in the S3 FASTED cohort)	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S4	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
S5	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension
Multiple Dose Cohorts			
Cohort	**Planned Treatment***	**No. of Subjects**	**Medication Type**
M1	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
M2	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
M3	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension

* Dose (active or placebo) is in 10 mL of suspension.

8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 9.7.2, PTEs and AEs.

Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure outlined in Section 9.7.4, Collection and Reporting of SAEs.

In the event of an overdose, supportive measures should be employed as needed, e.g., administration of supportive therapy as dictated by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract, or initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive a unique randomization number.

The clinical site will use the unique identifier to facilitate the pre-labeling of PK samples. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory and will be used by the laboratory to report the subject data results. This unique identifier should only be used for the purposes described in this section. This identifier will be assigned upon randomization in the order in which subjects receive their first dose of the study drug.

8.3 Randomization Code Creation and Storage

The sponsor or their designee will generate the randomization schedule and provide a copy to the site pharmacist and bioanalytical laboratory prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigative staff unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality assessments should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted to discuss the need for unblinding before the investigational drug blind is broken.

Unblinding envelopes will be supplied to the site prior to the first subject dosing and stored in a central and secure place to ensure access in the event of an emergency. Study staff will be trained on unblinding procedures.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information (except the time) must be recorded on the eCRF.

If any site personnel inadvertently become unblinded, the sponsor must be notified, and the SRG will determine whether to discontinue dosing or withdraw from the study of all affected subjects.

No change should be made to any assessment of the subject after unblinding.

Following assessment of the AE data and pre-defined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis. Based on a review of unblinded data, the sponsor, in consultation with the Investigator, will decide if and how it is appropriate for the study to proceed.

The Randomization schedule for all subjects will be released for analysis after the database for these cohorts is locked. The Investigator will be unblinded after database lock for all the cohorts if necessary.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication, the investigator must maintain records of all study medication delivery to the site, site inventory used by each subject, and return to the sponsor or designee.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list, ensure the quantity is correct, and the medication is received within the labeled storage conditions. If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and send via email and per instructions provided on the form. If any discrepancies exist between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file. The investigator must maintain 100% accountability for all study medication received and dispensed during their entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all study medication on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of the Investigator, site identifier and number, description of study medication, expiry date, and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the ICF are described in Section 14.2.

The ICF must be obtained prior to the subject entering the study and before any protocol-related procedures are performed.

A unique subject screening number (of the form xx-xxx), the first two numbers for the site, subsequent three numbers for subject identification will be assigned to each subject when the ICF is obtained. This subject ID will be used until the subject is assigned their 4-digit randomization number.

9.1.1.1 Pharmacogenomic and Cerebrospinal Fluid Informed Consent Procedure

Pharmacogenomics and cerebrospinal fluid informed consent is a component of the overall study ICF. The requirements are described in Section 14.2.

The pharmacogenomic and (for applicable cohorts) cerebrospinal fluid sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, ethnicity, race as described by the subject, smoking status, and caffeine consumption at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped at or prior to signing the ICF. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days before signing ICF.

9.1.3 Physical Examination Procedure

A physical examination performed by the investigator or medical officer consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) abbreviated neurological exam; and (12) other.

Any abnormal change from the baseline physical examination (Screening and Inpatient Check-in [Day -1]) must be assessed as not CS or CS by the investigator and recorded in the source document and eCRF.

All CS findings/changes, as determined by the investigator, from the baseline physical examination will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 9.8.1 or Section 9.8.2.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug Inpatient Check-in (Day -1) must be assessed as not clinically significant (NCS) or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

Height is recorded centimeters without decimal places, and for weight, it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/[\text{height (m)}]^2$

Results for BMI will be expressed with 1 decimal place.

Example:

Height=176 cm (or 1.76 m), weight=79.2 kg; $BMI=79.2/1.76^2=25.57$ kg/m^2 captured as 25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs will include tympanic body temperature, respiration, pulse, and blood pressure and be collected at timepoints specified in the Schedule of Study Procedures (Appendix A). For eligibility determination, the pulse will not be derived from ECG. Pulse and blood pressure will be measured after at least 5 minutes supine and again after 2 minutes standing.

Vital signs should be measured at the same time (+/- 1 hour) of the day across visits if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority, and vital signs will be obtained within approximately 0.25 hours before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of ICF through the end of the study), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at the signing of ICF. This includes CS laboratory, ECG, or physical examination abnormalities noted at Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 ECG Procedure

Standard 12-lead ECGs will be recorded at timepoints specified in the Schedule of Study Procedures (Appendix A). Triplicate ECGs will be taken at each scheduled time. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

When an ECG is scheduled at the same time as blood draws or vital signs, then the blood draws and vital signs will take priority, and the ECG will be obtained within 0.5 hour before or after the scheduled blood draw/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence, followed by the meal.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-minute rest period for ECG recordings. Should technical difficulties occur during the recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

ECGs will be read automatically, and also, the investigator or sub-investigator will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not CS, or abnormal and CS. Abnormal QTc readings will be manually recalculated and reported by the Investigator on the eCRF. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary. Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals. Paper ECG traces will be recorded for 10 seconds at a standard paper speed of 25 mm/sec, and gain of 10 m/mV or digital recordings will be used.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

All ECGs will be recorded at the time points detailed in Appendix A.

9.1.9 Pharmacogenomic Sample Collection

Every subject must sign ICF/be consented to the sampling of whole blood for pharmacogenomic analysis to participate in the study.

One whole blood sample for DNA isolation and genotyping will be collected at time points specified in the Schedule of Study Procedures (Appendix A) into plastic dipotassium ethylenediamine-tetra acetic acid (K_2EDTA) spray-coated tubes and stored under frozen conditions. In addition, two whole blood samples will be collected at time points specified in the Schedule of Study Procedures (Appendix A) for ribonucleic acid (RNA) pharmacogenomic analysis. The pre-dose RNA blood samples should be collected under fasted conditions and prior to any other blood collection.

DNA may be evaluated for the genetic contribution to how the drug is broken down or affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN766
- Finding out more information about how CVN766 works
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN766
- Identifying variations in genes related to the biological target of CVN766

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN766 and other study medications and for improving the efficiency, design, and study methods of future research studies.

The samples will be stored no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by the sponsor or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from the sponsor. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; every subject must sign the ICF in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA and RNA from the first sample was not successful or possible.

Samples will be frozen at -70°C or lower and shipped separately on dry ice prior to extraction and storage at -70°C or lower. Samples should not be allowed to thaw until processed.

Detailed instructions for the handling and shipping of samples are provided in a separate lab manual.

Genotyping on collected samples may be deferred until after the completion of the study's in-life activities.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 4-digit randomization number.

9.1.10 PK Sample Collection

9.1.10.1 Collection of Blood for PK Sampling

Blood samples for analysis of CVN766 plasma concentrations will be collected into chilled Vacutainers containing K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in a separate lab manual.

In all single-dose cohorts, serial blood samples to determine CVN766 concentrations in plasma will be collected according to Table 7.

Table 6 Collection of Blood Samples for PK Analysis in Single-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24-, 36-, 48-, and 72-hours post-dose.

In all cohorts for Part 2, serial blood samples for determination of CVN766 concentrations in plasma will be collected according to Table 8.

Table 7 Collection of Blood Samples for PK Analysis in Multiple-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 (Day 2 pre-dose) hours post-dose.
	3,4,5,6	Pre-dose (within 15 minutes prior to dosing)
	7	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, and 72 [(a)] hours post-dose.

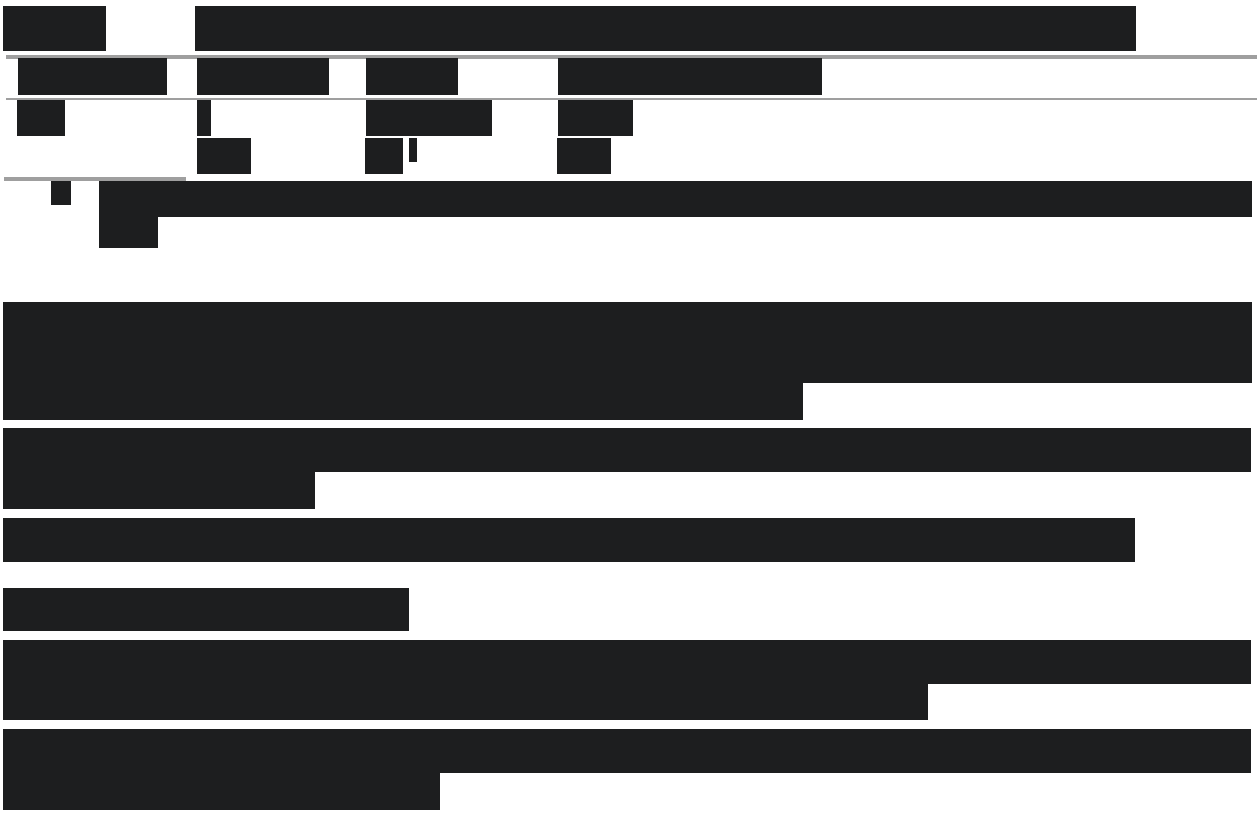
(a) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the 72-hour timepoint is unnecessary.

The PK samples will be collected at the nominal time point; all other assessments will be collected, before or after, within the allowable windows. The actual time of sample collection will be recorded on the source document and eCRF.

Sampling time points may be adjusted or added based on the preliminary emerging PK data collected from prior cohort(s). Still, the total number of samples collected per subject should not exceed the planned number by more than 4.

Placebo samples will not be analyzed by the bioanalytical laboratory except 2 samples per subject receiving placebo, 1 pre-dose, and the other around the expected time at which C_{max} occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional subjects could have been on active treatment.

[redacted]



9.1.11 PK Parameters

PK parameters of CVN766 will be derived using non-compartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma and CSF:

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from the time of dosing to the time of the last measurable concentration
AUC_∞	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_\infty=AUC_t+C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration.
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours, calculated using the linear trapezoidal rule.
AUC_τ	Area under the plasma concentration-time curve over the dosing interval (τ)
C_{max}	Maximum observed plasma concentration.
C_{min}	Minimum observed plasma concentration; pre dose trough concentration
	Minimum observed plasma concentration at steady state, on last day of dosing
CL/F	Apparent clearance after extravascular administration, calculated as $Dose/AUC_\infty$ after a single dose.
CL/F_{ss}	Apparent clearance after extravascular administration at steady state, calculated as $Dose/AUC_{tau}$

Symbol/Term	Definition
Plasma	
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.
V_z/Fss	Apparent volume of distribution during the terminal phase after extravascular administration at a steady-state, calculated as $(CL/F_{ss})/\lambda_z$
CSF	
plasma: CSF ratio	ratio of the drug concentration in plasma vs. CSF

Additional PK parameters may be calculated as appropriate.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures on the days/times stipulated in the Schedule of Study Procedures (Appendix A).

Table 6 lists the tests that will be obtained for each laboratory specimen.

Table 10 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets PT/INR	ALT Albumin Alkaline phosphatase Lipase (d) AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc.	Prolactin TSH (and if abnormal) reflex FT4
Diagnostic Screening:			

Serum	Urine/ Blood
Serum hCG (a) FSH (b) Hepatitis panel, including HBsAg and anti-HCV (e) Human Immunodeficiency Virus (HIV) antibody	Drug screen including amphetamines (AMP), barbiturates (BAR), benzodiazepines (BZO), cannabinoids, cocaine (COC), opiates (OPI), alcohol, cotinine © methamphetamines, methadone (MET), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), tetrahydrocannabinol (TCH)

FT4= free T4, FSH= follicle-stimulating hormone, GGT=γ-glutamyl transferase, hCG= human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells, TSH= thyrotropin, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening, Check-in (Day -1), and Inpatient Discharge or Early Termination and at the Follow-up Visit if the subject is brought back to the clinic for re-evaluation.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.
(c) To be performed at Screening and Inpatient Check-in (Day -1).
(d) To be performed at Day -1 and 24- and 48-hours post-dose.
(e) Screening Visit only

The local laboratory will perform all clinical laboratory tests. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to the sponsor or designee in the format requested by the sponsor. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the Investigator or sub-investigator, indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Subjects will be referred to their primary care physician for follow-up of any clinically significant findings or where the investigator or medically trained sub-investigator deems appropriate.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

(Please refer to Section 7.5 for discontinuation criteria and Section 9.8.3 for the appropriate guidance on Reporting of Abnormal LFT in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN).

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 9.8.3 Reporting of Abnormal LFT for reporting requirements).

9.1.13 Contraception and Pregnancy Avoidance Procedure

From the date of signing of ICF, throughout the duration of the study, and for 30 days after the last dose of study medication, females of childbearing potential* must use **two** acceptable methods of contraception and must agree not to donate eggs; Nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use **two** acceptable method(s) of contraception throughout the duration of the study, and for 90 days after the last dose of study medication. In addition, males must be advised not to donate sperm for 90 days after the last dose of study medication.

Females of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal.

Menopause is defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented. Male subjects with potentially postmenopausal partners who are under the age of 55 years must use condoms unless their partner's postmenopausal status has been confirmed by FSH level.

**Sterilized males should be at least 90 days post-vasectomy and confirm that they have obtained documentation of the absence of sperm in the ejaculate.

Acceptable and highly effective methods of contraception are:

- Hormonal methods of contraception including oral contraceptives containing combined estrogen and progesterone, a vaginal ring, injectable and implantable hormonal contraceptives, intrauterine hormone-releasing system (e.g. Mirena) and progestogen-only hormonal contraception associated with inhibition of ovulation
- Nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomised subject/partner with documented azoospermia 90 days after procedure, if that partner is the sole sexual partner

For female participants, hormonal contraceptives should begin at least 1 month prior to screening to ensure contraceptive is in full effect.

Complete abstinence, defined as the complete avoidance of heterosexual intercourse - is an acceptable form of contraception if used consistently throughout the duration of study and for the durations after dosing specified for males and females above. It is not necessary to use any other method of contraception when complete abstinence is elected. Females of childbearing potential who choose complete abstinence must continue to have pregnancy tests as per protocol. The reliability of sexual abstinence needs to be evaluated by the Investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Subjects will be provided with information on acceptable methods of contraception as part of the subject's informed consent process and will be asked to sign an ICF stating that they understand the requirements for avoidance of pregnancy, egg donation, and sperm donation during the study.

9.1.14 Pregnancy

Women who are pregnant or breastfeeding will not be included in this study.

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of the blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to the final outcome using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted for 8 weeks.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign ICF. If the subject is not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal
- Study termination
- Other

Subject numbers assigned to subjects who fail screening should not be reused.

If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were two separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.

2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The study-related procedures schedule for all evaluations is shown in Appendix A and is not duplicated in the following sections.

9.3.1 Screening

Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures. Subjects who are screening failures may be screened a second time if their reason for failing screening is thought to be resolved. Rescreened subjects will receive a new Screening number.

9.3.2 Inpatient Check-In

All subjects will be admitted to the study clinic the day prior to randomization and first dose. Subjects participating in the food effect cohorts will also check into the study clinic the day prior to the scheduled dosing.

9.3.3 Final Visit (discharge day from clinic)

Subjects will be confined to the study clinic for the duration of the treatment period to permit supervised dosing of study drug and repeat study assessments. Subjects participating in the single-dose study and food effect assessment will be discharged no sooner than 48 hours post-dose, and subjects participating in the multiple-dose study will be discharged no sooner than 48 hours following their last dose.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

Subjects who discontinue dosing or decide to check out of the study clinic early will be advised to allow the Investigator (or authorized designees) to complete early termination assessments for safety purposes prior to discharge. The reason for discontinuation must be documented in the source document and eCRF.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit

The Follow-up Visit will occur by telephone approximately 14 days (±2) after the final dose of study drug for the SAD cohorts and MAD cohorts unless abnormal CS findings were observed upon discharge or the SRG has determined additional PK sampling timepoints are indicated. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.

9.4 Biological Sample Retention and Destruction

In all cohorts except S3 (fed), blood serum will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed. Samples will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law.

Blood specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. After extraction and purification, the genetic material will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law. Blood and urine samples for PK analysis will be collected as described in Section 9.1.12, PK Sample Collection. Once PK analysis is complete, backup plasma and urine samples will be preserved and retained at a biorepository selected by the sponsor for up to, but not longer than, 15 years or as required by applicable law, to enable the conduct of exploratory, qualitative, metabolite identification studies or measurement of target related biomarkers, should the sponsor decide these are informative. The sponsor has put a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personally identifying information, but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. The Investigator will notify the sponsor of any subject who has withdrawn consent for the DNA and RNA analysis.

9.5 Blood Volume

Direct venipuncture or intravenous cannula is the preferred method of blood collection. Any other method will need to be approved by the sponsor. The maximum volume of blood at any single day is approximately 111 mL, with the maximum amount not to exceed 500mL for the duration of study participation.

9.6 CSF Volume

CSF will be collected by lumbar puncture, performed by a skilled and qualified individual. The maximum volume of CSF to be collected will be approximately 10 mL per subject.

9.7 Definitions

9.7.1 PTE

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed the ICF to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.7.2 AE

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a CS abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

9.7.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs)
- Necessitate therapeutic intervention
- Require an invasive diagnostic procedure
- Require discontinuation or a change in dose of study medication or a concomitant medication
- Be considered unfavorable by the investigator for any reason
- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be CS (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention
- If abnormal laboratory values or ECG findings are the results of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of the ICF) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays, etc.) should NOT be recorded as PTEs unless related to study procedures.
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy), any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious, or severe in nature; that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., "worsening of…")
- If a subject has a concurrent degenerative condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…")

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE.
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Changes in severity of AEs /Serious PTEs:
- If the subject experiences changes in the severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF

9.7.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE-THREATENING
   - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization
4. Results in persistent or significant DISABILITY/INCAPACITY
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above
   - May expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization
   - Includes any event or synonym described in the Medically Significant AE List (Table 11)

Table 11 Medically Significant AE List (categorized as Serious Adverse Events)

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 9.8.1 and 9.8.2).

9.7.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

9.7.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from the administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from the administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

9.7.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is a reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

9.7.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

9.7.9 Stop Date

The stop date of the AE/serious PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

9.7.10 Frequency

Episodic AEs/serious PTE (e.g., vomiting) or those which repeatedly occur over a period of consecutive days are intermittent. All other events are continuous.

9.7.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE
- Dose not changed – the particular AE did not require stopping a study medication
- Unknown – only to be used if it has not been possible to determine what action has been taken
- Not Applicable – a study medication was stopped for a reason other than the particular AE, e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE

9.7.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/serious PTE
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/serious PTE with the condition remaining "recovering/resolving"
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms, or laboratory value on the last day of the observed study period had got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/serious PTE state remaining "Not recovered/not resolved"
- Resolved with sequelae – the subject recovered from an acute AE/serious PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis
- Fatal – the AEs/PTEs which are considered as the cause of death
- Unknown – the course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study

9.8 Procedures

9.8.1 Collection and Reporting of AEs

9.8.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication Day 1 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs will be collected for the duration of study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1. Routine collection of AEs will continue until 14 days following last dose.

9.8.1.2 PTE and AE Reporting

At each study visit, the investigator or designee will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not be followed up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

9.8.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE form must be completed in English and signed by the investigator immediately or within 24 hours of the first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study medication(s)
- Causality assessment

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

9.8.3 Reporting of Abnormal LFT

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 9.8.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the SAE form (as per Section 9.8.3).

9.9 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resuspension or permanent outcome of the event. The timelines and procedures for follow-up reports are the same as those for the initial report.

9.9.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.0 STUDY-SPECIFIC COMMITTEES

The Safety Review Group (SRG) will be comprised of the Investigator, Medical Monitor, Cerevance Medical Officer and may include other sponsor representatives. A pharmacokineticist and other subject matter experts may participate as needed. Responsibilities of the SRG are outlined in Section 6.1.3.

11.0 DATA HANDLING AND RECORDKEEPING

AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary. All terms will be coded using the dictionary version available at the start of the study.

11.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The Investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure the accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without the written permission of the sponsor.

11.2 Record Retention

The investigator agrees to keep the records stipulated in Section 11.2 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), an electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study

records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of the subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to unblinding of the subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

12.1.1 Analysis Sets

Safety Set

The Safety Analysis Set will consist of all subjects who are enrolled and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Set

The PK set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration.

If any subjects are found to be non-compliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.

12.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for pooled placebo, CVN766 dose level, CVN766 overall, and overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for pooled placebo, each CVN766 dose level, CVN766 overall, and overall. Individual subject demographic and baseline characteristics data will be listed.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

12.1.3 PK Analysis

The concentration of CVN766 in plasma, and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically. Descriptive statistics (arithmetic mean, SD, median, minimum and maximum) will be used to summarize the plasma and CSF PK parameters for CVN766. In addition, geometric mean and coefficient of variation will be computed

The effect of fed/fasting state on PK and bioavailability of CVN766 will be characterized.

Plots of C_{max} and AUCs, as well as dose-normalized C_{max} and AUCs, versus doses, will be generated.

Dose proportionality will be tested for CVN766 C_{max} and AUCs using a power model.

A more detailed analysis will be presented in the SAP.

12.1.4 Safety Analysis

12.1.4.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. Treatment-emergent AEs with onset occurring within 30 days (onset date – last date of dose +1 ≤30) after study drug administration will be listed and included in the summary tables. Treatment-emergent AEs will be summarized by pooled placebo, each CVN766 dose level and CVN766 overall by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs. not-related), severity of AEs, and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs, including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs. All AEs will be listed.

12.1.4.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that are abnormal and CS will be summarized and listed. Baseline, post-dose, and change from baseline to post-dose laboratory data will be summarized for pooled placebo, each CVN766 dose level, and CVN766 overall. All clinical laboratory data will be listed.

12.1.4.3 Vital Signs

Individual results of vital signs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from Baseline in vital sign measurements will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. All vital sign data will be provided in the data listings.

12.1.4.4 ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from baseline in quantitative ECG parameters will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. Shift tables may be generated for the investigator's ECG interpretations that changed from baseline to the post-dose collections by the above groups. All ECG data will be provided in the data listings.

12.1.4.5 Other Variables

Physical exam findings and suicidal assessments will be presented in data listings.

12.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

12.3 Determination of Sample Size

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) is considered to be sufficient for the evaluation of the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 12 defines the windows allowed for sample collections.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 12 Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes pre-dose	0 hour
±5	immediately post-dose to ≤6 hours
±10	>6 hours to ≤12 hours post-dose
±15	>12 hours to ≤24 hours
±30	>24 hours

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of Australia (i.e., Therapeutic Goods Administration [TGA]) and foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 13.1.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICFs, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before the commencement of the study (i.e., before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from a competent authority to begin the trial. Until the site receives drug/notification, no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence on participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without providing a reason and without prejudice to their other medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and the subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

Subjects who consented and provided a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

14.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and the accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study, including data and information generated by the investigator, without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, the sponsor will register this clinical trial on ClinicalTrials.gov (and possibly on other publicly accessible websites) before the start of study.

Sponsor contact information, along with the investigator's city, state, country, and recruiting status, will be registered and available for public viewing. Once subjects receive investigator contact information, they may call the site and request enrollment into the trial. The investigative site(s) are encouraged to handle such trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

14.4.3 Clinical Trial Results Disclosure

If required at the conclusion of the study, the sponsor will post the results on ClinicalTrials.gov or other publicly accessible websites, as required by applicable national and local laws and/or regulations.

14.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

15.0 REFERENCES

FDA Guidance for Industry: Food-effect bioavailability and fed bioequivalence studies (Dec 2002).

FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 06 July 2005. Publication No. 5541.

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Appendix A Schedule of Study Procedures

SAD Cohorts 1, 2, 4, 5	Screening	Check-in	Dosing & Observation			Discharge (a)	utpatient Visit	Early Termination	Follow-up
Study Day:	-28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 8		Day 14 (±2) (b)
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics and medical history	X								
Medication history	X								
Abbreviated Neuro Exam		X	X	X	X	X			
Physical examination	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X	
Urine drug & cotinine screen	X	X							
Concomitant medications (e)	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X								
FSH (g)	X								
Serum Pregnancy test (hCG)	X								
Urine Pregnancy test						X	X	X	
CV Telemetry (n)			X	X					
ECG (h)	X	X	X	X	X	X	X	X	
PGx DNA sample collection (i)			X						
PGx RNA collection (j)			X						
PK blood collection (k)			X	X	X	X		X	
Study drug dosing			X						
PTE assessment (l)	X	X	X						
AE assessment (m)			X	X	X	X	X	X	X

PGx=pharmacogenomic.
(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) 2.5 mL whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples (6 mL) for PK analyses will be collected at time points indicated in Table 7.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) CV telemetry to telemetry should be recorded at 12 hours prior to dosing, and up to 24 hours after dosing

Cohort 3 SAD **Fasted-Fed Crossover**	**Screening**	**Dosing and Observation Inpatient**				**D/C**		**Inpatient** No sooner than +14 days or 4 half-lives of Day 8 visit					**+4 days post D/C**	**E/T**	**Follow-up**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**			**Day 14 (±2) (b)**
Informed consent	**X**							X							
Inclusion/exclusion criteria	X	X						X							
Admitted to the Clinic		X													
Demographics and medical history	X														
Medication history	X							X							
Abbreviated Neuro Exam		X	X	X	X	X		X	X	X	X	X			
Physical examination	X	X				X	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X				X	X	X	
Urine drug & cotinine screen	X	X						X							
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X						X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X		X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X														
Urine Pregnancy test						X	X					X	X	X	
CV Telemetry (n)			X	X				X	X	X					
ECG (h)	X	X	X	X	X	X	X		X	X	X	X	X	X	
PGx DNA sample collection (i)			X						X						
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X			X	X	X	X		X	
Lumbar puncture & CSF collection (k)			X												

Standardized pre-dose meal									X						
Study drug dosing			X					X	X						
PTE assessment (l)	X	X	X					X	X						
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X
Discharged from Clinic						X						X		X	

*S3 Cohort will return no sooner than Day 14 or 4 half-lives (whichever is greater) after Day 8 for the Fed portion. The Fed portion will commence on Day -1 will all the same schedule of events with the exception of **dosing will be post-meal.**

PGx=pharmacogenomic.
(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) 2.5 mL whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples (6 mL) for PK analyses will be collected at time points indicated in Table 7.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.

(n) CV telemetry to telemetry should be recorded at least 12 hours prior to dosing, and up to 24 hours after dosing

Multiple-Dose Regimen Cohorts	SCR	Check-in	Inpatient Dosing & Observation								Inpatient Discharge (a)	Outpatient Visit		E/T	Follow-up
Study Day:	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	(model for additional dosing days) Day 6	Day of last dose (e.g. Day 7)	1 day after last dose (e.g. Day 8)	2 days after last dose (e.g. Day 9)	3 days ±0 after last dose (e.g. Day 10) (o)	7 days ±1 after last dose (e.g. Day 14)		14 days ±2 after last dose (e.g. Day 21 ±2) (b)
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics and medical history	X														
Medication history	X														
Abbreviated neuro exam		X	X						X		X		X	X	
Physical examination	X	X	X						X		X		X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X		X	X	
Weight, height, and BMI (d)	X	X	X						X		X		X	X	
Urine drug & cotinine screen	X	X													
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X													
Clinical laboratory tests (f)	X	X	X		X		X		X	X	X		X	X	
Hepatitis panel	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X	X									X		X	X	
ECG (h)	X	X	X	X	X	X	X	X	X	X	X		X	X	
[redacted]															

Multiple-Dose Regimen Cohorts	SCR	Check-in	Inpatient Dosing & Observation								Inpatient Discharge (a)	Outpatient Visit		E/T	Follow-up
Study Day:	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	(model for additional dosing days) Day 6	Day of last dose (e.g. Day 7)	1 day after last dose (e.g. Day 8)	2 days after last dose (e.g. Day 9)	3 days ±0 after last dose (e.g. Day 10) (o)	7 days ±1 after last dose (e.g. Day 14)		14 days ±2 after last dose (e.g. Day 21 ±2) (b)
PGx DNA sample collection (i)			X												
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X	X	X	X	X	X	X		X	
Lumbar puncture & CSF collection (k)									X						
Study drug dosing			X	X	X	X	X	X	X						
PTE assessment (l)	X	X	X												
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X

PGx=pharmacogenomic.
(a) Events listed as occurring at "Inpatient Discharge" visit will occur on that day prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 21 (±2) unless abnormal CS findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per Investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 and Day 7 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Day 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Days 1 through 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days). Hormone laboratory tests (PRL, thyrotropin [TSH], and FT4) will be collected on Days 1 and 7 (morning [fasting] and 3 hours after dosing), Day 9, and Day 14 under fasted conditions. Fasting lipase tests will be collected at Day -1, Days 2, 7, and 8 (pre-dose). An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Screening, Inpatient Check-in (Day -1), Days 1 and 7 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Days 8 and 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days).
(i) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) 2.5 mL whole blood samples will be collected on Day 1 and Day 7 (pre-dose, 8- and 24-hours post-dose) for RNA pharmacogenomic analysis.
(k) Blood samples (6 mL) for PK analyses will be collected at time points indicated in Table 8. CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in cohorts M1 and M2, as indicated in Table 10. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.
(l) PTEs will be collected from signing of ICF up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) 24-hour urine collection is only done for cohort M1, predose and over 24 hours
(o) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the Day 10 visit is not necessary.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (non-routine/nonstandard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conforms to local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in local regulations, are met.
8. Obtain valid ICF from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entering into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Cerevance will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, and Japan), including the following:

- Cerevance, its affiliates, and licensing partners
- Business partners assisting Cerevance, its affiliates, and licensing partners
- Regulatory agencies and other health authorities
- IRBs and IECs
- Investigator's personal information may be retained, processed, and transferred by Cerevance and these other parties for research purposes, including the following:
- Assessment of the suitability of Investigator for the study and/or other clinical studies
- Management, monitoring, inspection, and audit of the study
- Analysis, review, and verification of the study results
- Safety reporting and pharmacovigilance relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication
- Inspections and investigations by regulatory authorities relating to the study
- Self-inspection and internal audit within Cerevance, its affiliates, and licensing partners
- Archiving and audit of study records
- Posting Investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites
- Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the Investigator's own country.
- Investigator acknowledges and consents to the use of his or her personal information by Cerevance and other parties for the purposes described above.

PROTOCOL

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects

Short Title: Phase 1 SAD/MAD Study of CVN766

Sponsor:	Cerevance Gamma, Inc. One Marina Park Drive, Suite 1410 Boston, MA 02210
Study Number:	CVN766-101
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Compound:	CVN766
Protocol Version:	2.0
Date:	21 October 2021

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	TBD
Medical Monitor (carries overall responsibility for the conduct of the study)	TBD
Responsible Medical Officer (medical advice on protocol and compound)	[redacted], MD

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations

SIGNATURES

Approved by:

Signature [redacted] Date: 2021.10.22 01:44:11 +02'00' Date _____

[redacted] M.D.
Medical Monitor

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation, E6 GCP: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 9.9 of this protocol
- Terms outlined in the Clinical Study Site Agreement
- Appendix B – Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

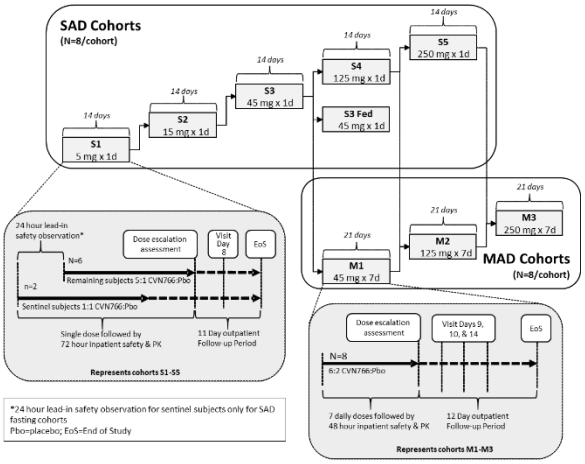
TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance, Inc.	**Compound:** 
Title of Protocol: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects	**IND No.:** **EudraCT No.:** Not Applicable
Study Number: CVN766-101	**Phase:** 1

Study Design:

This is a Phase 1, randomized, double-blind, placebo-controlled, single- and multiple-dose ascending study in healthy subjects with concurrent PK sampling from blood plasma, urine, and cerebrospinal fluid. The overall study design is outlined below:

Part 1: Single-Dose Regimen and Fasted-Fed Crossover

For the single-dose regimen, approximately 40 healthy male or female subjects will be enrolled in 1 of 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. Each cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a single oral dose of CVN766 suspension, and 2 subjects will receive a matching placebo suspension under overnight fasted conditions. Subjects will remain fasted for 4 hours post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 or placebo to the remainder of subjects within the cohort. After blinded review by the Safety Review Group (SRG) of 24-hour, post-dose safety and tolerability data from the sentinel group, the remaining 6 subjects of each cohort may be dosed provided that the adverse event (AE) profile in the first 2 subjects is considered acceptable. To accommodate the lumbar puncture in the S3 fasted cohort, after the sentinel group, the remaining 6 subjects dosing may be staggered every two days. The planned dose levels will be 5, 15, 45, 125, and 250 mg CVN766. The SRG will review all available blinded safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and pharmacokinetic (PK) data after each cohort and before subsequent dose escalation. Each following dose level may be higher, lower, or remain the same as the preceding cohort, dependent on the recommendation of the SRG.

Additional cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. For example, if cohort S5 is well-tolerated, additional cohorts with higher dose levels may be considered. Such additional cohorts will follow the same schedule of events as for cohorts S1 through S5. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

To assess the effect of food on CVN766 bioavailability in suspension formulation, the single-dose administration

will be repeated in a single cohort (S3) after ingestion of a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the S3 cohort dose level has been assessed, the S3 cohort subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives, has lapsed based on preliminary PK data, whichever is longer). They will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish the entire content of their breakfast within 25 minutes and will receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

Subjects for all cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments. On Day 1, subjects will undergo safety monitoring and PK sampling from blood plasma through 72 hours post-dose and, for cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. The total confinement period will be 4 nights, unless extended at the discretion of the Investigator, e.g., for monitoring and/or management of AEs. Follow-up assessments will occur on approximately Days 8 and 14 and +21 and +28 for cohort S3.

A summary of the single-dose regimen visit schedule is presented below:

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK, Safety and Lumbar Puncture Site Assessments (S3 fasted)	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. S3 subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required at Day -1.

(b) CSF collection will apply only to cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal, clinically significant (CS) findings were observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 healthy male and female subjects age 18 to 50 years old will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. The dose levels planned to be studied in the multiple-dose regimen are 45, 125, and 250 mg CVN766 for multiple-dose cohorts M1 through M3, respectively. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily oral dose of CVN766, and 2 subjects will receive a matching placebo for 7 days. Dosing will be administered in the fasting state; this can be changed by the SRG if exposure is found to be higher in the fed state. The planned dosing duration for the multiple-dose cohorts is 7 days. However, the duration may be increased to ≤14 days at the discretion of the SRG if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. For each dose on intensive PK sampling days (first and last days of dosing, e.g., Days 1 and 7), subjects will remain fasted for 4 hours post-dose. On other dosing days (Days 2-6), subjects will remain fasted for 1-hour post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 (minimally including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of dose level may be modified by the SRG after the available blinded safety, tolerability, clinical laboratory results,

and PK data in the preceding multiple-dose and corresponding single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in cohort M1 only, from urine through 24 hours post-dose. In cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7), subjects will additionally undergo PK sampling from CSF via lumbar puncture at 3 hours post-dose. If needed to resolve questions arising from prior cohorts' data, subjects in cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., $t_{½}$). The total confinement period will be 9 nights unless extended for additional dosing days or management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose.

A summary of the multiple-dose regimen visit schedule is presented below:

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g., Days 8-9)	3 days ±0 after last dose (e.g., Day 10) & 7 days ± 1 after last dose (e.g., Day 14)	14 days ±2 after last dose (e.g., Day 21)

(a) CSF sampling will occur on Day 7 in cohorts M1 and M2. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or, if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal, clinically significant (CS) findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in cohort M1.

Safety Review Group (SRG)

The SRG will be comprised of the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for ongoing review of safety, tolerability, and clinical laboratory results, and available PK data and deciding:

1. Expand each single-dose cohort from the sentinel cohort to the entire cohort (based on a review of at least 24 hours post-dose safety data from each of the sentinel subjects),
2. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data including at least 72 hours post-dose safety data and clinical laboratory results from each of the subjects in the current cohort),
3. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data including at least 48 hours post 7th dose safety

data from each of the subjects in the current cohort),

4. Add additional dose cohort(s) in either the single- or multiple-dose studies,
5. Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days,

In addition, if 2 or more subjects in a single cohort experience the same type of serious or medically significant event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

Primary Objective:

To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects, and to determine the recommended phase 2 dose (RP2D).

Secondary Objectives:

- To characterize the single-dose PK profile of CVN766 in plasma and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma and CSF
- To assess the effect of food on the bioavailability of CVN766

Exploratory Objectives:

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

[redacted]

Subject Population: Healthy male and female subjects 18 to 50 years old

Number of Subjects:	**Number of Sites:**
Each dose cohort: 8 subjects (6 active:2 placebo) Estimated total: 64 subjects (5 single-dose cohorts, 3 multiple-dose cohorts)	1 (Australia)
Dose Level(s): Planned single-dose levels are placebo, 5 mg, 15 mg, 45 mg, 125 mg, and 250 mg CVN766. Planned multiple dose levels are placebo, 45 mg, 125 mg, and 250 mg CVN766.	**Route of Administration:** Oral
Duration of Treatment: Single or daily oral doses for up to 7 days (+7 days as necessary to reach steady-state and as required by Safety Review Group).	**Period of Evaluation:** Screening Period: up to 28 days Treatment Period: 1-7 days (+7 days, as necessary). Food Effect washout period (for select cohort only): at least 14 days Follow-up Period: approximately 14 days Total Duration: • Single-dose cohorts: approximately 6 weeks • Food effect cohort: approximately 8 weeks • Multiple-dose cohorts: approximately 7 weeks

Main Criteria for Inclusion:

Healthy male and female subjects who are 18 to 55 years of age, inclusive and have a body mass index (BMI) between 18.0 and 32.0 kg/m^2 inclusive at Screening.

A complete list of inclusion criteria is provided in Section 7.1.

Main Criteria for Exclusion:

Subjects have a known hypersensitivity to any component of the formulation of CVN766. Subjects have evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, allergic skin rash, psychiatric disorder, or other abnormality that may impact the ability of the subject to participate or potentially confound the study results. Any finding in the subject's medical history, physical examination, or safety laboratory tests gives reasonable suspicion of a condition that might interfere with the conduct or interpretation of the study.

A complete list of exclusion criteria is provided in Section 7.2.

In addition, subjects may not use any excluded medications (including oral contraceptives as listed in Table 3), supplements, or food products. Concomitant medications and dietary products to be excluded are listed in Table 3.

Main Criteria for Evaluation and Analyses:

- Safety:

Safety parameters will include AEs, clinical laboratory results, vital signs, physical examinations, electrocardiogram (ECG). AEs will be collected from signing the informed consent form (ICF) up until dosing on Day 1 as pretreatment events (PTEs), and any event that occurs from dosing until 14 days after the last dose will be captured as an AE. Vital signs will be recorded at Screening, Inpatient Check-in (Day -1), and throughout the dosing period. Vital signs will include tympanic body temperature measurement, blood pressure, respiration rate, and pulse (beats per minute [bpm]). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day -1) 15 minutes apart. Heart rate and blood pressure will be measured after at least 5 minutes supine and again at 2 minutes after standing for all scheduled timepoints.

Standard 12-lead ECGs will be recorded at Screening, Inpatient Check-in (Day -1), and periodically throughout the dosing period. Triplicate ECGs will be taken at each timepoint.

A complete list of safety assessments is provided in Section 9.1, and the full Schedule of Study Procedures is provided in Appendix A.

- PK:

The plasma PK parameters are used as PK endpoints to determine drug exposure at each dose and facilitate dose escalations.

Plasma samples will be collected for the determination of concentrations of CVN766 throughout the study as prescribed in the Schedule of Study Procedures (Appendix A). Cerebrospinal fluid (CSF) samples will be collected for the determination of concentrations of CVN766 as described in Section 9.6 and the Schedule of Study Procedures (Appendix A). PK sampling timepoints may be modified or added based on emerging PK data to most appropriately characterize the PK profile of CVN766 as determined by the SRG.

PK parameters of CVN766 will be derived using noncompartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma: C_{max}, AUC from time 0 to the last quantifiable concentration (AUC_t), AUC from time 0 to infinity (AUC_∞), AUC from time 0 to 24 hours (AUC_{24}), time to reach C_{max} (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2z}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F). Multiple-dose PK will also include AUC over the dosing interval (AUC_{tau}), apparent clearance at steady state (CL/F_{ss}), apparent volume of distribution at steady state (Vz/F_{ss}), steady-state nadir concentrations, and accumulation ratios

The PK parameters to be determined from concentrations of CVN766 in CSF will include plasma: CSF ratio by time point. - Pharmacogenomics:

One 6 mL whole blood sample will be collected at pre-dose on Day 1 for pharmacogenomic analysis; this will only be collected once per subject. Two 2.5 mL whole blood samples will be collected at pre-dose on Day 1 and at multiple timepoints post-dose for ribonucleic acid (RNA) pharmacogenomic analysis. The pre-dose RNA blood samples should be collected under fasted conditions and prior to any other blood collection. The samples will be stored for no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from Cerevance. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personal identifying

information, but key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; eligible subjects sign the ICF, which outlines the retention of pharmacogenomic and genotyping analysis in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of this gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

- Endpoints:

The primary endpoints of this study will be the following: percentage of subjects who experience at least one treatment-emergent adverse event (TEAE); percentage of subjects with abnormal and CS safety laboratory, vital signs, or ECG test results at least once post-dose.

The secondary endpoints will be the following plasma PK parameters of CVN766: C_{max}, AUC_{24}, AUC_{∞}, $t_{1/2z}$, AUC from time 0 to end of the dosing interval, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}.

The additional endpoints may include the following plasma PK parameters of CVN766: t_{max}, CL/F, V_z/F, CL/F_{ss}, Vz/F_{ss}, and plasma: CSF ratio.

Exploratory endpoints may include characterization of metabolic enzyme and transporter polymorphisms and/or

[redacted]

Statistical Considerations:

Safety:

AEs will be presented in listings, and TEAEs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be recorded at baseline and post-dose, and changes from baseline will be summarized using shift tables. Individual vital signs will be recorded and observed values and changes from baseline will be summarized. Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and observed values and changes from baseline will be summarized. All summaries will be performed by placebo, each CVN766 dose level (fasted and fed separately), and CVN766 single-dose overall, and separately CVN766 multiple-dose cohorts overall. Placebo data will be pooled across single-dose cohorts and separately pooled across multiple-dose cohorts. Physical exam findings will be presented in data listings.

PK Measures:

Concentrations of CVN766 in plasma and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma and CSF concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically.

PK parameters of CVN766 will be summarized by dose using descriptive statistics. Dose proportionality will be assessed graphically and using a power model.

The concentrations of CVN766 in plasma and CSF will be compared.

Sample Size Justification:

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) is considered sufficient for evaluating the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

3.0 STUDY REFERENCE INFORMATION

3.1 List of Abbreviations

λ_z	terminal elimination rate constant
AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUCτ	area under the plasma concentration-time curve over the dosing interval (τ)
BMI	body mass index
CL/F	apparent clearance after extravascular administration
CL/F_{ss}	apparent clearance after extravascular administration at steady state
[redacted]	[redacted]
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	follicle-stimulating hormone
FT4	free T4
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human-equivalent dose
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
K_2EDTA	dipotassium ethylenediamine tetraacetic acid
LFT	liver function test
MAD	multiple-ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
MRSD	maximum recommended starting dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
Ox1R	orexin 1 receptor
Ox2R	orexin 2 receptor
PK	pharmacokinetic
PRL	prolactin
PT	preferred term
PTE	pretreatment event
QTcB	QT interval with Bazett's correction method
QTcF	QT interval with Fridericia's correction method
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAD	single-ascending dose
SAP	statistical analysis plan
SOC	system organ class
SRG	Safety Review Group
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution after extravascular administration
V_z/F_{ss}	apparent volume of distribution after extravascular administration at steady state
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

The neuropeptide orexin, also known as hypocretin, is produced exclusively in the orexigenic neurons in the hypothalamus. There are two forms of orexin, Orexin-A and orexin-B that are alternatively spliced from the same gene, HCRT. There are two orexin receptors, orexin 1 receptor (Ox1R) and orexin 2 receptors (Ox2R), both of which are G-protein coupled receptors. Both orexin-A and orexin-B can bind to either receptor and in each case, agonist binding results in an increase in intracellular calcium levels. However, while orexin-A is equipotent at both receptors, orexin-B shows a 10-fold selectivity for Ox2R.

Ox1R is selectively expressed in key brain areas relating to psychiatric disorders. Ox1R-expressing neurons in the bed nucleus of the stria terminalis, amygdala, locus coeruleus, raphe nucleus, and the ventral tegmental area are important in regulating emotions of stress, anxiety, motivation, and reward. CVN766 is a potent and highly selective small-molecule Ox1R antagonist with no significant off-target activity. Nonclinical PK and toxicology studies with CVN766 and other Ox1R antagonists have established their pharmacological characteristics and probable safety profile.

Ox2R is expressed in some overlapping areas, including the raphe nucleus, ventral tegmental area, but also areas important to arousal and sleep regulation, including the tuberomammillary nucleus.

The widely used sleep aid suvorexant (Belsomra®), approved for use in Australia, is a dual Ox1R and Ox2R antagonist, but its sleep-inducing effects are generally attributed to its activity on Ox2R. A second dual Ox1R and Ox2R antagonist, lemborexant, appeared safe and effective in clinical studies, has been approved in many countries worldwide, and has been submitted for marketing authorization in Australia.

Clinical effects to be expected of a selective Ox1R antagonist remain uncertain. CVN766 has not yet been studied in humans. Other selective Ox1R antagonists have reported early-stage human clinical trials, notably JNJ-61393215 (ClinicalTrials.gov Identifier: NCT04080752; Salvadore *et al.*, 2020) and ACT-539313 (NCT01954589; Kaufmann *et al.*, 2020; Kaufmann et al., 2021). Both drugs were well tolerated and deemed safe for investigational use, the most common AEs being somnolence and mild headache.

4.2 Rationale for the Proposed Study

CVN766 is a highly selective orexin-1 receptor (Ox1R) antagonist and may have utility as treatment for psychiatric disorders including schizophrenia, panic disorder and anxiety, and addiction. Its safety and PK profile have been preliminarily established in nonclinical toxicology studies. The present study will be the first conducted in humans with CVN766 and will examine the compound's safety, tolerability, and PK in healthy subjects.

Nonclinical pharmacology, toxicity, and pharmacokinetic (PK) studies support the proposed escalating single- and multiple-dose study of CVN766 in healthy subjects with a starting dose of 5 mg. Section 6.2 outlines the justification for the planned dose ranges.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects.

5.1.2 Secondary Objectives

- To characterize the single-dose PK profile of CVN766 in plasma, and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma, and CSF
- To assess the effect of food on the bioavailability of CVN766 in the current formulation

5.1.3 Exploratory Objectives

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints of this study will be the following:

- Percentage of subjects who experience at least one treatment-emergent adverse event (TEAE)
- Percentage of subjects with abnormal and clinically significant (CS) safety laboratory test results at least once post-dose
- Percentage of subjects with abnormal and CS electrocardiogram (ECG) test results at least once post-dose
- Percentage of subjects with abnormal and CS vital sign measurements at least once post-dose

5.2.2 Secondary Endpoints

- Single-dose plasma PK parameters of CVN766 including time to maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to 24 (AUC_{24}) and time 0 to infinity ($AUC\infty$), and terminal elimination half-life (t1/2z)

- Multiple-dose plasma PK parameters of CVN766 including C_{max}, AUC from time 0 to the end of dosing interval, t1/2z, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}
- Single-dose and multiple-dose CSF concentrations and CSF: plasma ratios of CVN766

5.2.3 Additional Endpoints

- Change from baseline in safety laboratory and ECG test results and vital signs
- Additional plasma PK parameters of CVN766 ie, ,CL/F and V_z/F

[redacted]

- Characterization of metabolic enzyme and transporter polymorphisms

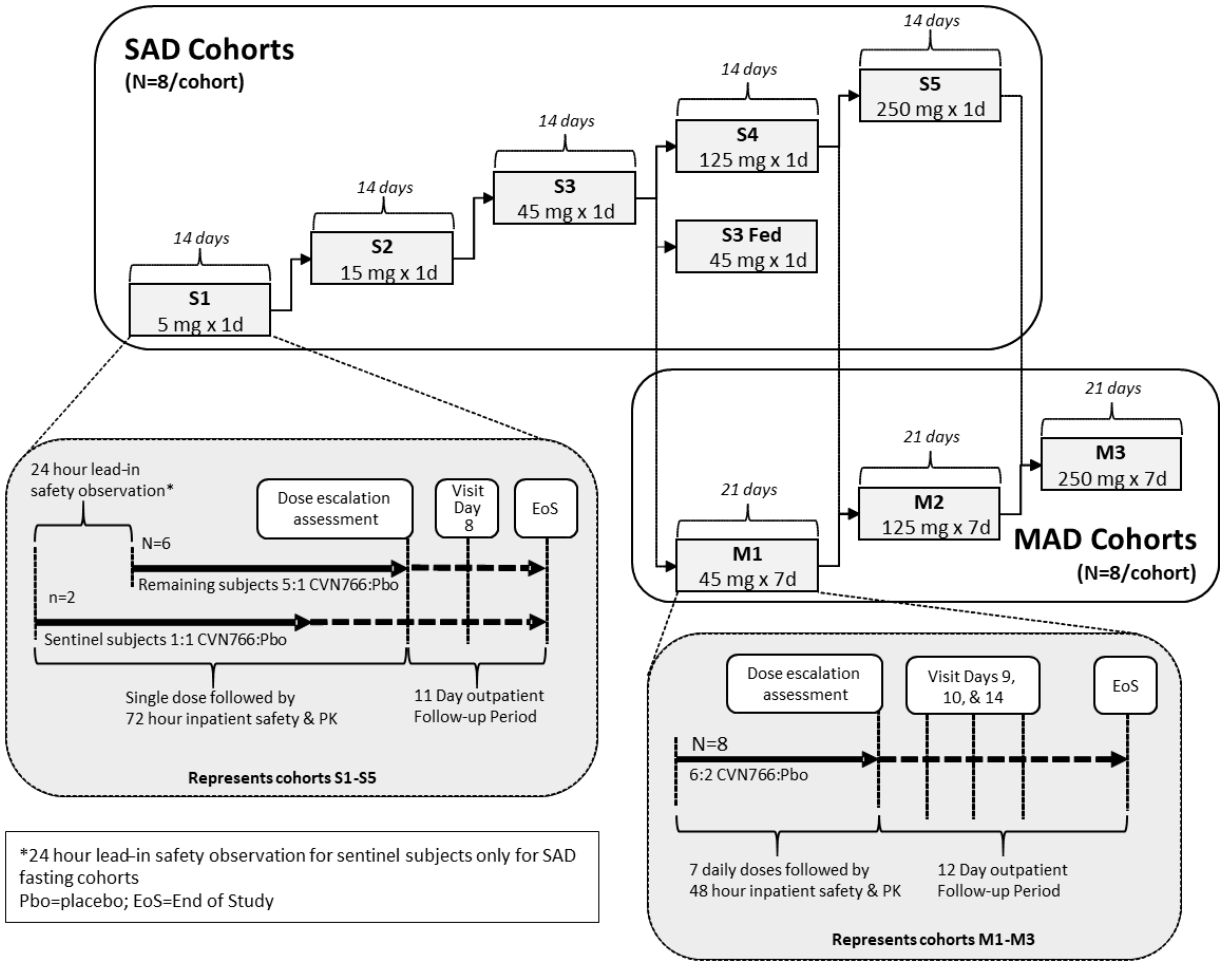
[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled, single- and multi-dose ascending study in healthy subjects. Figure 1 provides a schematic illustration of the study.

Figure 1 CVN766-101 Study Schematic



6.1.1 Part 1: Single-Dose Regimen and Fasted-Fed Crossover

Approximately 40 subjects will be enrolled in 1 of the 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. Dose escalation will only occur after a fully blinded review of all available safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and available PK data, including at least a 72-hour follow-up of the most recent cohort.

The planned dose levels are provided in Table 5. Each cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a single dose of CVN766 and 2 subjects will receive a matching placebo under overnight fasted conditions.

Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 to the remainder of subjects within the cohort. After blinded review of 24-hour post-dose safety and tolerability data, the remaining 6 subjects of each cohort may be dosed provided that the adverse event (AE) profile of CVN766 in the first 2 subjects is considered acceptable.

Subjects for all cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments at least 72 hours after dosing. On Day 1, subjects will undergo safety monitoring (including labs, physical exam, abbreviated neuro exam, cardia telemetry at 12-hours pre-dose) and PK sampling from blood plasma through 72 hours post-dose. In addition, for cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. For subjects participating in the SAD cohorts, the total confinement period will be 4 nights unless extended for management of AEs at the discretion of the Investigator. Follow-up assessments will occur on approximately Days 8 and 14.

To assess the effect of food on bioavailability of CVN766 in suspension formulation, single-dose administration will be repeated in a single cohort after ingestion of a standardized high-fat high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the S3 cohort dose level has been assessed, the S3 cohort subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives has lapsed based on preliminary PK data, whichever is longer) and will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish the entire content of their breakfast within 25 minutes and will receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

An outline of the single-dose study visit schedule is included in Table 1. A Schedule of Study Procedures is listed in Appendix A.

Table 1 Single-Dose Visit Schedule

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK & Safety Assessments	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. Subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required at Day -1.

(b) CSF collection will apply only to cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

6.1.2 Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 subjects will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. Dosing will be administered in the fasting state; this can be changed by the SRG if exposure is found to be higher in the fed state. The dose levels planned to be studied in the multiple-dose regimen (M1 through M3) are provided in Table 5. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily dose of CVN766, and 2 subjects will receive matching placebo for 7 days. However, the duration may be increased to ≤14 days at the discretion of the safety review group (SRG) if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in cohort M1 only, from urine through 24 hours post-dose. In cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7), subjects will additionally undergo PK sampling from CSF via lumbar puncture at 3 hours post-dose. If needed to resolve questions arising from prior cohorts' data, subjects in cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional plasma PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., t½. The total confinement period will be 9 nights unless extended for additional dosing days or for management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose. A summary of multiple-dose study visits is included in Appendix A.

Table 2 Multiple Dose Visit Schedule

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a,f]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g. Days 8-9)	3 days ±0 after last dose (e.g. Day 10) & 7 days ± 1 after last dose (e.g. Day 14)	14 days ±2 after last dose (e.g. Day 21)

(a) CSF sampling will occur on Day 7 in cohorts M1 and M2. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after the last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in cohort M1.

6.1.3 Dose Escalation

The SRG will be comprised of the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for ongoing review of safety, tolerability, clinical laboratory results, and available PK data and deciding to:

- Expand each single-dose cohort from the sentinel cohort to the full cohort (based on a review of at least 24 hours post-dose safety data from each of the sentinel subjects),
- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data including at least 72 hours post-dose safety data and clinical laboratory results from each of the subjects in the current cohort),
- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data including at least 48 hours post 7th dose safety data from each of the subjects in the current cohort),
- Add additional dose cohort(s) in either the single- or multiple-dose studies,
- Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days

If 2 or more subjects in a single cohort experience the same type of serious or medically adverse event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

For each cohort (including sentinel subjects, where applicable), the SRG will carefully review the available blinded safety, tolerability, clinical laboratory results, and PK data to determine whether dosing should stop or continue (and, if continued, at what dose, including whether to repeat the previous dose), whether additional sequential dosing should be implemented in future cohorts or whether the blind should be broken to identify whether the subjects received CVN766 or placebo. However, precautions must be taken not to unblind the study staff, including the investigator.

If all doses are tolerated, then additional cohorts with higher doses may be considered; The actual choice of the subsequent dose level will occur after the full review of the available blinded safety, tolerability, clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level. If necessary, additional cohort(s) may be added to fully characterize the safety and tolerability of CVN766.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all available safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 (minimally including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of dose level may be modified by the SRG after review of the available blinded safety, tolerability, and clinical laboratory results and PK data in the preceding multiple-dose and next-higher-dosage single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose

cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

All AEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge, will be evaluated to assess the need for the subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (Section 6.3.1).

Additionally, the SRG may decide not to escalate the dose for a particular cohort but rather administer the same or a lower dose level to the next cohort. Additional/ Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

6.2 Justification for Study Design, Dose, and Endpoints

The study is double-blind and placebo-controlled to avoid subjective bias in the assessment of the safety and tolerability of CVN766. Dose escalation will be predicated on a review of available blinded safety, tolerability, and PK data observations for each prior dose cohort.

The sponsor has selected the starting dose level considering the FDA Guidance for Industry (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 06 July 2005) and providing additional safety factors to the initial calculations based on the principles outlined in the guidance. The toxicity profile of CVN766 after oral dosing was examined in repeat dosing studies in rats and dogs. Scaling based on body surface area was conducted by multiplying the NOAELs for the most sensitive animal species by the appropriate conversion factors. Based on these calculations and applying a 10-fold safety margin below the NOAEL human-equivalent dose (HED), the maximum recommended starting dose (MRSD) for this first-in-human study is 167 mg for a 60 kg subject. The selected starting dose level is 5 mg.

The study's multiple-ascending dose (MAD) portion seeks to prepare for subsequent repeat dosing studies in subjects. Each MAD dose level will have been studied or exceeded in the SAD portion of the study before its use in a MAD cohort.

Nonclinical toxicity study data provide a basis for calculating the maximum exposure level that can be presumed safe. Escalating to the HED of the NOAEL in the most sensitive animal species, the maximum dose for clinical use is 1670 mg/day.

The projected $t_{1/2z}$ in animal species ranged up to 6.5 hours, so sample collection through Inpatient Discharge 72 hours post-dose is expected to correspond to more than 5 half-lives and is anticipated to be adequate to document elimination of CVN766. The study design allows for collecting additional PK samples at later timepoints if preliminary emerging PK results are indicated.

AEs, physical exams, vital signs, ECG findings, and clinical laboratory results are used as safety assessments to determine dose tolerability and dose-limiting effects of CVN766. The plasma PK and CSF parameters and PK endpoints will help elucidate the pharmacology of CVN766.

Samples for DNA analysis will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety of the study medication indicates an adverse change in the risk profile for the compound, such that the SRG or Institutional Review Board (IRB) considers the risk is no longer acceptable for subjects participating in the study.

In addition, if any of the following occur, further dosing will be withheld until the SRG reviews the relevant data, including unblinded data (if deemed necessary by the SRG request), and will decide whether it is safe to suspend dosing or continue dosing at either the planned or alternative dose levels or decides to prematurely terminate the study:

1. Two or more subjects in any single cohort or across more than 1 cohort experience the same type of serious or Medically Significant event as defined by the Investigator
2. Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limits of normal (ULN) in the absence of a concomitant bilirubin increase (see point 3 below)
3. One or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN in the presence of a total bilirubin increase >2 ×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., “Hy’s Law cases”)
4. Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate study performance, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an IRB/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; applicable investigational sites will follow the procedure during the course of termination or study suspension.

7.0 SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days prior to randomization or first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the investigator's opinion, the subject can understand and sign the Informed Consent Form and comply with all protocol requirements.
2. The subject is a healthy male or female adult who is 18 to 55 years of age, inclusive at the time of ICF.
3. Subject weighs at least 45 kg (99 lbs) and has a BMI between 18.0 and 32.0 kg/m^2, inclusive at Screening.
4. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agree to use two forms of adequate contraception* from signing the ICF throughout the study and for 90 days after the last dose.

   *Definitions and acceptable methods of contraception are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities are defined in Section 9.1.14 Pregnancy.

5. A female subject of childbearing potential who complies with contraception requirements* or a female with no childbearing potential, defined as the subject has been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (defined as continuous amenorrhea of at least 2 years and FSH>40 IU/L).

   Note: hormoral contraceptives are not permitted as referenced in Table 3.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Subject has received any investigational compound within 30 days prior to the first dose of study medication or within 5 half-lives, whichever is greater.
2. Subject is a study site employee or an immediate family member of a study site employee.
3. Subject has evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, full-body allergic skin rash (including hives), psychiatric disorder, evidence of abnormal liver function test, evidence of abnormal renal function tests or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.

   Note: Healthy volunteers with pre-existing stable disease, defined as diseases not requiring significant change in therapy or hospitalization for worsening disease during the 6 wks before enrolment, may be included at the discretion of the Investigator.

4. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking CVN766 or a similar drug in the same class or that might interfere with the conduct of the study
5. Subject has a known hypersensitivity to any component of the formulation of CVN766.
6. Subject has a positive urine result for drugs of abuse at Screening or Inpatient Check-in (Day -1).
7. Subject has a history of a major psychiatric illness or currently receiving therapy for a psychiatric condition
8. Subject has a history of drug abuse or a history of alcohol abuse (more than 14 units/week) within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
9. Subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table as listed in Table 3: Excluded Medications and Dietary Products.
10. Male subjects who do not agree to all the following rules: when sexually active with a female partner(s) of childbearing potential during the study, and for 90 days after the last dose of study drug: a) must use two acceptable methods of birth control (condom or surgical sterilization combined with highly effective method of contraception for the female partner) and b) refrain from sexual activity with female partners who do not use an acceptable method of birth control. Barrier contraception (condom) must be used by all-male subjects who were not surgically sterilized at least 90 days prior to screening. Male subjects must also agree to refrain from sperm donation during the study and until 90 days after the last dose of the study drug.
11. Female subjects who are pregnant or breastfeeding or plan to become pregnant or donate ova during the study or 30 days after the last dose of the study drug. Women of childbearing potential must agree to practice an acceptable method of birth control (e.g., , intrauterine device, barrier, abstinence).
    Note: Hormonal contraceptives are not permitted as referenced in Table 3.

    *Definitions and acceptable methods of contraception are defined in Section 9.1.13. Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.14 Pregnancy.
12. Subject has previously had a seizure or convulsion (lifetime, with the exception of febrile seizures), including absence seizure.
13. Subject has current o recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (i.e., a history of malabsorption, any surgical intervention known to impact absorption [e.g., bariatric surgery or bowel resection], esophageal reflux, peptic ulcer disease, erosive esophagitis, or frequent [i.e., more than once per week] occurrence of heartburn).
14. Subject has a history of cancer or other malignancy, except for basal cell carcinoma or squamous cell carcinoma that has been in remission for at least 3 years prior to Day 1.

15. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or a human immunodeficiency virus infection at Screening.
16. Subject who regularly use nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum). The casual users may participate but must agree to refrain from the time of Screening for the duration of the study or a positive urine cotinine test at Inpatient Check-in (Day 1).
17. Subject has poor peripheral venous access (defined as more than three failed attempts to cannulate.
18. Subject has donated or lost 450 mL or more of their blood volume (including plasmapheresis) or had a transfusion of any blood product within 45 days prior to Day 1.
19. Subject has an abnormal (CS) ECG at Screening or Inpatient Check-in (Day -1). Entry of any subject with an abnormal (NCS) ECG must be approved and documented by signature by the Investigator or medically qualified sub-investigator.
20. Subject has a supine blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 40 to 90 mm Hg for diastolic, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).
21. Subject has a resting heart rate outside the range of 40 to 100 bpm, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).
22. Subject has a QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms, confirmed with one repeat testing at the Screening Visit or Inpatient Check-in (Day -1) Visit.
23. Subject has abnormal Screening or Inpatient Check-in (Day -1) laboratory values that suggest a CS underlying disease or subject with the following lab abnormalities: ALT and/or AST >1.5 the ULN, confirmed with one repeat testing.
24. Subject has a risk of suicide according to the investigator's clinical judgment or has made a suicide attempt in the previous 2 years.

7.3 Excluded Medications and Dietary Products

Use of the agents in Table 3 (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 3 Prohibited Medications and Dietary Products

28 days prior to Inpatient Check-in	7 days prior to Inpatient Check-in	72 hours prior to Inpatient Check-in
Prescription medications (including hormonal contraceptives)	OTC medications, including antacids, proton-pump inhibitors, and H2 receptor antagonists [(a)]	Products containing caffeine or xanthine (e.g., tea or coffee)
Nicotine-containing products	Vitamin supplements	poppy seeds
Nutraceuticals (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Orexin receptor antagonists including suvorexant (Belsomra®), lemborexant (Dayvigo®), and related compounds	
Immunization/Vaccines [(b)]	Alcohol-containing products	
Known strong inhibitors/inducers of CYPs 3A4/5 [(c)]		

CYP= cytochrome P-450, OTC=over the counter.

[(a)] Occasional use of acetaminophen (~1 g/day) and 400mg ibuprofen TDS when required or other medication as approved by the sponsor's Medical Monitor on a case-by-case basis is allowed except on Day 1

[(b)] Inclusive of but not limited to H1N1 and flu vaccinations. Subjects who have received the COVID-19 Vaccine between -10 and -28 days may participate provided they did not experience any side effects of any description. COVID-19 vaccine doses may be administered 7 days post-study medication dosing.

[(c)] e.g., chloramphenicol, clarithromycin, ketoconazole.

Subjects must be instructed not to take any medications during study participation, including over-the-counter drug products, without first consulting with the investigator.

7.4 Diet, Fluid, Activity Control

Subjects will be confined to the clinic for each of the dosing days as well as a period of time sufficient to collect additional post-dose PK samples and monitor for safety and tolerability (Day -1 through Day 4 for single-dose cohorts and Day-1 through Day 9 for multiple-dose cohorts). During confinement, subjects will be provided 3 standard meals and a snack per day, each containing approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be similar in nutritional content for each subject in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study. Breakfast will not be provided on dosing days until at least 1 hour after dose administration unless otherwise indicated (i.e., Days 2-6 for MAD cohorts). The meal start and stop times and percentage of the meal consumed will be recorded in the source and appropriate electronic case report form (eCRF) for all meals served on dosing days.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence, followed by the study procedure and then the meal.

Subjects will remain in bed at a semi-supine position for 4 hours following the dose administration, except as necessitated by the occurrence of an AE or study procedures (e.g., obtaining a 12-lead ECG). Subjects must refrain from strenuous exercise from 72 hours before Inpatient Check-in and until check-out.

On the dosing days where extensive PK and/or CSF sampling is indicated (i.e., single-dosing Day 1 and first and last multiple-dose days, e.g., days 1 and 7), CVN766 or placebo suspension will be administered with approximately 240 mL of water after a fast of at least 10 hours. Subjects will continue to fast for an additional 4 hours after dosing and eat lunch following the 4-hour PK blood and CSF collection. Subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration.

For the food effect cohort (S3), single-dose administration will be administered after ingesting a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Subjects will finish the entire content of their breakfast within 25 minutes and will receive an investigational product 30 minutes (±5 minutes) after beginning the meal. The S3 (food effect) cohort meals may be staggered to ensure dosing occurs 30 minutes after the beginning of the meal.

Subjects will also fast for at least 10 hours prior to safety laboratory collection times as indicated. However, consumption of water as desired is permitted during this time, except for dosing days, as indicated above.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, Section 9.1.15.

1. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status) if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 × ULN, or
   – ALT or AST >5 × ULN and persists for more than 2 weeks, or
   – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or
   – ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
3. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to reach the subject must be documented.

5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal, and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

6. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator must discontinue a subject's study participation at any time during the study when the subject meets the study discontinuation criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's involvement be terminated, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects may be replaced at the Sponsor's discretion.

Participants who withdraw from the study prior to dosing may be replaced. If a participant withdraws after the first dose of study medication or placebo, no replacement will occur.

8.0 CLINICAL TRIAL MANAGEMENT

8.1 Study Medication and Materials

This section contains information regarding all medication and materials provided directly by the sponsor and/or sourced by other means required by the study protocol, including important sections describing the management of clinical trial material.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN766 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral suspensions as needed throughout the study.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN766 and Matching Placebo

CVN766 drug substance is supplied as a bulk powder to the clinical site and then compounded into oral suspensions. A matching placebo suspension containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor. See Table 4 for the composition of the drug product and matching placebo suspensions.

The oral suspensions will be labeled with the appropriate study information and caution statements.

Table 4 Composition of CVN766 Oral Suspension and Matching Placebo

Component	CVN766 Oral Suspension (individual dose)					Matching Placebo
CVN766 drug substance	5 mg	15 mg	45 mg	125 mg	250 mg	NA
Commercial suspending vehicle[a]	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL

NA=Not applicable;

[a] An off-the-shelf commercial suspending vehicle will be used, and the details of the vehicle will be provided in the Pharmacy Manual.

8.1.1.2 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or the sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

[redacted]

8.1.2 Drug Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN766 drug substance is stored at room temperature. CVN766 oral suspension and matching placebo should be stored according to instructions in the Pharmacy Manual.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the Investigator and in fed or fasting conditions as outlined in Section 7.4.

The exact time of dose will be recorded in the source documents and on the appropriate eCRF.

The planned dose levels to be studied are provided in Table 5. If the planned highest dose level does not reach the desired exposure, then additional cohorts with higher dose levels may be considered. If all planned dose levels are not tolerated in an earlier cohort, the following cohorts may study lower doses at the discretion of the Investigator and the SRG. The actual choice of the subsequent dose level will occur after a full review of the available blinded safety, tolerability, and clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Table 5 describes the treatment and medication type that would be provided for each cohort.

Table 5 Planned Single and Multiple Dose Levels by Cohort

Single-Dose Cohorts			
Cohort	**Planned Treatment***	**No. of Subjects**	**Medication Type**
S1	CVN766 5 mg	6	oral suspension
	Placebo	2	oral suspension
S2	CVN766 15 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fasted	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fed (Same 8 subjects as in the S3 FASTED cohort)	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S4	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
S5	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension
Multiple Dose Cohorts			
Cohort	**Planned Treatment***	**No. of Subjects**	**Medication Type**
M1	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
M2	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
M3	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension

* Dose (active or placebo) is in 10 mL of suspension.

8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 9.7.2, PTEs and AEs.

Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure outlined in Section 9.7.4, Collection and Reporting of SAEs.

In the event of an overdose, supportive measures should be employed as needed, e.g., administration of supportive therapy as dictated by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract, or initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive a unique randomization number.

The clinical site will use the unique identifier to facilitate the pre-labeling of PK samples. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory and will be used by the laboratory to report the subject data results. This unique identifier should only be used for the purposes described in this section. This identifier will be assigned upon randomization in the order in which subjects receive their first dose of the study drug.

8.3 Randomization Code Creation and Storage

The sponsor or their designee will generate the randomization schedule and provide a copy to the site pharmacist and bioanalytical laboratory prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigative staff unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality assessments should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted to discuss the need for unblinding before the investigational drug blind is broken.

Unblinding envelopes will be supplied to the site prior to the first subject dosing and stored in a central and secure place to ensure access in the event of an emergency. Study staff will be trained on unblinding procedures.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information (except the time) must be recorded on the eCRF.

If any site personnel inadvertently become unblinded, the sponsor must be notified, and the SRG will determine whether to discontinue dosing or withdraw from the study of all affected subjects.

No change should be made to any assessment of the subject after unblinding.

Following assessment of the AE data and pre-defined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis. Based on a review of unblinded data, the sponsor, in consultation with the Investigator, will decide if and how it is appropriate for the study to proceed.

The Randomization schedule for all subjects will be released for analysis after the database for these cohorts is locked. The Investigator will be unblinded after database lock for all the cohorts if necessary.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication, the investigator must maintain records of all study medication delivery to the site, site inventory used by each subject, and return to the sponsor or designee.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list, ensure the quantity is correct, and the medication is received within the labeled storage conditions. If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and send via email and per instructions provided on the form. If any discrepancies exist between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file. The investigator must maintain 100% accountability for all study medication received and dispensed during their entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all study medication on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of the Investigator, site identifier and number, description of study medication, expiry date, and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the ICF are described in Section 14.2.

The ICF must be obtained prior to the subject entering the study and before any protocol-related procedures are performed.

A unique subject screening number (of the form xx-xxx), the first two numbers for the site, subsequent three numbers for subject identification will be assigned to each subject when the ICF is obtained. This subject ID will be used until the subject is assigned their 4-digit randomization number.

9.1.1.1 Pharmacogenomic and Cerebrospinal Fluid Informed Consent Procedure

Pharmacogenomics and cerebrospinal fluid informed consent is a component of the overall study ICF. The requirements are described in Section 14.2.

The pharmacogenomic and (for applicable cohorts) cerebrospinal fluid sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, ethnicity, race as described by the subject, smoking status, and caffeine consumption at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped at or prior to signing the ICF. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days before signing ICF.

9.1.3 Physical Examination Procedure

A physical examination performed by the investigator or medical officer consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) abbreviated neurological exam; and (12) other.

Any abnormal change from the baseline physical examination (Screening and Inpatient Check-in [Day -1]) must be assessed as not CS or CS by the investigator and recorded in the source document and eCRF.

All CS findings/changes, as determined by the investigator, from the baseline physical examination will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 9.8.1 or Section 9.8.2.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug Inpatient Check-in (Day -1) must be assessed as not clinically significant (NCS) or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

Height is recorded centimeters without decimal places, and for weight, it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/[\text{height (m)}]^2$

Results for BMI will be expressed with 1 decimal place.

Example:

Height=176 cm (or 1.76 m), weight=79.2 kg; $BMI=79.2/1.76^2=25.57$ kg/m^2 captured as 25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs will include tympanic body temperature, respiration, pulse, and blood pressure and be collected at timepoints specified in the Schedule of Study Procedures (Appendix A). For eligibility determination, the pulse will not be derived from ECG. Pulse and blood pressure will be measured after at least 5 minutes supine and again after 2 minutes standing.

Vital signs should be measured at the same time (+/- 1 hour) of the day across visits if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority, and vital signs will be obtained within approximately 0.25 hours before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of ICF through the end of the study), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at the signing of ICF. This includes CS laboratory, ECG, or physical examination abnormalities noted at Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 ECG Procedure

Standard 12-lead ECGs will be recorded at timepoints specified in the Schedule of Study Procedures (Appendix A). Triplicate ECGs will be taken at each scheduled time. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

When an ECG is scheduled at the same time as blood draws or vital signs, then the blood draws and vital signs will take priority, and the ECG will be obtained within 0.5 hour before or after the scheduled blood draw/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence, followed by the meal.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-minute rest period for ECG recordings. Should technical difficulties occur during the recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

ECGs will be read automatically, and also, the investigator or sub-investigator will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not CS, or abnormal and CS. Abnormal QTc readings will be manually recalculated and reported by the Investigator on the eCRF. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary. Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals. Paper ECG traces will be recorded for 10 seconds at a standard paper speed of 25 mm/sec, and gain of 10 m/mV or digital recordings will be used.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

All ECGs will be recorded at the time points detailed in Appendix A.

9.1.9 Pharmacogenomic Sample Collection

Every subject must sign ICF/be consented to the sampling of whole blood for pharmacogenomic analysis to participate in the study.

One whole blood sample for DNA isolation and genotyping will be collected at time points specified in the Schedule of Study Procedures (Appendix A) into plastic dipotassium ethylenediamine-tetra acetic acid (K_2EDTA) spray-coated tubes and stored under frozen conditions. In addition, two whole blood samples will be collected at time points specified in the Schedule of Study Procedures (Appendix A) for ribonucleic acid (RNA) pharmacogenomic analysis. The pre-dose RNA blood samples should be collected under fasted conditions and prior to any other blood collection.

DNA may be evaluated for the genetic contribution to how the drug is broken down or affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN766
- Finding out more information about how CVN766 works
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN766
- Identifying variations in genes related to the biological target of CVN766

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN766 and other study medications and for improving the efficiency, design, and study methods of future research studies.

The samples will be stored no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by the sponsor or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from the sponsor. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; every subject must sign the ICF in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA and RNA from the first sample was not successful or possible.

Samples will be frozen at -70°C or lower and shipped separately on dry ice prior to extraction and storage at -70°C or lower. Samples should not be allowed to thaw until processed.

Detailed instructions for the handling and shipping of samples are provided in a separate lab manual.

Genotyping on collected samples may be deferred until after the completion of the study's in-life activities.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 4-digit randomization number.

9.1.10 PK Sample Collection

9.1.10.1 Collection of Blood for PK Sampling

Blood samples for analysis of CVN766 plasma concentrations will be collected into chilled Vacutainers containing K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in a separate lab manual.

In all single-dose cohorts, serial blood samples to determine CVN766 concentrations in plasma will be collected according to Table 7.

Table 6 Collection of Blood Samples for PK Analysis in Single-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24-, 36-, 48-, and 72-hours post-dose.

In all cohorts for Part 2, serial blood samples for determination of CVN766 concentrations in plasma will be collected according to Table 7.

Table 7 Collection of Blood Samples for PK Analysis in Multiple-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 (Day 2 pre-dose) hours post-dose.
	3,4,5,6	Pre-dose (within 15 minutes prior to dosing)
	7	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, and 72 [(a)] hours post-dose.

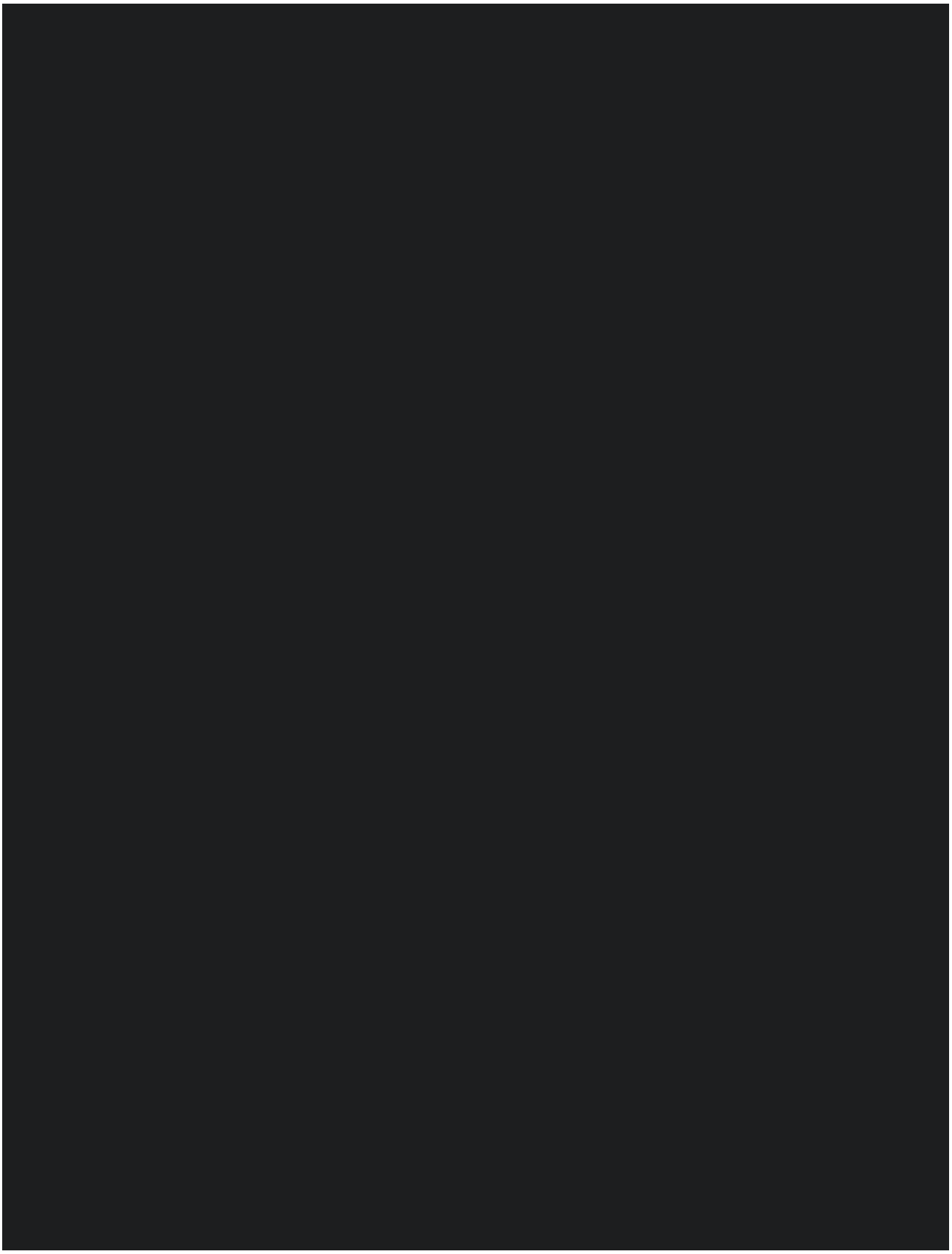
(a) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the 72-hour timepoint is unnecessary.

The PK samples will be collected at the nominal time point; all other assessments will be collected, before or after, within the allowable windows. The actual time of sample collection will be recorded on the source document and eCRF.

Sampling time points may be adjusted or added based on the preliminary emerging PK data collected from prior cohort(s). Still, the total number of samples collected per subject should not exceed the planned number by more than 4.

Placebo samples will not be analyzed by the bioanalytical laboratory except 2 samples per subject receiving placebo, 1 pre-dose, and the other around the expected time at which C_{max} occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional subjects could have been on active treatment.

[redacted]



9.1.11 PK Parameters

PK parameters of CVN766 will be derived using non-compartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma and CSF:

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from the time of dosing to the time of the last measurable concentration
AUC_∞	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_\infty=AUC_t+C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration.
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours, calculated using the linear trapezoidal rule.
AUC_τ	Area under the plasma concentration-time curve over the dosing interval (τ)
C_{max}	Maximum observed plasma concentration.
C_{min}	Minimum observed plasma concentration; pre dose trough concentration
	Minimum observed plasma concentration at steady state, on last day of dosing
CL/F	Apparent clearance after extravascular administration, calculated as Dose/AUC_∞ after a single dose.
CL/F_{ss}	Apparent clearance after extravascular administration at steady state, calculated as $Dose/AUC_{tau}$
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.
V_z/Fss	Apparent volume of distribution during the terminal phase after extravascular administration at a steady-state, calculated as $(CL/F_{ss})/\lambda_z$
CSF	
plasma: CSF ratio	ratio of the drug concentration in plasma vs. CSF

Additional PK parameters may be calculated as appropriate.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures on the days/times stipulated in the Schedule of Study Procedures (Appendix A).

Table 1 lists the tests that will be obtained for each laboratory specimen.

Table 10 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
RBC	ALT	pH	Prolactin

WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets PT/INR	Albumin Alkaline phosphatase Lipase (d) AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc.	TSH (and if abnormal) reflex FT4

Diagnostic Screening:

Serum	**Urine/ Blood**
Serum hCG (a) FSH (b) Hepatitis panel, including HBsAg and anti-HCV (e) Human Immunodeficiency Virus (HIV) antibody	Drug screen including amphetamines (AMP), barbiturates (BAR), benzodiazepines (BZO), cannabinoids, cocaine (COC), opiates (OPI), alcohol, cotinine © methamphetamines, methadone (MET), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), tetrahydrocannabinol (THC) Urine Pregnancy Test (a)

FT4= free T4, FSH= follicle-stimulating hormone, GGT=γ-glutamyl transferase, hCG= human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells, TSH= thyrotropin, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening,
Urine Pregnancy Test will be done at Check-in (Day -1).
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.
(c) To be performed at Screening and Inpatient Check-in (Day -1).
(d) To be performed at Day -1 and 24- and 48-hours post-dose.
(e) Screening Visit only

The local laboratory will perform all clinical laboratory tests. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to the sponsor or designee in the format requested by the sponsor. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the Investigator or sub-investigator, indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Subjects will be referred to their primary care physician for follow-up of any clinically significant findings or where the investigator or medically trained sub-investigator deems appropriate.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will

be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

(Please refer to Section 7.5 for discontinuation criteria and Section 9.8.3 for the appropriate guidance on Reporting of Abnormal LFT in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN).

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 9.8.3 Reporting of Abnormal LFT for reporting requirements).

9.1.13 Contraception and Pregnancy Avoidance Procedure

From the date of signing of ICF, throughout the duration of the study, and for 30 days after the last dose of study medication, females of childbearing potential* must use **two** acceptable methods of contraception and must agree not to donate eggs; Nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use **two** acceptable method(s) of contraception throughout the duration of the study, and for 90 days after the last dose of study medication. In addition, males must be advised not to donate sperm for 90 days after the last dose of study medication.

Females of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal.

Menopause is defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented. Male subjects with potentially postmenopausal partners who are under the age of 55 years must use condoms unless their partner's postmenopausal status has been confirmed by FSH level.

**Sterilized males should be at least 90 days post-vasectomy and confirm that they have obtained documentation of the absence of sperm in the ejaculate.

Acceptable and highly effective methods of contraception are:

Note: hormonal contraceptives are not permitted as referenced in Table 3.

- Nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomised subject/partner with documented azoospermia 90 days after procedure, if that partner is the sole sexual partner
- Same-sex intercourse, if used consistently for the duration of the study and post dosing as specified above

Complete abstinence, defined as the complete avoidance of heterosexual intercourse - is an acceptable form of contraception if used consistently throughout the duration of study and for the durations after dosing specified for males and females above. It is not necessary to use any other method of contraception when complete abstinence is elected. Females of childbearing potential who choose complete abstinence must continue to have pregnancy tests as per protocol. The reliability of sexual abstinence needs to be evaluated by the Investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Subjects will be provided with information on acceptable methods of contraception as part of the subject's informed consent process and will be asked to sign an ICF stating that they understand the requirements for avoidance of pregnancy, egg donation, and sperm donation during the study.

9.1.14 Pregnancy

Women who are pregnant or breastfeeding will not be included in this study.

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of the blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to the final outcome using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted for 8 weeks.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign ICF. If the subject is not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria
- Significant protocol deviation
- Lost to follow-up

- Voluntary withdrawal
- Study termination
- Other

Subject numbers assigned to subjects who fail screening should not be reused.

If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were two separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The study-related procedures schedule for all evaluations is shown in Appendix A and is not duplicated in the following sections.

9.3.1 Screening

Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures. Subjects who are screening failures may be screened a second time if their reason for failing screening is thought to be resolved. Rescreened subjects will receive a new Screening number.

9.3.2 Inpatient Check-In

All subjects will be admitted to the study clinic the day prior to randomization and first dose. Subjects participating in the food effect cohorts will also check into the study clinic the day prior to the scheduled dosing.

9.3.3 Final Visit (discharge day from clinic)

Subjects will be confined to the study clinic for the duration of the treatment period to permit supervised dosing of study drug and repeat study assessments. Subjects participating in the single-dose study and food effect assessment will be discharged no sooner than 72 hours post-dose, and subjects participating in the multiple-dose study will be discharged no sooner than 48 hours following their last dose.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

Subjects who discontinue dosing or decide to check out of the study clinic early will be advised to allow the Investigator (or authorized designees) to complete early termination assessments for safety purposes prior to discharge. The reason for discontinuation must be documented in the source document and eCRF.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit

The Follow-up Visit will occur by telephone approximately 14 days (±2) after the final dose of study drug for the SAD cohorts and MAD cohorts unless abnormal CS findings were observed upon discharge or the SRG has determined additional PK sampling timepoints are indicated. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.

9.4 Biological Sample Retention and Destruction

In all cohorts except S3 (fed), blood serum will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed. Samples will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law.

Blood specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. After extraction and purification, the genetic material will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law. Blood and urine samples for PK analysis will be collected as described in Section 9.1.12, PK Sample Collection. Once PK analysis is complete, backup plasma and urine samples will be preserved and retained at a biorepository selected by the sponsor for up to, but not longer than, 15 years or as required by applicable law, to enable the conduct of exploratory, qualitative, metabolite identification studies or measurement of target related biomarkers, should the sponsor decide these are informative. The sponsor has put a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with

code numbers; the samples are stripped of all personally identifying information, but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. The Investigator will notify the sponsor of any subject who has withdrawn consent for the DNA and RNA analysis.

9.5 Blood Volume

Direct venipuncture or intravenous cannula is the preferred method of blood collection. Any other method will need to be approved by the sponsor. The maximum volume of blood at any single day is approximately 111 mL, with the maximum amount not to exceed 500mL for the duration of study participation.

9.6 CSF Volume

CSF will be collected by lumbar puncture, performed by a skilled and qualified individual. The maximum volume of CSF to be collected will be approximately 10 mL per subject.

9.7 Definitions

9.7.1 PTE

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed the ICF to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.7.2 AE

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a CS abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

9.7.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs)
- Necessitate therapeutic intervention
- Require an invasive diagnostic procedure
- Require discontinuation or a change in dose of study medication or a concomitant medication
- Be considered unfavorable by the investigator for any reason

- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be CS (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention
- If abnormal laboratory values or ECG findings are the results of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of the ICF) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays, etc.) should NOT be recorded as PTEs unless related to study procedures.
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy), any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious, or severe in nature; that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., "worsening of…")
- If a subject has a concurrent degenerative condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…")

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE.
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Changes in severity of AEs /Serious PTEs:
- If the subject experiences changes in the severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs,but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF

9.7.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE-THREATENING
    - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization
4. Results in persistent or significant DISABILITY/INCAPACITY
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above
    - May expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization
    - Includes any event or synonym described in the Medically Significant AE List (Table 11)

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 9.8.1 and 9.8.2).

Table 11 Medically Significant AE List (categorized as Serious Adverse Events)

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

9.7.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

9.7.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from the administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from the administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

9.7.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is a reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

9.7.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

9.7.9 Stop Date

The stop date of the AE/serious PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

9.7.10 Frequency

Episodic AEs/serious PTE (e.g., vomiting) or those which repeatedly occur over a period of consecutive days are intermittent. All other events are continuous.

9.7.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE
- Dose not changed – the particular AE did not require stopping a study medication
- Unknown – only to be used if it has not been possible to determine what action has been taken
- Not Applicable – a study medication was stopped for a reason other than the particular AE, e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE

9.7.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/serious PTE
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/serious PTE with the condition remaining “recovering/resolving”
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms, or laboratory value on the last day of the observed study period had got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/serious PTE state remaining “Not recovered/not resolved”
- Resolved with sequelae – the subject recovered from an acute AE/serious PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis
- Fatal – the AEs/PTEs which are considered as the cause of death
- Unknown – the course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study

9.8 Procedures

9.8.1 Collection and Reporting of AEs

9.8.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication Day 1 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs will be collected for the duration of study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1. Routine collection of AEs will continue until 14 days following last dose.

9.8.1.2 PTE and AE Reporting

At each study visit, the investigator or designee will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not be followed up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

9.8.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE form must be completed in English and signed by the investigator immediately or within 24 hours of the first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study medication(s)
- Causality assessment

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

9.8.3 Reporting of Abnormal LFT

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 9.8.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the SAE form (as per Section 9.8.3).

9.9 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resuspension or permanent outcome of the event. The timelines and procedures for follow-up reports are the same as those for the initial report.

9.9.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.0 STUDY-SPECIFIC COMMITTEES

The Safety Review Group (SRG) will be comprised of the Investigator, Medical Monitor, Cerevance Medical Officer and may include other sponsor representatives. A pharmacokineticist and other subject matter experts may participate as needed. Responsibilities of the SRG are outlined in Section 6.1.3.

11.0 DATA HANDLING AND RECORDKEEPING

AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary. All terms will be coded using the dictionary version available at the start of the study.

11.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The Investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure the accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without the written permission of the sponsor.

11.2 Record Retention

The investigator agrees to keep the records stipulated in Section 11.2 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), an electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study

records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of the subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to unblinding of the subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

12.1.1 Analysis Sets

Safety Set

The Safety Analysis Set will consist of all subjects who are enrolled and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Set

The PK set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration.

If any subjects are found to be non-compliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.

12.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for pooled placebo, CVN766 dose level, CVN766 overall, and overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for pooled placebo, each CVN766 dose level, CVN766 overall, and overall. Individual subject demographic and baseline characteristics data will be listed.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

12.1.3 PK Analysis

The concentration of CVN766 in plasma, and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically. Descriptive statistics (arithmetic mean, SD, median, minimum and maximum) will be used to summarize the plasma and CSF PK parameters for CVN766. In addition, geometric mean and coefficient of variation will be computed

The effect of fed/fasting state on PK and bioavailability of CVN766 will be characterized.

Plots of C_{max} and AUCs, as well as dose-normalized C_{max} and AUCs, versus doses, will be generated.

Dose proportionality will be tested for CVN766 C_{max} and AUCs using a power model.

A more detailed analysis will be presented in the SAP.

12.1.4 Safety Analysis

12.1.4.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. Treatment-emergent AEs with onset occurring within 30 days (onset date – last date of dose +1 ≤30) after study drug administration will be listed and included in the summary tables. Treatment-emergent AEs will be summarized by pooled placebo, each CVN766 dose level and CVN766 overall by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs. not-related), severity of AEs, and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs, including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs. All AEs will be listed.

12.1.4.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that are abnormal and CS will be summarized and listed. Baseline, post-dose, and change from baseline to post-dose laboratory data will be summarized for pooled placebo, each CVN766 dose level, and CVN766 overall. All clinical laboratory data will be listed.

12.1.4.3 Vital Signs

Individual results of vital signs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from Baseline in vital sign measurements will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. All vital sign data will be provided in the data listings.

12.1.4.4 ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from baseline in quantitative ECG parameters will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. Shift tables may be generated for the investigator's ECG interpretations that changed from baseline to the post-dose collections by the above groups. All ECG data will be provided in the data listings.

12.1.4.5 Other Variables

Physical exam findings and suicidal assessments will be presented in data listings.

12.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

12.3 Determination of Sample Size

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) is considered to be sufficient for the evaluation of the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 12 defines the windows allowed for sample collections.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 12 Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes pre-dose	0 hour
±5	immediately post-dose to ≤6 hours
±10	>6 hours to ≤12 hours post-dose
±15	>12 hours to ≤24 hours
±30	>24 hours

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of Australia (i.e., Therapeutic Goods Administration [TGA]) and foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 13.1.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICFs, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before the commencement of the study (i.e., before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from a competent authority to begin the trial. Until the site receives drug/notification, no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence on participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without providing a reason and without prejudice to their other medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and the subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

Subjects who consented and provided a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

14.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and the accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study, including data and information generated by the investigator, without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, the sponsor will register this clinical trial on ClinicalTrials.gov (and possibly on other publicly accessible websites) before the start of study.

Sponsor contact information, along with the investigator's city, state, country, and recruiting status, will be registered and available for public viewing. Once subjects receive investigator contact information, they may call the site and request enrollment into the trial. The investigative site(s) are encouraged to handle such trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

14.4.3 Clinical Trial Results Disclosure

If required at the conclusion of the study, the sponsor will post the results on ClinicalTrials.gov or other publicly accessible websites, as required by applicable national and local laws and/or regulations.

14.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

15.0 REFERENCES

FDA Guidance for Industry: Food-effect bioavailability and fed bioequivalence studies (Dec 2002).

FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 06 July 2005. Publication No. 5541.

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Appendix A Schedule of Study Procedures

SAD Cohorts 1, 2, 4, 5	Screening	Check-in	Dosing & Observation			Discharge (a)	Outpatient Visit	Early Termination	Follow-up
Study Day:	**-28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**		**Day 14 (±2) (b)**
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics and medical history	X								
Medication history	X								
Abbreviated Neuro Exam		X	X	X	X	X			
Physical examination	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X	
Urine drug & cotinine screen	X	X							
Concomitant medications (e)	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X								
FSH (g)	X								
Serum Pregnancy test (hCG)	X								
Urine Pregnancy test		X							
CV Telemetry (n)			X	X					
ECG (h)	X	X	X	X	X	X	X	X	
PGx DNA sample collection (i)			X						
PGx RNA collection (j)			X						
PK blood collection (k)			X	X	X	X		X	
Standardized pre-dose meal (S3 fed cohorts only)			X						

Study drug dosing			X						
PTE assessment (l)	X	X	X						
AE assessment (m)			X	X	X	X	X	X	X

PGx=pharmacogenomic.
(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) 2.5 mL whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples (6 mL) for PK analyses will be collected at time points indicated in Table 7.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) CV telemetry should be recorded at least 12 hours prior to dosing, and up to 24 hours after dosing

Cohort 3 SAD Fasted-Fed Crossover	**Screening**	**Dosing and Observation Inpatient**				**D/C**		**Inpatient** No sooner than +14 days or 4 half-lives of Day 8 visit					**+4 days post D/C**	**E/T**	**Follow-up**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**			**Day 14 (±2) (b)**
Informed consent	**X**							X							
Inclusion/exclusion criteria	X	X						X							
Admitted to the Clinic		X													
Demographics and medical history	X														
Medication history	X							X							
Abbreviated Neuro Exam		X	X	X	X	X		X	X	X	X	X			
Physical examination	X	X				X	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X				X	X	X	
Urine drug & cotinine screen	X	X						X							
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X						X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X		X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X														
Urine Pregnancy test		X						X							
CV Telemetry (n)			X	X				X	X	X					
ECG (h)	X	X	X	X	X	X	X		X	X	X	X	X	X	
PGx DNA sample collection (i)			X						X						
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X			X	X	X	X		X	
Lumbar puncture & CSF collection (k)			X												
Standardized pre-dose meal									X						

Study drug dosing			X						X						
PTE assessment (l)	X	X	X					X	X						
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X
Discharged from Clinic						X						X		X	

*S3 Cohort will return no sooner than Day 14 or 4 half-lives (whichever is greater) after Day 8 for the Fed portion. The Fed portion will commence on Day -1 will all the same schedule of events with the exception of **dosing will be post-meal.**

PGx=pharmacogenomic.
(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) 2.5 mL whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples (6 mL) for PK analyses will be collected at time points indicated in Table 7.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) CV telemetry should be recorded at least 12 hours prior to dosing, and up to 24 hours after dosing

Multiple-Dose Regimen Cohorts	SCR	Check-in	Inpatient Dosing & Observation								Inpatient Discharge (a)	Outpatient Visit		E/T	Follow-up
Study Day:	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	(model for additional dosing days) Day 6	Day of last dose (e.g. Day7)	1 day after last dose (e.g. Day 8)	2 days after last dose (e.g. Day 9)	3 days ±0 after last dose (e.g. Day 10) (o)	7 days ±1 after last dose (e.g. Day 14)		14 days ±2 after last dose (e.g. Day 21 ±2) (b)
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics and medical history	X														
Medication history	X														
Abbreviated neuro exam		X	X						X		X		X	X	
Physical examination	X	X	X						X		X		X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X		X	X	
Weight, height, and BMI (d)	X	X	X						X		X		X	X	
Urine drug & cotinine screen	X	X													
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X													
Clinical laboratory tests (f)	X	X	X		X		X		X	X	X		X	X	
Hepatitis panel	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X														
Urine Pregnancy Test		X													
ECG (h)	X	X	X	X	X	X	X	X	X	X	X		X	X	

Multiple-Dose Regimen Cohorts	SCR	Check-in	Inpatient Dosing & Observation								Inpatient Discharge (a)	Outpatient Visit		E/T	Follow-up
Study Day:	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	(model for additional dosing days) Day 6	Day of last dose (e.g. Day7)	1 day after last dose (e.g. Day 8)	2 days after last dose (e.g. Day 9)	3 days ±0 after last dose (e.g. Day 10) (o)	7 days ±1 after last dose (e.g. Day 14)		14 days ±2 after last dose (e.g. Day 21 ±2) (b)
[redacted]															
PGx DNA sample collection (i)			X												
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X	X	X	X	X	X	X		X	
Lumbar puncture & CSF collection (k)									X						
Study drug dosing			X	X	X	X	X	X	X						
PTE assessment (l)	X	X	X												
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X

PGx=pharmacogenomic (a) Events listed as occurring at "Inpatient Discharge" visit will occur on that day prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 21 (±2) unless abnormal CS findings were observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per Investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 and Day 7 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Day 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Days 1 through 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days). Hormone laboratory tests (PRL, thyrotropin [TSH], and FT4) will be collected on Days 1 and 7 (morning [fasting] and 3 hours after dosing), Day 9, and Day 14 under fasted conditions. Fasting lipase tests will be collected at Day -1, Days 2, 7, and 8 (pre-dose). An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Screening, Inpatient Check-in (Day -1), Days 1 and 7 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Days 8 and 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days).
(i) One blood sample (6 mL) will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) 2.5 mL whole blood samples will be collected on Day 1 and Day 7 (pre-dose, 8- and 24-hours post-dose) for RNA pharmacogenomic analysis.
(k) Blood samples (6 mL) for PK analyses will be collected at time points indicated in Table 8. CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in cohorts M1 and M2, as indicated in Table 10. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.
(l) PTEs will be collected from signing of ICF up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) 24-hour urine collection is only done for cohort M1, predose and over 24 hours
(o) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the Day 10 visit is not necessary.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (non-routine/nonstandard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conforms to local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in local regulations, are met.
8. Obtain valid ICF from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entering into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Cerevance will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, and Japan), including the following:

- Cerevance, its affiliates, and licensing partners
- Business partners assisting Cerevance, its affiliates, and licensing partners
- Regulatory agencies and other health authorities
- IRBs and IECs
- Investigator's personal information may be retained, processed, and transferred by Cerevance and these other parties for research purposes, including the following:
- Assessment of the suitability of Investigator for the study and/or other clinical studies
- Management, monitoring, inspection, and audit of the study
- Analysis, review, and verification of the study results
- Safety reporting and pharmacovigilance relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication
- Inspections and investigations by regulatory authorities relating to the study
- Self-inspection and internal audit within Cerevance, its affiliates, and licensing partners
- Archiving and audit of study records
- Posting Investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites
- Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the Investigator's own country.
- Investigator acknowledges and consents to the use of his or her personal information by Cerevance and other parties for the purposes described above.

PROTOCOL

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects

Short Title: Phase 1 SAD/MAD Study of CVN766

Sponsor:	Cerevance Gamma, Inc. One Marina Park Drive, Suite 1410 Boston, MA 02210
Study Number:	CVN766-101
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Compound:	CVN766
Protocol Version:	3.0, Amendment 2
Date:	26 November 2021

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	TBD
Medical Monitor (carries overall responsibility for the conduct of the study)	TBD
Responsible Medical Officer (medical advice on protocol and compound)	[redacted], MD

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations

SIGNATURES

Approved by:

Signatur [redacted] Date 26-Nov-2021

[redacted], M.D.
Medical Monitor

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation, E6 GCP: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Regulatory requirements for reporting serious adverse events (SAEs) are defined in Section 9.9 of this protocol
- Terms outlined in the Clinical Study Site Agreement
- Appendix B – Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

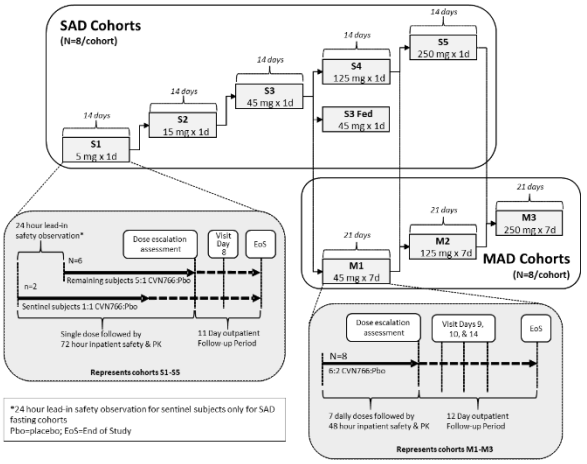
TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance, Inc.	**Compound:** 	
Title of Protocol: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects	**IND No.:**	**EudraCT No.:** Not Applicable
Study Number: CVN766-101	**Phase:** 1	

Study Design:

This is a Phase 1, randomized, double-blind, placebo-controlled, single- and multiple-dose ascending study in healthy subjects with concurrent PK sampling from blood plasma, urine, and cerebrospinal fluid. The overall study design is outlined below:

Part 1: Single-Dose Regimen and Fasted-Fed Crossover

For the single-dose regimen, approximately 40 healthy male or female subjects will be enrolled in 1 of 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. Each cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a single oral dose of CVN766 suspension, and 2 subjects will receive a matching placebo suspension under overnight fasted conditions. Subjects will remain fasted for 4 hours post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 or placebo to the remainder of subjects within the cohort. After blinded review by the Investigator of 24-hour post-dose adverse event listings (as applicable) from the sentinel group, the Investigator will advise the sponsor on acceptability to enroll the remaining 6 subjects in each cohort. In the event that a safety signal emerges in the sentinel group, a Safety Review Group (SRG) meeting may be required as requested by Investigator or Sponsor. To accommodate the lumbar puncture in the S3 fasted cohort, the remaining 6 subjects dosing may be staggered every two days after the sentinel group. The planned dose levels will be 5, 15, 45, 125, and 250 mg CVN766. The SRG will review all available blinded safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and pharmacokinetic (PK) data after each cohort and before subsequent dose escalation. Each following dose level may be higher, lower, or remain the same as the preceding cohort, dependent on the recommendation of the SRG.

Additional cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. For example, if cohort S5 is well-tolerated, additional cohorts with higher dose levels may be considered. Such additional cohorts will follow the same schedule of events as for cohorts S1 through S5. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

To assess the effect of food on CVN766 bioavailability in suspension formulation, the single-dose administration will be repeated in a single cohort (S3) after ingestion of a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the S3 cohort dose level has been assessed, the S3 cohort subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives, has lapsed based on preliminary PK data, whichever is longer). They will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish at least approximately 85% of their breakfast within 30 minutes and receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

Subjects for all cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments. On Day 1, subjects will undergo safety monitoring and PK sampling from blood plasma through 72 hours post-dose and, for cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. The total confinement period will be 4 nights, unless extended at the discretion of the Investigator, e.g., for monitoring and/or management of AEs. Follow-up assessments will occur on approximately Days 8 and 14 and +21 and +28 for cohort S3.

A summary of the single-dose regimen visit schedule is presented below:

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK, Safety and Lumbar Puncture Site Assessments (S3 fasted)	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. S3 subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required at Day -1.

(b) CSF collection will apply only to cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal, clinically significant (CS) findings were observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 healthy male and female subjects aged 18 to 55 will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. The dose levels planned to be studied in the multiple-dose regimen are 45, 125, and 250 mg CVN766 for multiple-dose cohorts M1 through M3, respectively. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily oral dose of CVN766, and 2 subjects will receive matching placebo for 7 days. Dosing will be administered in the fasting state; the SRG can change this if exposure is higher in the fed state. The planned dosing duration for the multiple-dose cohorts is 7 days. However, the duration may be increased to ≤14 days at the discretion of the SRG if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. For each dose on intensive PK sampling days (first and last days of dosing, e.g., Days 1 and 7), subjects will remain fasted for 4 hours post-dose. On other dosing days (Days 2-6), subjects will remain fasted for 1-hour post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 (minimally including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of

dose level may be modified by the SRG after the available blinded safety, tolerability, clinical laboratory results, and PK data in the preceding multiple-dose and corresponding single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in cohort M1 only, from urine through 24 hours post-dose. In cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7), subjects will additionally undergo PK sampling from CSF via lumbar puncture at 3 hours post-dose. If needed to resolve questions arising from prior cohorts' data, subjects in cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., $t_{½}$). The total confinement period will be 9 nights unless extended for additional dosing days or management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose.

A summary of the multiple-dose regimen visit schedule is presented below:

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g., Days 8-9)	3 days ±0 after last dose (e.g., Day 10) & 7 days ± 1 after last dose (e.g., Day 14)	14 days ±2 after last dose (e.g., Day 21)

(a) CSF sampling will occur on Day 7 in cohorts M1 and M2. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or, if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal, clinically significant (CS) findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in cohort M1.

Safety Review Group (SRG)

The SRG will be comprised of the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for ongoing review of safety, tolerability, and clinical laboratory results, and available PK data and deciding:

1. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data including at least 72 hours post-dose safety data and clinical laboratory results from each of the subjects in the current cohort),
2. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data including at least 48 hours post 7th dose safety data from each of the subjects in the current cohort),

3. Add additional dose cohort(s) in either the single- or multiple-dose studies,
4. Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days,

In addition, if 2 or more subjects in a single cohort experience the same type of serious or medically significant event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

Primary Objective:

To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects and determine the recommended phase 2 dose (RP2D).

Secondary Objectives:

- To characterize the single-dose PK profile of CVN766 in plasma and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma and CSF
- To assess the effect of food on the bioavailability of CVN766

Exploratory Objectives:

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

[redacted]

Subject Population: Healthy male and female subjects 18 to 55 years old

Number of Subjects:	**Number of Sites:**
Each dose cohort: 8 subjects (6 active:2 placebo) Estimated total: 64 subjects (5 single-dose cohorts, 3 multiple-dose cohorts)	1 (Australia)
Dose Level(s): Planned single-dose levels are placebo, 5 mg, 15 mg, 45 mg, 125 mg, and 250 mg CVN766. Planned multiple dose levels are placebo, 45 mg, 125 mg, and 250 mg CVN766.	**Route of Administration:** Oral
Duration of Treatment: Single or daily oral doses for up to 7 days (+7 days as necessary to reach steady-state and as required by Safety Review Group).	**Period of Evaluation:** Screening Period: up to 28 days Treatment Period: 1-7 days (+7 days, as necessary). Food Effect washout period (for select cohort only): at least 14 days Follow-up Period: approximately 14 days Total Duration: • Single-dose cohorts: approximately 6 weeks • Food effect cohort: approximately 8 weeks • Multiple-dose cohorts: approximately 7 weeks

Main Criteria for Inclusion:

Healthy male and female subjects who are 18 to 55 years of age, inclusive and have a body mass index (BMI) between 18.0 and 32.0 kg/m^2 inclusive at Screening.

A complete list of inclusion criteria is provided in Section 7.1.

Main Criteria for Exclusion:

Subjects have a known hypersensitivity to any component of the formulation of CVN766. Subjects have evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, allergic skin rash, psychiatric disorder, or other abnormality that may impact the ability of the subject to participate or potentially confound the study results. Any finding in the subject's medical history, physical examination, or safety laboratory tests gives reasonable suspicion of a condition that might interfere with the conduct or interpretation of the study.

A complete list of exclusion criteria is provided in Section 7.2.

In addition, subjects may not use any excluded medications (including oral contraceptives as listed in Table 3), supplements, or food products. Concomitant medications and dietary products to be excluded are listed in Table 3.

Main Criteria for Evaluation and Analyses:

- Safety:

Safety parameters will include AEs, clinical laboratory results, vital signs, physical examinations, electrocardiogram (ECG). AEs will be collected from signing the informed consent form (ICF) up until dosing on Day 1 as pretreatment events (PTEs), and any event that occurs from dosing until 14 days after the last dose will be captured as an AE. Vital signs will be recorded at Screening, Inpatient Check-in (Day -1), and throughout the dosing period. Vital signs will include tympanic body temperature measurement, blood pressure, respiration rate, and pulse (beats per minute [bpm]). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day -1) 15 minutes apart (the average will be used to determine eligibility). Heart rate and blood pressure will be measured after at least 5 minutes supine and again at 2 minutes after standing for all scheduled timepoints.

Standard 12-lead ECGs will be recorded at Screening, Inpatient Check-in (Day -1), and periodically throughout the dosing period. Triplicate ECGs will be taken at each timepoint.

A complete list of safety assessments is provided in Section 9.11, and the full Schedule of Study Procedures is provided in Appendix A.

- PK:

The plasma PK parameters are used as PK endpoints to determine drug exposure at each dose and facilitate dose escalations.

Plasma samples will be collected for the determination of concentrations of CVN766 throughout the study as prescribed in the Schedule of Study Procedures (Appendix A). Cerebrospinal fluid (CSF) samples will be collected for the determination of concentrations of CVN766 as described in Section 9.6 and the Schedule of Study Procedures (Appendix A). PK sampling timepoints may be modified or added based on emerging PK data to most appropriately characterize the PK profile of CVN766 as determined by the SRG.

PK parameters of CVN766 will be derived using noncompartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma: C_{max}, AUC from time 0 to the last quantifiable concentration (AUC_t), AUC from time 0 to infinity (AUC_∞), AUC from time 0 to 24 hours (AUC_{24}), time to reach C_{max} (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2z}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F). Multiple-dose PK will also include AUC over the dosing interval (AUC_{tau}), apparent clearance at steady state (CL/F_{ss}), apparent volume of distribution at steady state (Vz/F_{ss}), steady-state nadir concentrations, and accumulation ratios

The PK parameters to be determined from concentrations of CVN766 in CSF will include plasma: CSF ratio by time point.

- Pharmacogenomics:

One whole blood sample will be collected at pre-dose on Day 1 for pharmacogenomic analysis; this will only be collected once per subject. Two whole blood samples will be collected at pre-dose on Day 1 and at multiple timepoints post-dose for ribonucleic acid (RNA) pharmacogenomic analysis. The pre-dose RNA blood samples should be collected under fasted conditions and prior to any other blood collection. The samples will be stored for no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from Cerevance. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personally identifying information, but

key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; eligible subjects sign the ICF, which outlines the retention of pharmacogenomic and genotyping analysis in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of this gene in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

- Endpoints:

The primary endpoints of this study will be the following: percentage of subjects who experience at least one treatment-emergent adverse event (TEAE); percentage of subjects with abnormal and CS safety laboratory, vital signs, or ECG test results at least once post-dose.

The secondary endpoints will be the following plasma PK parameters of CVN766: C_{max}, AUC_{24}, AUC_{∞}, $t_{1/2z}$, AUC from time 0 to end of the dosing interval, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}.

The additional endpoints may include the following plasma PK parameters of CVN766: t_{max}, CL/F, V_z/F, CL/F_{ss}, Vz/F_{ss}, and plasma: CSF ratio.

Exploratory endpoints may include characterization of metabolic enzyme and transporter polymorphisms and/or

[redacted]

Statistical Considerations:

Safety:

AEs will be presented in listings, and TEAEs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be recorded at baseline and post-dose, and changes from baseline will be summarized using shift tables. Individual vital signs will be recorded, and observed values and changes from baseline will be summarized. Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed, and observed values and changes from baseline will be summarized. All summaries will be performed by placebo, each CVN766 dose level (fasted and fed separately), and CVN766 single-dose overall, and separately CVN766 multiple-dose cohorts overall. Placebo data will be pooled across single-dose cohorts and separately pooled across multiple-dose cohorts. Physical exam findings will be presented in data listings.

PK Measures:

Concentrations of CVN766 in plasma and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma and CSF concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically.

PK parameters of CVN766 will be summarized by dose using descriptive statistics. Dose proportionality will be assessed graphically and using a power model.

The concentrations of CVN766 in plasma and CSF will be compared.

Sample Size Justification:

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) is considered sufficient for evaluating the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

3.0 STUDY REFERENCE INFORMATION

3.1 List of Abbreviations

λ_z	terminal elimination rate constant
AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUCτ	area under the plasma concentration-time curve over the dosing interval (τ)
BMI	body mass index
CL/F	apparent clearance after extravascular administration
CL/F_{ss}	apparent clearance after extravascular administration at steady state
[redacted]	[redacted]
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
[redacted]	[redacted]
FSH	follicle-stimulating hormone
FT4	free T4
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human-equivalent dose
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
K_2EDTA	dipotassium ethylenediamine tetraacetic acid
LFT	liver function test
MAD	multiple-ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
MRSD	maximum recommended starting dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
Ox1R	orexin 1 receptor
Ox2R	orexin 2 receptor
PK	pharmacokinetic
PRL	prolactin
PT	preferred term
PTE	pretreatment event
QTcB	QT interval with Bazett's correction method
QTcF	QT interval with Fridericia's correction method
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAD	single-ascending dose
SAP	statistical analysis plan
SOC	system organ class
SRG	Safety Review Group
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution after extravascular administration
V_z/F_{ss}	apparent volume of distribution after extravascular administration at steady state
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

The neuropeptide orexin, also known as hypocretin, is produced exclusively in the orexigenic neurons in the hypothalamus. There are two forms of orexin, Orexin-A, and orexin-B, alternatively spliced from the same gene, HCRT. There are two orexin receptors, orexin 1 receptor (Ox1R) and orexin 2 receptors (Ox2R), both of which are G-protein coupled receptors. Both orexin-A and orexin-B can bind to either receptor, and in each case, agonist binding results in an increase in intracellular calcium levels. However, while orexin-A is equipotent at both receptors, orexin-B shows a 10-fold selectivity for Ox2R.

Ox1R is selectively expressed in key brain areas relating to psychiatric disorders. Ox1R-expressing neurons in the bed nucleus of the stria terminalis, amygdala, locus coeruleus, raphe nucleus, and the ventral tegmental area are important in regulating emotions of stress, anxiety, motivation, and reward. CVN766 is a potent and highly selective small-molecule Ox1R antagonist with no significant off-target activity. Nonclinical PK and toxicology studies with CVN766 and other Ox1R antagonists have established their pharmacological characteristics and probable safety profile.

Ox2R is expressed in some overlapping areas, including the raphe nucleus, ventral tegmental area, but also areas important to arousal and sleep regulation, including the tuberomammillary nucleus.

The widely used sleep aid suvorexant (Belsomra®), approved for use in Australia, is a dual Ox1R and Ox2R antagonist, but its sleep-inducing effects are generally attributed to its activity on Ox2R. A second dual Ox1R and Ox2R antagonist, lemborexant, appeared safe and effective in clinical studies, has been approved in many countries worldwide, and has been submitted for marketing authorization in Australia.

Clinical effects to be expected of a selective Ox1R antagonist remain uncertain. CVN766 has not yet been studied in humans. Other selective Ox1R antagonists have reported early-stage human clinical trials, notably JNJ-61393215 (ClinicalTrials.gov Identifier: NCT04080752; Salvadore *et al.*, 2020) and ACT-539313 (NCT01954589; Kaufmann *et al.*, 2020; Kaufmann et al., 2021). Both drugs were well tolerated and deemed safe for investigational use, the most common AEs being somnolence and mild headache.

4.2 Rationale for the Proposed Study

CVN766 is a highly selective orexin-1 receptor (Ox1R) antagonist and may have utility as treatment for psychiatric disorders including schizophrenia, panic disorder and anxiety, and addiction. Its safety and PK profile have been preliminarily established in nonclinical toxicology studies. The present study will be the first conducted in humans with CVN766 and will examine the compound's safety, tolerability, and PK in healthy subjects.

Nonclinical pharmacology, toxicity, and pharmacokinetic (PK) studies support the proposed escalating single- and multiple-dose study of CVN766 in healthy subjects with a starting dose of 5 mg. Section 6.2 outlines the justification for the planned dose ranges.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects.

5.1.2 Secondary Objectives

- To characterize the single-dose PK profile of CVN766 in plasma, and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma, and CSF
- To assess the effect of food on the bioavailability of CVN766 in the current formulation

5.1.3 Exploratory Objectives

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints of this study will be the following:

- Percentage of subjects who experience at least one treatment-emergent adverse event (TEAE)
- Percentage of subjects with abnormal and clinically significant (CS) safety laboratory test results at least once post-dose
- Percentage of subjects with abnormal and CS electrocardiogram (ECG) test results at least once post-dose
- Percentage of subjects with abnormal and CS vital sign measurements at least once post-dose

5.2.2 Secondary Endpoints

- Single-dose plasma PK parameters of CVN766 including time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 to 24 (AUC_{24}) and time 0 to infinity ($AUC\infty$), and terminal elimination half-life (t1/2z)

- Multiple-dose plasma PK parameters of CVN766 including C_{max}, AUC from time 0 to the end of dosing interval, t1/2z, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}
- Single-dose and multiple-dose CSF concentrations and CSF: plasma ratios of CVN766

5.2.3 Additional Endpoints

- Change from baseline in safety laboratory and ECG test results and vital signs
- Additional plasma PK parameters of CVN766, i.e., CL/F and V_z/F

[redacted]

- Characterization of metabolic enzyme and transporter polymorphisms

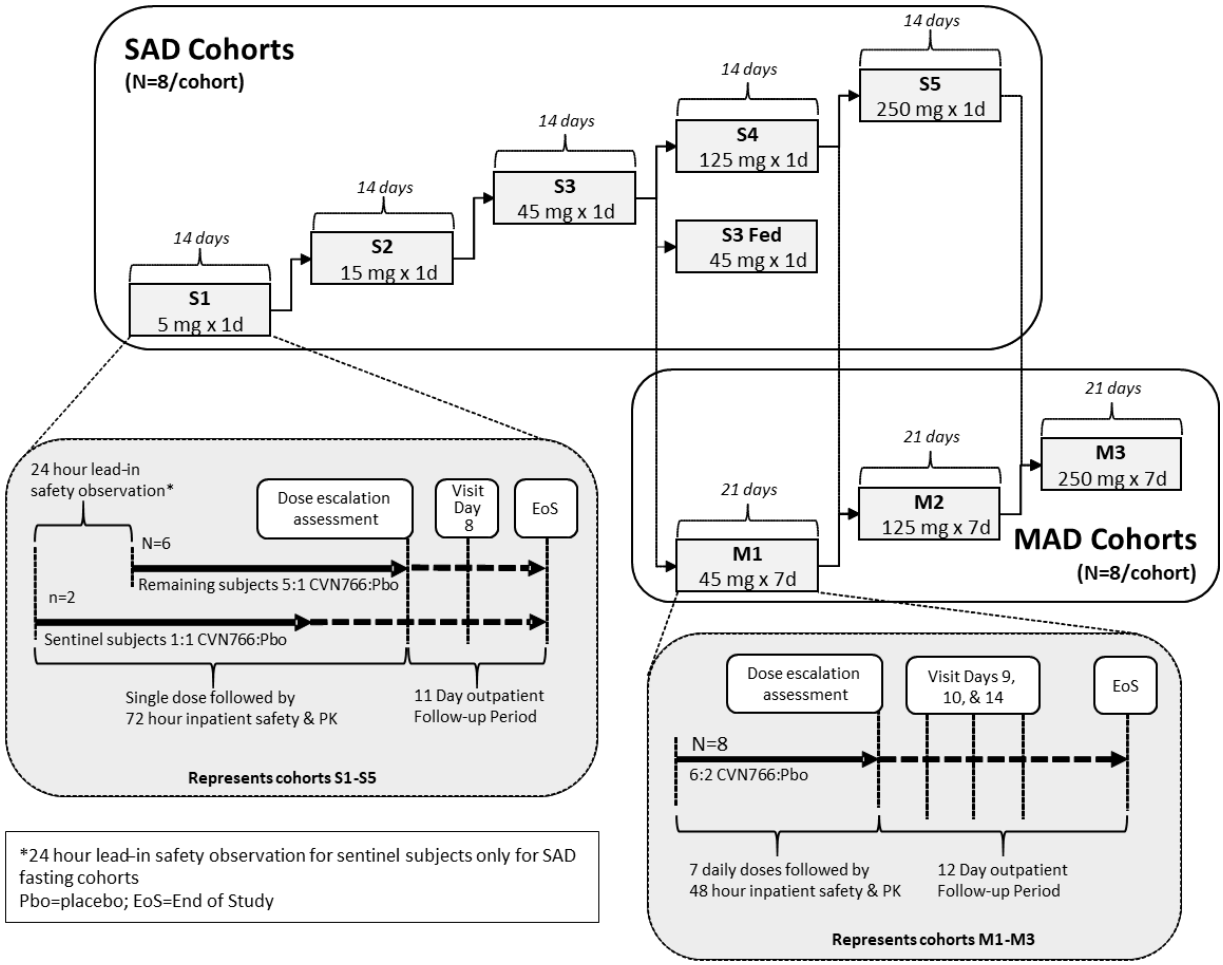
[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, randomized, double-blind, placebo-controlled, single- and multi-dose ascending study in healthy subjects. Figure 1 provides a schematic illustration of the study.

Figure 1 CVN766-101 Study Schematic



6.1.1 Part 1: Single-Dose Regimen and Fasted-Fed Crossover

Approximately 40 subjects will be enrolled in 1 of the 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. Dose escalation will only occur after a fully blinded review of all available safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and available PK data, including at least a 72-hour follow-up of the most recent cohort.

The planned dose levels are provided in Table 5. Each cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a single dose of CVN766 and 2 subjects will receive a matching placebo under overnight fasted conditions.

Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 to the remainder of subjects within the cohort. After blinded review of 24-hour post-dose safety and tolerability data, the remaining 6 subjects of each cohort may be dosed provided that the adverse event (AE) profile of CVN766 in the first 2 subjects is considered acceptable.

Subjects for all cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments at least 72 hours after dosing. On Day 1, subjects will undergo safety monitoring (including labs, physical exam, neurological exam, cardia telemetry at 12-hours pre-dose) and PK sampling from blood plasma through 72 hours post-dose. In addition, for cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. For subjects participating in the SAD cohorts, the total confinement period will be 4 nights unless extended for management of AEs at the discretion of the Investigator. Follow-up assessments will occur on approximately Days 8 and 14.

To assess the effect of food on bioavailability of CVN766 in suspension formulation, single-dose administration will be repeated in a single cohort after ingestion of a standardized high-fat high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the S3 cohort dose level has been assessed, the S3 cohort subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives has lapsed based on preliminary PK data, whichever is longer) and will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish at least approximately 85% of their breakfast within 30 minutes and will receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

An outline of the single-dose study visit schedule is included in Table 1. A Schedule of Study Procedures is listed in Appendix A.

Table 1 Single-Dose Visit Schedule

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK & Safety Assessments	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. Subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required at Day -1.

(b) CSF collection will apply only to cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

6.1.2 Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 subjects will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. Dosing will be administered in the fasting state; this can be changed by the SRG if exposure is found to be higher in the fed state. The dose levels planned to be studied in the multiple-dose regimen (M1 through M3) are provided in Table 5. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily dose of CVN766, and 2 subjects will receive matching placebo for 7 days. However, the duration may be increased to ≤14 days at the discretion of the safety review group (SRG) if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in cohort M1 only, from urine through 24 hours post-dose. In cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7), subjects will additionally undergo PK sampling from CSF via lumbar puncture at 3 hours post-dose. If needed to resolve questions arising from prior cohorts' data, subjects in cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional plasma PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., t½. The total confinement period will be 9 nights unless extended for additional dosing days or for management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose. A summary of multiple-dose study visits is included in Appendix A.

Table 2 Multiple Dose Visit Schedule

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a,f]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g. Days 8-9)	3 days ±0 after last dose (e.g. Day 10) & 7 days ± 1 after last dose (e.g. Day 14)	14 days ±2 after last dose (e.g. Day 21)

(a) CSF sampling will occur on Day 7 in cohorts M1 and M2. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after the last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in cohort M1.

6.1.3 Dose Escalation

The SRG will be comprised of the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for ongoing review of safety, tolerability, clinical laboratory results, and available PK data and deciding to:

- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data including at least 72 hours post-dose safety data and clinical laboratory results from each of the subjects in the current cohort),
- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data including at least 48 hours post 7th dose safety data from each of the subjects in the current cohort),
- Add additional dose cohort(s) in either the single- or multiple-dose studies,
- Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days

If 2 or more subjects in a single cohort experience the same type of serious or medically adverse event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

For each cohort (including sentinel subjects, where applicable), the SRG will carefully review the available blinded safety, tolerability, clinical laboratory results, and PK data to determine whether dosing should stop or continue (and, if continued, at what dose, including whether to repeat the previous dose), whether additional sequential dosing should be implemented in future cohorts or whether the blind should be broken to identify whether the subjects received CVN766 or placebo. However, precautions must be taken not to unblind the study staff, including the investigator.

If all doses are tolerated, then additional cohorts with higher doses may be considered; The actual choice of the subsequent dose level will occur after the full review of the available blinded safety, tolerability, clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level. If necessary, additional cohort(s) may be added to fully characterize the safety and tolerability of CVN766.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all available safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 (minimally including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of dose level may be modified by the SRG after review of the available blinded safety, tolerability, and clinical laboratory results and PK data in the preceding multiple-dose and next-higher-dosage single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

All AEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge, will be evaluated to assess the need for the subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (Section 6.3.1).

Additionally, the SRG may decide not to escalate the dose for a particular cohort but rather administer the same or a lower dose level to the next cohort. Additional/ Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

6.2 Justification for Study Design, Dose, and Endpoints

The study is double-blind and placebo-controlled to avoid subjective bias in the assessment of the safety and tolerability of CVN766. Dose escalation will be predicated on a review of available blinded safety, tolerability, and PK data observations for each prior dose cohort.

The sponsor has selected the starting dose level considering the FDA Guidance for Industry (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 06 July 2005) and providing additional safety factors to the initial calculations based on the principles outlined in the guidance. The toxicity profile of CVN766 after oral dosing was examined in repeat dosing studies in rats and dogs. Scaling based on body surface area was conducted by multiplying the NOAELs for the most sensitive animal species by the appropriate conversion factors. Based on these calculations and applying a 10-fold safety margin below the NOAEL human-equivalent dose (HED), the maximum recommended starting dose (MRSD) for this first-in-human study is 167 mg for a 60 kg subject. The selected starting dose level is 5 mg.

The study's multiple-ascending dose (MAD) portion seeks to prepare for subsequent repeat dosing studies in subjects. Each MAD dose level will have been studied or exceeded in the SAD portion of the study before its use in a MAD cohort.

Nonclinical toxicity study data provide a basis for calculating the maximum exposure level that can be presumed safe. Escalating to the HED of the NOAEL in the most sensitive animal species, the maximum dose for clinical use is 1670 mg/day.

The projected $t_{1/2z}$ in animal species ranged up to 6.5 hours, so sample collection through Inpatient Discharge 72 hours post-dose is expected to correspond to more than 5 half-lives and is anticipated to be adequate to document elimination of CVN766. The study design allows for collecting additional PK samples at later timepoints if preliminary emerging PK results are indicated.

AEs, physical exams, vital signs, ECG findings, and clinical laboratory results are used as safety assessments to determine dose tolerability and dose-limiting effects of CVN766. The plasma PK and CSF parameters and PK endpoints will help elucidate the pharmacology of CVN766.

Samples for DNA analysis will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety of the study medication indicates an adverse change in the risk profile for the compound, such that the SRG or Institutional Review Board (IRB) considers the risk is no longer acceptable for subjects participating in the study.

In addition, if any of the following occur, further dosing will be withheld until the SRG reviews the relevant data, including unblinded data (if deemed necessary by the SRG request), and will decide whether it is safe to suspend dosing or continue dosing at either the planned or alternative dose levels or decides to prematurely terminate the study:

1. Two or more subjects in any single cohort or across more than 1 cohort experience the same type of serious or Medically Significant event as defined by the Investigator
2. Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limits of normal (ULN) in the absence of a concomitant bilirubin increase (see point 3 below)
3. One or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN in the presence of a total bilirubin increase >2 ×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., “Hy’s Law cases”)
4. Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate study performance, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an IRB/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; applicable investigational sites will follow the procedure during the course of termination or study suspension.

7.0 SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days prior to randomization or first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the investigator's opinion, the subject can understand and sign the Informed Consent Form and comply with all protocol requirements.
2. The subject is a healthy male or female adult who is 18 to 55 years of age, inclusive at the time of ICF.
3. Subject weighs at least 45 kg (99 lbs) and has a BMI between 18.0 and 32.0 kg/m^2, inclusive at Screening.
4. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agree to use two forms of adequate contraception* from signing the ICF throughout the study and for 90 days after the last dose.

   *Definitions and acceptable methods of contraception are defined in Section 9.1.13 Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities are defined in Section 9.1.14 Pregnancy.

5. A female subject of childbearing potential who complies with contraception requirements* or a female with no childbearing potential, defined as the subject has been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (defined as continuous amenorrhea of at least 2 years and FSH>40 IU/L).

   Note: hormonal contraceptives are not permitted for female participants, as referenced in Table 3. Female partners of male participants can use hormonal contraceptives.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Subject has received any investigational compound within 30 days prior to the first dose of study medication or within 5 half-lives, whichever is greater.
2. Subject is a study site employee or an immediate family member of a study site employee.
3. Subject has evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, full-body allergic skin rash (including hives), psychiatric disorder, evidence of abnormal liver function test, evidence of abnormal renal function tests or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.

   Note: Healthy volunteers with pre-existing stable disease, defined as diseases not requiring significant change in therapy or hospitalization for worsening disease during the 6 wks before enrolment, may be included at the discretion of the Investigator.

4. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking CVN766 or a similar drug in the same class or that might interfere with the conduct of the study
5. Subject has a known hypersensitivity to any component of the formulation of CVN766.
6. Subject has a positive urine result for drugs of abuse at Screening or Inpatient Check-in (Day -1).
7. Subject has a history of a major psychiatric illness or currently receiving therapy for a psychiatric condition
8. Subject has a history of drug abuse or a history of alcohol abuse (more than 14 units/week) within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
9. Subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table as listed in Table 3.
10. Male subjects who do not agree to all the following rules: when sexually active with a female partner(s) of childbearing potential during the study, and for 90 days after the last dose of study drug: a) must use two acceptable methods of birth control (condom or surgical sterilization combined with highly effective method of contraception for the female partner) and b) refrain from sexual activity with female partners who do not use an acceptable method of birth control. Barrier contraception (condom) must be used by all-male subjects who were not surgically sterilized at least 90 days prior to screening. Male subjects must also agree to refrain from sperm donation during the study and until 90 days after the last dose of the study drug.
11. Female subjects who are pregnant or breastfeeding or plan to become pregnant or donate ova during the study or 30 days after the last dose of the study drug. Women of childbearing potential must agree to practice an acceptable method of birth control (e.g., intrauterine device, barrier, abstinence).

    Note: hormonal contraceptives are not permitted for female participants, as referenced in Table 3. Female partners of male participants can use hormonal contraceptives.

    *Definitions and acceptable methods of contraception are defined in Section 9.1.13. Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.14 Pregnancy.
12. Subject has previously had a seizure or convulsion (lifetime, with the exception of febrile seizures), including absence seizure.
13. Subject has current o recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (i.e., a history of malabsorption, any surgical intervention known to impact absorption [e.g., bariatric surgery or bowel resection], esophageal reflux, peptic ulcer disease, erosive esophagitis, or frequent [i.e., more than once per week] occurrence of heartburn).
14. Subject has a history of cancer or other malignancy, except for basal cell carcinoma or squamous cell carcinoma that has been in remission for at least 3 years prior to Day 1.

15. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or a human immunodeficiency virus infection at Screening.
16. Subject who regularly use nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum). The casual users (≤ 10 cigarettes/week) may participate but must agree to refrain from the time of Screening for the duration of the study or a positive urine cotinine test at Inpatient Check-in (Day -1).
17. Subject has poor peripheral venous access (defined as more than three failed attempts to cannulate.
18. Subject has donated or lost 450 mL or more of their blood volume (including plasmapheresis) or had a transfusion of any blood product within 45 days prior to Day 1.
19. Subject has an abnormal (CS) ECG at Screening or Inpatient Check-in (Day -1). Entry of any subject with an abnormal (NCS) ECG must be approved and documented by signature by the Investigator or medically qualified sub-investigator.
20. Subject has a supine blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 40 to 90 mm Hg for diastolic, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).
21. Subject has a resting heart rate outside the range of 40 to 100 bpm, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).
22. Subject has a QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms, confirmed with one repeat testing at the Screening Visit or Inpatient Check-in (Day -1) Visit.
23. Subject has abnormal Screening or Inpatient Check-in (Day -1) laboratory values that suggest a CS underlying disease or subject with the following lab abnormalities: ALT and/or AST >1.5 the ULN, confirmed with one repeat testing.
24. Subject has a risk of suicide according to the investigator's clinical judgment or has made a suicide attempt in the previous 2 years.

7.3 Excluded Medications and Dietary Products

Use of the agents in Table 3 (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

Table 3 Prohibited Medications and Dietary Products

28 days prior to Inpatient Check-in	14 days prior to Inpatient Check-in	7 days prior to Inpatient Check-in	72 hours prior to Inpatient Check-in	48 hours prior to Inpatient Check-in	24 hours prior to Inpatient Check-in
Nutraceuticals (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Prescription medications [(d)](including hormonal contraceptives[(e)])	OTC medications, including antacids, proton-pump inhibitors, and H2 receptor antagonists [(a)]	Nicotine-containing products	Alcohol-containing products	Products containing caffeine or xanthine (e.g., tea or coffee)
Immunization/ Vaccines [(b)]		Vitamin supplements	Poppy seeds		
Known strong inhibitors/inducers of CYPs 3A4/5 [(c)]		Orexin receptor antagonists including suvorexant (Belsomra®), lemborexant (Dayvigo®), and related compounds			

CYP= cytochrome P-450, OTC=over the counter.

(a) Occasional use of acetaminophen (~1 g/day) and 400mg ibuprofen TDS when required or other medication as approved by the sponsor's Medical Monitor on a case-by-case basis is allowed except on Day 1

(b) Inclusive of but not limited to H1N1 and flu vaccinations. Subjects who have received the COVID-19 Vaccine between -10 and -28 days may participate provided they did not experience any side effects of any description. COVID-19 vaccine doses may be administered 7 days post-study medication dosing.

(c) e.g., chloramphenicol, clarithromycin, ketoconazole.

(d) Certain prescription medications may be allowed on a case-by-case basis at the discretion of the Investigator and Sponsor.

(e) Hormonal contraceptives are not permitted for female participants, as referenced in Table 3. Female partners of male participants can use hormonal contraceptives.

Subjects must be instructed not to take any medications during study participation, including over-the-counter drug products, without first consulting with the investigator.

7.4 Diet, Fluid, Activity Control

Subjects will be confined to the clinic for each of the dosing days as well as a period of time sufficient to collect additional post-dose PK samples and monitor for safety and tolerability (Day -1 through Day 4 for single-dose cohorts and Day-1 through Day 9 for multiple-dose cohorts). During confinement, subjects will be provided 3 standard meals and a snack per day, each containing approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be similar in nutritional content for each subject in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor following

treatment. Breakfast will not be provided on dosing days until at least 4 hours after dose administration unless otherwise indicated (i.e., Days 2-6 for MAD cohorts). The meal start and stop times and percentage of the meal consumed will be recorded in the source, and appropriate electronic case report form (eCRF) for all meals served on dosing days.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence, followed by the study procedure and then the meal.

Subjects will remain in bed at a semi-supine position for 4 hours following the dose administration, except as necessitated by the occurrence of an AE or study procedures (e.g., obtaining a 12-lead ECG). Subjects must refrain from strenuous exercise from 72 hours before Inpatient Check-in and until check-out.

On the dosing days where extensive PK and/or CSF sampling is indicated (i.e., single-dosing Day 1 and first and last multiple-dose days, e.g., days 1 and 7), CVN766 or placebo suspension will be administered with approximately 240 mL of water after a fast of at least 10 hours. Subjects will continue to fast for an additional 4 hours after dosing and eat lunch following the 4-hour PK blood and CSF collection. Subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration.

For the food effect cohort (S3), single-dose administration will be administered after ingesting a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Subjects will finish at least approximately 85% of their breakfast within 30 minutes and will receive an investigational product 30 minutes (±5 minutes) after beginning the meal. The S3 (food effect) cohort meals may be staggered to ensure dosing occurs 30 minutes after the beginning of the meal.

Subjects will also fast for at least 10 hours prior to safety laboratory collection times as indicated. However, consumption of water as desired is permitted during this time, except for dosing days, as indicated above.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, Section 9.1.15.

1. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status) if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 × ULN, or

   – ALT or AST >5 × ULN and persists for more than 2 weeks, or

- ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic, and attempts to contact the subject were unsuccessful. Attempts to reach the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal, and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).
6. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator must discontinue a subject's study participation at any time during the study when the subject meets the study discontinuation criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's involvement be terminated, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects may be replaced at the Sponsor's discretion.
Participants who withdraw from the study prior to dosing may be replaced. If a participant withdraws after the first dose of study medication or placebo, no replacement will occur.

8.0 CLINICAL TRIAL MANAGEMENT

8.1 Study Medication and Materials

This section contains information regarding all medication and materials provided directly by the sponsor and/or sourced by other means required by the study protocol, including important sections describing the management of clinical trial material.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN766 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral suspensions as needed throughout the study.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN766 and Matching Placebo

CVN766 drug substance is supplied as a bulk powder to the clinical site and then compounded into oral suspensions. A matching placebo suspension containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor. See Table 4 for the composition of the drug product and matching placebo suspensions.

The oral suspensions will be labeled with the appropriate study information and caution statements.

Table 4 Composition of CVN766 Oral Suspension and Matching Placebo

Component	CVN766 Oral Suspension (individual dose)					Matching Placebo
CVN766 drug substance	5 mg	15 mg	45 mg	125 mg	250 mg	NA
Commercial suspending vehicle[a]	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL

NA=Not applicable

[a] An off-the-shelf commercial suspending vehicle will be used, and the details of the vehicle will be provided in the Pharmacy Manual.

8.1.1.2 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or the sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

[redacted]

8.1.2 Drug Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN766 drug substance is stored at room temperature. CVN766 oral suspension and matching placebo should be stored according to instructions in the Pharmacy Manual.

8.1.3 Dose and Regimen

The investigator or investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the Investigator and in fed or fasting conditions as outlined in Section 7.4.

The exact time of dose will be recorded in the source documents and on the appropriate eCRF.

The planned dose levels to be studied are provided in Table 5. If the planned highest dose level does not reach the desired exposure, then additional cohorts with higher dose levels may be considered. If all planned dose levels are not tolerated in an earlier cohort, the following cohorts may study lower doses at the discretion of the Investigator and the SRG. The actual choice of the subsequent dose level will occur after a full review of the available blinded safety, tolerability, and clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Table 5 describes the treatment and medication type that would be provided for each cohort.

Table 5 Planned Single and Multiple Dose Levels by Cohort

Single-Dose Cohorts			
Cohort	**Planned Treatment***	**No. of Subjects**	**Medication Type**
S1	CVN766 5 mg	6	oral suspension
	Placebo	2	oral suspension
S2	CVN766 15 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fasted	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fed (Same 8 subjects as in the S3 FASTED cohort)	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S4	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
S5	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension
Multiple Dose Cohorts			
Cohort	**Planned Treatment***	**No. of Subjects**	**Medication Type**
M1	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
M2	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
M3	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension

* Dose (active or placebo) is in 10 mL of suspension.

8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 9.7.2, PTEs and AEs.

Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure outlined in Section 9.7.4, Collection and Reporting of SAEs.

In the event of an overdose, supportive measures should be employed as needed, e.g., administration of supportive therapy as dictated by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract, or the initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive a unique randomization number.

The clinical site will use the unique identifier to facilitate the pre-labeling of PK samples. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory and will be used by the laboratory to report the subject data results. This unique identifier should only be used for the purposes described in this section. This identifier will be assigned upon randomization in the order in which subjects receive their first dose of the study drug.

8.3 Randomization Code Creation and Storage

The sponsor or their designee will generate the randomization schedule and provide a copy to the site pharmacist and bioanalytical laboratory prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigative staff unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality assessments should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted to discuss the need for unblinding before the investigational drug blind is broken.

Unblinding envelopes will be supplied to the site prior to the first subject dosing and stored in a central and secure place to ensure access in the event of an emergency. Study staff will be trained on unblinding procedures.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information (except the time) must be recorded on the eCRF.

If any site personnel inadvertently become unblinded, the sponsor must be notified, and the SRG will determine whether to discontinue dosing or withdraw from the study of all affected subjects.

No change should be made to any assessment of the subject after unblinding.

Following assessment of the AE data and pre-defined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis. Based on a review of unblinded data, the sponsor, in consultation with the Investigator, will decide if and how it is appropriate for the study to proceed.

The Randomization schedule for all subjects will be released for analysis after the database for these cohorts is locked. The Investigator will be unblinded after database lock for all the cohorts if necessary.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication, the investigator must maintain records of all study medication delivery to the site, site inventory used by each subject, and return to the sponsor or designee.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list, ensure the quantity is correct, and the medication is received within the labeled storage conditions. If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and send via email and per instructions provided on the form. If any discrepancies exist between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file. The investigator must maintain 100% accountability for all study medication received and dispensed during their entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all study medication on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of the Investigator, site identifier and number, description of study medication, expiry date, and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction, or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the ICF are described in Section 14.2.

The ICF must be obtained prior to the subject entering the study and before any protocol-related procedures are performed.

A unique subject screening number (of the form xx-xxx), the first two numbers for the site, subsequent three numbers for subject identification will be assigned to each subject when the ICF is obtained. This subject ID will be used until the subject is assigned their 4-digit randomization number.

9.1.1.1 Pharmacogenomic and Cerebrospinal Fluid Informed Consent Procedure

Pharmacogenomics and cerebrospinal fluid informed consent is a component of the overall study ICF. The requirements are described in Section 14.2.

The pharmacogenomic and (for applicable cohorts) cerebrospinal fluid sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, ethnicity, race as described by the subject, smoking status, and caffeine consumption at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped at or prior to signing the ICF. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days before signing ICF.

9.1.3 Physical Examination Procedure

A physical examination performed by the investigator or medical officer consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the baseline physical examination (Screening and Inpatient Check-in [Day -1]) must be assessed as not CS or CS by the investigator and recorded in the source document and eCRF.

All CS findings/changes, as determined by the investigator, from the baseline physical examination will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 9.8.1 or Section 9.8.2.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug Inpatient Check-in (Day -1) must be assessed as not clinically significant (NCS) or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

Height is recorded centimeters without decimal places, and for weight, it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/[\text{height (m)}]^2$

Results for BMI will be expressed with 1 decimal place.

Example:

Height=176 cm (or 1.76 m), weight=79.2 kg; $BMI=79.2/1.76^2=25.57$ kg/m^2 captured as 25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs will include tympanic body temperature, respiration, pulse, and blood pressure and be collected at timepoints specified in the Schedule of Study Procedures (Appendix A). For eligibility determination, the pulse will not be derived from ECG. Pulse and blood pressure will be measured after at least 5 minutes supine and again after 2 minutes standing.

Vital signs should be measured at the same time (+/- 1 hour) of the day across visits if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority, and vital signs will be obtained within approximately 0.25 hours before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from the signing of ICF through the end of the study), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at the signing of ICF. This includes CS laboratory, ECG, or physical examination abnormalities noted at Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 ECG Procedure

Standard 12-lead ECGs will be recorded at timepoints specified in the Schedule of Study Procedures (Appendix A). Triplicate ECGs will be taken at least 1-minute apart at each scheduled time. The average of the ECG measurements will be used for determining eligibility. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

When an ECG is scheduled at the same time as blood draws or vital signs, then the blood draws and vital signs will take priority, and the ECG will be obtained within 0.5 hour before or after the scheduled blood draw/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence, followed by the meal.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-minute rest period for ECG recordings. Should technical difficulties occur during the recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

ECGs will be read automatically, and also, the investigator or sub-investigator will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not CS, or abnormal and CS. Abnormal QTc readings will be manually recalculated and reported by the Investigator on the eCRF. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary. Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals. Paper ECG traces will be recorded for 10 seconds at a standard paper speed of 25 mm/sec, and gain of 10 m/mV or digital recordings will be used.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

All ECGs will be recorded at the time points detailed in Appendix A.

9.1.9 Pharmacogenomic Sample Collection

Every subject must sign ICF/be consented to the sampling of whole blood for pharmacogenomic analysis to participate in the study.

One whole blood sample for DNA isolation and genotyping will be collected at time points specified in the Schedule of Study Procedures (Appendix A) into plastic dipotassium ethylenediamine-tetra acetic acid (K_2EDTA) spray-coated tubes and stored under frozen conditions. In addition, two whole blood samples will be collected at time points specified in the Schedule of Study Procedures (Appendix A) for ribonucleic acid (RNA) pharmacogenomic

analysis. The pre-dose RNA blood samples should be collected under fasted conditions and prior to any other blood collection.

DNA may be evaluated for the genetic contribution to how the drug is broken down or affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN766
- Finding out more information about how CVN766 works
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN766
- Identifying variations in genes related to the biological target of CVN766

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN766 and other study medications and for improving the efficiency, design, and study methods of future research studies.

The samples will be stored no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by the sponsor or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from the sponsor. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; every subject must sign the ICF in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA and RNA from the first sample was not successful or possible.

Samples will be frozen at -70°C or lower and shipped separately on dry ice prior to extraction and storage at -70°C or lower. Samples should not be allowed to thaw until processed.

Detailed instructions for the handling and shipping of samples are provided in a separate lab manual.

Genotyping on collected samples may be deferred until after the completion of the study's in-life activities.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 4-digit randomization number.

9.1.10 PK Sample Collection

9.1.10.1 Collection of Blood for PK Sampling

Blood samples for analysis of CVN766 plasma concentrations will be collected into chilled Vacutainers containing K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in a separate lab manual.

In all single-dose cohorts, serial blood samples to determine CVN766 concentrations in plasma will be collected according to Table 6.

Table 6 Collection of Blood Samples for PK Analysis in Single-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24-, 36-, 48-, and 72-hours post-dose.

In all cohorts for Part 2, serial blood samples for determination of CVN766 concentrations in plasma will be collected according to Table 7.

Table 7 Collection of Blood Samples for PK Analysis in Multiple-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 (Day 2 pre-dose) hours post-dose.
	3,4,5,6	Pre-dose (within 15 minutes prior to dosing)
	7	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, and 72 [(a)] hours post-dose.

(a) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the 72-hour timepoint is unnecessary.

The PK samples will be collected at the nominal time point; all other assessments will be collected, before or after, within the allowable windows. The actual time of sample collection will be recorded on the source document and eCRF.

Sampling time points may be adjusted or added based on the preliminary emerging PK data collected from prior cohort(s). Still, the total number of samples collected per subject should not exceed the planned number by more than 4.

Placebo samples will not be analyzed by the bioanalytical laboratory except 2 samples per subject receiving placebo, 1 pre-dose, and the other around the expected time at which C_{max} occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional subjects could have been on active treatment.

[redacted]

[redacted]

9.1.11 PK Parameters

PK parameters of CVN766 will be derived using non-compartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled

sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma and CSF:

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from the time of dosing to the time of the last measurable concentration
AUC_∞	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_\infty=AUC_t+C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration.
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours, calculated using the linear trapezoidal rule.
AUC_τ	Area under the plasma concentration-time curve over the dosing interval (τ)
C_{max}	Maximum observed plasma concentration.
C_{min}	Minimum observed plasma concentration; pre-dose trough concentration
	Minimum observed plasma concentration at steady state, on last day of dosing
CL/F	Apparent clearance after extravascular administration, calculated as $Dose/AUC_\infty$ after a single dose.
CL/F_{ss}	Apparent clearance after extravascular administration at steady state, calculated as $Dose/AUC_{tau}$
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.
V_z/Fss	Apparent volume of distribution during the terminal phase after extravascular administration at a steady-state, calculated as $(CL/F_{ss})/\lambda_z$
CSF	
plasma: CSF ratio	ratio of the drug concentration in plasma vs. CSF

Additional PK parameters may be calculated as appropriate.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures on the days/times stipulated in the Schedule of Study Procedures (Appendix A).

Table 10 lists the tests that will be obtained for each laboratory specimen.

Table 10 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Special
RBC	ALT	pH	Prolactin
WBC with differential (% and absolute)	Albumin	Specific gravity	TSH
	Alkaline phosphatase	Protein	(and if abnormal) reflex FT4
Hemoglobin	Lipase (d)	Glucose	
Hematocrit	AST	Blood	

Platelets PT/INR	Total bilirubin Direct bilirubin Total protein Creatinine BUN/Urea Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc.
Diagnostic Screening:		
Serum		**Urine/ Blood**
Serum hCG (a) FSH (b) Hepatitis panel, including HBsAg and anti-HCV (e) Human Immunodeficiency Virus (HIV) antibody		Drug screen including amphetamines (AMP), barbiturates (BAR), benzodiazepines (BZO), cannabinoids, cocaine (COC), opiates (OPI), alcohol, cotinine [c] methamphetamines, methadone (MET), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), tetrahydrocannabinol (THC) Urine Pregnancy Test (a) Alcohol (can be performed via breath test)

FT4= free T4, FSH= follicle-stimulating hormone, GGT=γ-glutamyl transferase, hCG= human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells, TSH= thyrotropin, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening, Urine Pregnancy Test will be done at Check-in (Day -1).
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.
(c) To be performed at Inpatient Check-in (Day -1).
(d) To be performed at Day -1 and 24- and 48-hours post-dose.
(e) Screening Visit only

The local laboratory will perform all clinical laboratory tests. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to the sponsor or designee in the format requested by the sponsor. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the Investigator or sub-investigator, indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Subjects will be referred to their primary care physician for follow-up of any clinically significant findings or where the investigator or medically trained sub-investigator deems appropriate.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level, or a satisfactory explanation has been obtained.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

(Please refer to Section 7.5 for discontinuation criteria and Section 9.8.3 for the appropriate guidance on Reporting of Abnormal LFT in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN).

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 9.8.3 Reporting of Abnormal LFT for reporting requirements).

9.1.13 Contraception and Pregnancy Avoidance Procedure

From the date of signing of ICF, throughout the duration of the study, and for 30 days after the last dose of study medication, females of childbearing potential* must use **two** acceptable methods of contraception and must agree not to donate eggs; Nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use **two** acceptable method(s) of contraception throughout the duration of the study, and for 90 days after the last dose of study medication. In addition, males must be advised not to donate sperm for 90 days after the last dose of study medication.

Females of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal.

Menopause is defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented. Male subjects with potentially postmenopausal partners who are under the age of 55 years must use condoms unless their partner's postmenopausal status has been confirmed by FSH level.

**Sterilized males should be at least 90 days post-vasectomy and confirm that they have obtained documentation of the absence of sperm in the ejaculate.

Acceptable and highly effective methods of contraception are:

Note: hormonal contraceptives are not permitted for female participants, as referenced in Table 3. Female partners of male participants can use hormonal contraceptives..

- Nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomised subject/partner with documented azoospermia 90 days after the procedure, if that partner is the sole sexual partner
- Same-sex intercourse, if used consistently for the duration of the study and post-dosing as specified above

Complete abstinence, defined as the complete avoidance of heterosexual intercourse - is an acceptable form of contraception if used consistently throughout the study and for the durations

after dosing specified for males and females above. It is not necessary to use any other method of contraception when complete abstinence is elected. Females of childbearing potential who choose complete abstinence must continue to have pregnancy tests as per protocol. The reliability of sexual abstinence needs to be evaluated by the Investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Subjects will be provided with information on acceptable methods of contraception as part of the subject's informed consent process and will be asked to sign an ICF stating that they understand the requirements for avoidance of pregnancy, egg donation, and sperm donation during the study.

9.1.14 Pregnancy

Women who are pregnant or breastfeeding will not be included in this study.

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of the blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to the final outcome using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted for 8 weeks.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign ICF. If the subject is not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal

- Study termination
- Other

Subject numbers assigned to subjects who fail screening should not be reused.

If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were two separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The study-related procedures schedule for all evaluations is shown in Appendix A and is not duplicated in the following sections.

9.3.1 Screening

Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures. Subjects who are screening failures may be screened a second time if their reason for failing screening is thought to be resolved. Rescreened subjects will receive a new Screening number.

9.3.2 Inpatient Check-In

All subjects will be admitted to the study clinic the day prior to randomization and first dose. Subjects participating in the food effect cohorts will also check into the study clinic the day prior to the scheduled dosing.

9.3.3 Final Visit (discharge day from clinic)

Subjects will be confined to the study clinic for the duration of the treatment period to permit supervised dosing of study drug and repeat study assessments. Subjects participating in the single-dose study and food effect assessment will be discharged no sooner than 72 hours post-dose, and subjects participating in the multiple-dose study will be discharged no sooner than 48 hours following their last dose.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

Subjects who discontinue dosing or decide to check out of the study clinic early will be advised to allow the Investigator (or authorized designees) to complete early termination assessments for safety purposes prior to discharge. The reason for discontinuation must be documented in the source document and eCRF.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit

The Follow-up Visit will occur by telephone approximately 14 days (±2) after the final dose of study drug for the SAD cohorts and MAD cohorts unless abnormal CS findings were observed upon discharge or the SRG has determined additional PK sampling timepoints are indicated. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.

9.4 Biological Sample Retention and Destruction

In all cohorts except S3 (fed), blood serum will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed. Samples will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law.

Blood specimens for genome/gene analysis will be collected as described in Section 9.1.9, Pharmacogenomic Sample Collection. After extraction and purification, the genetic material will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law. Blood and urine samples for PK analysis will be collected as described in Section 9.1.10, PK Sample Collection. Once PK analysis is complete, backup plasma and urine samples will be preserved and retained at a biorepository selected by the sponsor for up to, but not longer than, 15 years or as required by applicable law, to enable the conduct of exploratory, qualitative, metabolite identification studies or measurement of target related biomarkers, should the sponsor decide these are informative. The sponsor has put a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with

code numbers; the samples are stripped of all personally identifying information, but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. The Investigator will notify the sponsor of any subject who has withdrawn consent for the DNA and RNA analysis.

9.5 Blood Volume

Direct venipuncture or intravenous cannula is the preferred method of blood collection. Any other method will need to be approved by the sponsor. The maximum volume of blood at any single day is approximately 111 mL, with the maximum amount not to exceed 500mL for the duration of study participation.

9.6 CSF Volume

CSF will be collected by lumbar puncture, performed by a skilled and qualified individual. The maximum volume of CSF to be collected will be approximately 10 mL per subject.

9.7 Definitions

9.7.1 PTE

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed the ICF to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.7.2 AE

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a CS abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

9.7.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs)
- Necessitate therapeutic intervention
- Require an invasive diagnostic procedure
- Require discontinuation or a change in dose of study medication or a concomitant medication
- Be considered unfavorable by the investigator for any reason

- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be CS (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention
- If abnormal laboratory values or ECG findings are the results of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of the ICF) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays, etc.) should NOT be recorded as PTEs unless related to study procedures.
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy), any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious, or severe in nature; that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., “worsening of…”)
- If a subject has a concurrent degenerative condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of…”)

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE.
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Changes in severity of AEs /Serious PTEs:
- If the subject experiences changes in the severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF

9.7.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE-THREATENING
    - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization
4. Results in persistent or significant DISABILITY/INCAPACITY
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above
    - May expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization
    - Includes any event or synonym described in the Medically Significant AE List (Table 11)

PTEs that fulfill 1 or more of the serious criteria above are also considered SAEs and should be reported and followed up in the same manner (see Sections 9.8.1 and 9.8.2).

Table 11 Medically Significant AE List (categorized as Serious Adverse Events)

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of an infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

9.7.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

9.7.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from the administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from the administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

9.7.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is a reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

9.7.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

9.7.9 Stop Date

The stop date of the AE/serious PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

9.7.10 Frequency

Episodic AEs/serious PTE (e.g., vomiting) or those which repeatedly occur over a period of consecutive days are intermittent. All other events are continuous.

9.7.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE
- Dose not changed – the particular AE did not require stopping a study medication
- Unknown – only to be used if it has not been possible to determine what action has been taken
- Not Applicable – a study medication was stopped for a reason other than the particular AE, e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE

9.7.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/serious PTE
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/serious PTE with the condition remaining "recovering/resolving"
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms, or laboratory value on the last day of the observed study period had got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/serious PTE state remaining "Not recovered/not resolved."
- Resolved with sequelae – the subject recovered from an acute AE/serious PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis
- Fatal – the AEs/PTEs which are considered as the cause of death
- Unknown – the course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study

9.8 Procedures

9.8.1 Collection and Reporting of AEs

9.8.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication Day 1 or until screen failure. For subjects who discontinue prior to study medication administration, PTEs will be collected for the duration of study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1. Routine collection of AEs will continue until 14 days following last dose.

9.8.1.2 PTE and AE Reporting

At each study visit, the investigator or designee will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not be followed up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date and time
3. Frequency
4. Severity
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs)
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
7. Action concerning study medication (not applicable for PTEs)
8. Outcome of event
9. Seriousness

9.8.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

An SAE form must be completed in English and signed by the investigator immediately or within 24 hours of the first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study medication(s)
- Causality assessment

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

9.8.3 Reporting of Abnormal LFT

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 9.8.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the SAE form (as per Section 9.8.3).

9.9 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee if requested.

All SAEs should be followed up until resuspension or the permanent outcome of the event. The timelines and procedures for follow-up reports are the same as those for the initial report.

9.9.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.0 STUDY-SPECIFIC COMMITTEES

The Safety Review Group (SRG) will be comprised of the Investigator, Medical Monitor, Cerevance Medical Officer and may include other sponsor representatives. A pharmacokineticist and other subject matter experts may participate as needed. The responsibilities of the SRG are outlined in Section 6.1.3.

11.0 DATA HANDLING AND RECORDKEEPING

AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary. All terms will be coded using the dictionary version available at the start of the study.

11.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change. Reasons for significant corrections should additionally be included.

The Investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure the accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without the written permission of the sponsor.

11.2 Record Retention

The investigator agrees to keep the records stipulated in Section 11.2 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), an electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study

records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of the subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to unblinding of the subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

12.1.1 Analysis Sets

Safety Set

The Safety Analysis Set will consist of all subjects who are enrolled and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Set

The PK set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration.

If any subjects are found to be non-compliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.

12.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for pooled placebo, CVN766 dose level, CVN766 overall, and overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for pooled placebo, each CVN766 dose level, CVN766 overall, and overall. Individual subject demographic and baseline characteristics data will be listed.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

12.1.3 PK Analysis

The concentration of CVN766 in plasma and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically. Descriptive statistics (arithmetic mean, SD, median, minimum and maximum) will be used to summarize the plasma and CSF PK parameters for CVN766. In addition, geometric mean and coefficient of variation will be computed

The effect of fed/fasting state on PK and bioavailability of CVN766 will be characterized.

Plots of C_{max} and AUCs, as well as dose-normalized C_{max} and AUCs, versus doses, will be generated.

Dose proportionality will be tested for CVN766 C_{max} and AUCs using a power model.

A more detailed analysis will be presented in the SAP.

12.1.4 Safety Analysis

12.1.4.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. Treatment-emergent AEs with onset occurring within 30 days (onset date – last date of dose +1 ≤30) after study drug administration will be listed and included in the summary tables. Treatment-emergent AEs will be summarized by pooled placebo, each CVN766 dose level and CVN766 overall by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs. not-related), severity of AEs, and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs, including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs. All AEs will be listed.

12.1.4.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that are abnormal and CS will be summarized and listed. Baseline, post-dose, and change from baseline to post-dose laboratory data will be summarized for pooled placebo, each CVN766 dose level, and CVN766 overall. All clinical laboratory data will be listed.

12.1.4.3 Vital Signs

Individual results of vital signs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from Baseline in vital sign measurements will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. All vital sign data will be provided in the data listings.

12.1.4.4 ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from baseline in quantitative ECG parameters will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. Shift tables may be generated for the investigator's ECG interpretations that changed from baseline to the post-dose collections by the above groups. All ECG data will be provided in the data listings.

12.1.4.5 Other Variables

Physical exam findings and suicidal assessments will be presented in data listings.

12.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

12.3 Determination of Sample Size

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) is considered to be sufficient for the evaluation of the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 12 defines the windows allowed for sample collections.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 12 Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes pre-dose	0 hour
±5	immediately post-dose to ≤6 hours
±10	>6 hours to ≤12 hours post-dose
±15	>12 hours to ≤24 hours
±30	>24 hours

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of Australia (i.e., Therapeutic Goods Administration [TGA]) and foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 13.1.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICFs, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before the commencement of the study (i.e., before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from a competent authority to begin the trial. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence on participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without providing a reason and without prejudice to their other medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines they will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and the subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

Subjects who consented and provided a pharmacogenomic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

14.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and the accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals, and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study, including data and information generated by the investigator, without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, the sponsor will register this clinical trial on ClinicalTrials.gov (and possibly on other publicly accessible websites) before the start of study.

Sponsor contact information, along with the investigator's city, state, country, and recruiting status, will be registered and available for public viewing. Once subjects receive investigator contact information, they may call the site and request enrollment into the trial. The investigative site(s) are encouraged to handle such trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

14.4.3 Clinical Trial Results Disclosure

If required at the conclusion of the study, the sponsor will post the results on ClinicalTrials.gov or other publicly accessible websites, as required by applicable national and local laws and/or regulations.

14.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, they should contact the sponsor or sponsor's designee.

15.0 REFERENCES

FDA Guidance for Industry: Food-effect bioavailability and fed bioequivalence studies (Dec 2002).

FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 06 July 2005. Publication No. 5541.

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Salvadore G, Bonaventure P, Shekhar A, Johnson PL, Lord B, Shireman BT, Lebold TP, Nepomuceno D, Dugovic C, Brooks S, Zuiker R, Bleys C, Tatikola K, Remmerie B, Jacobs GE, Schruers K, Moyer J, Nash A, Van Nueten LGM, Drevets WC. Translational evaluation of novel selective orexin-1 receptor antagonist JNJ-61393215 in an experimental model for panic in rodents and humans. Transl Psychiatry. 2020 Sep 7;10(1):308. doi: 10.1038/s41398-020-00937-9.

Appendix A: Schedule of Study Procedures

SAD Cohorts 1, 2, 4, 5	Screening	Check-in	Dosing & Observation			Discharge (a)	Outpatient Visit	Early Termination	Follow-up
Study Day:	-28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 8		Day 14 (±2) (b)
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics and medical history	X								
Medication history	X								
Neurological Exam (o)		X	X	X	X	X			
Physical examination	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X	
Urine drug screen	X	X							
Cotinine screen		X							
Concomitant medications (e)	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X								
FSH (g)	X								
Serum Pregnancy test (hCG)	X								
Urine Pregnancy test		X							
CV Telemetry (n)			X	X					
ECG (h)	X	X	X	X	X	X	X	X	
PGx DNA sample collection (i)			X						
PGx RNA collection (j)			X						

PK blood collection (k)			X	X	X	X		X	
Standardized pre-dose meal (S3 fed cohorts only)			X						
Study drug dosing			X						
PTE assessment (l)	X	X	X						
AE assessment (m)			X	X	X	X	X	X	X

PGx=pharmacogenomic.(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses asneeded.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) Whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples for PK analyses will be collected at time points indicated in Table 6.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) CV telemetry should be recorded at least 12 hours prior to dosing, and up to 24 hours after dosing
(o) Neurological exam to consist of light touch, power in limbs, and brief cranial nerve examination.

Cohort 3 SAD Fasted-Fed Crossover	**Screening**	**Dosing and Observation Inpatient**				**D/C**		**Inpatient** No sooner than +14 days or 4 half-lives of Day 8 visit					**+4 days post D/C**	**E/T**	**F/U**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**			**Day 14 (±2) (b)**
Informed consent	**X**														
Inclusion/exclusion criteria	X	X													
Admitted to the Clinic		X													
Demographics and medical history	X														
Medication history	X							X							
Neurological Exam (o)		X	X	X	X	X		X	X	X	X	X			
Physical examination	X	X				X	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X				X	X	X	
Urine drug screen	X	X						X							
Cotinine screen		X													
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X						X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X		X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X														
Urine Pregnancy test		X						X							
CV Telemetry (n)			X	X				X	X	X					
ECG (h)	X	X	X	X	X	X	X		X	X	X	X	X	X	
PGx DNA sample collection (i)			X												
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X			X	X	X	X		X	

Lumbar puncture & CSF collection (k)			X												
Standardized pre-dose meal									X						
Study drug dosing			X						X						
PTE assessment (l)	X	X	X					X	X						
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X
Discharged from Clinic						X						X		X	

*S3 Cohort will return no sooner than Day 14 or 4 half-lives (whichever is greater) after Day 8 for the Fed portion. The Fed portion will commence on Day -1 will all the same schedule of events with the exception of **dosing will be post-meal.**

PGx=pharmacogenomic.
(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) Whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples for PK analyses will be collected at time points indicated in Table 6.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) CV telemetry should be recorded at least 12 hours prior to dosing, and up to 24 hours after dosing
(o) Neurological exam to consist of light touch, power in limbs, and brief cranial nerve examination.

Multiple-Dose Regimen Cohorts	**SCR**	**Check-in**	**Inpatient Dosing & Observation**								**Inpatient Discharge (a)**	**Outpatient Visit**		**E/T**	**Follow-up**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**(model for additional dosing days) Day 6**	**Day of last dose (e.g. Day7)**	**1 day after last dose (e.g. Day 8)**	**2 days after last dose (e.g. Day 9)**	**3 days ±0 after last dose (e.g. Day 10) (o)**	**7 days ±1 after last dose (e.g. Day 14)**		**14 days ±2 after last dose (e.g. Day 21 ±2) (b)**
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics and medical history	X														
Medication history	X														
Neurological exam (p)		X	X						X		X		X	X	
Physical examination	X	X	X						X		X		X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X		X	X	
Weight, height, and BMI (d)	X	X	X						X		X		X	X	
Urine drug screen	X	X													
Cotinine screen		X													
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X													
Clinical laboratory tests (f)	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hepatitis panel and HIV antibody test	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X														
Urine Pregnancy Test		X													
ECG (h)	X	X	X	X	X	X	X	X	X	X	X		X	X	

Multiple-Dose Regimen Cohorts	SCR	Check-in	Inpatient Dosing & Observation								Inpatient Discharge (a)	Outpatient Visit		E/T	Follow-up
Study Day:	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	(model for additional dosing days) Day 6	Day of last dose (e.g. Day7)	1 day after last dose (e.g. Day 8)	2 days after last dose (e.g. Day 9)	3 days ±0 after last dose (e.g. Day 10) (o)	7 days ±1 after last dose (e.g. Day 14)		14 days ±2 after last dose (e.g. Day 21 ±2) (b)
[redacted]															
PGx DNA sample collection (i)			X												
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X	X	X	X	X	X	X		X	
[redacted]															
Study drug dosing			X	X	X	X	X	X	X						
PTE assessment (l)	X	X	X												
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X

PGx=pharmacogenomic (a) Events listed as occurring at "Inpatient Discharge" visit will occur on that day prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 21 (±2) unless abnormal CS findings are observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per Investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 and Day 7 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Day 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Days 1 through 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days). Hormone laboratory tests (PRL, thyrotropin [TSH], and FT4) will be collected on Days 1 and 7 (morning [fasting] and 3 hours after dosing), Day 9, and Day 14 under fasted conditions. Fasting lipase tests will be collected at Day -1, Days 2, 7, and 8 (pre-dose). An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Screening, Inpatient Check-in (Day -1), Days 1 and 7 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Days 8 and 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days).
(i) One blood sample will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) Whole blood samples will be collected on Day 1 and Day 7 (pre-dose, 8- and 24-hours post-dose) for RNA pharmacogenomic analysis.
(k) Blood samples for PK analyses will be collected at time points indicated in Table 7. CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in cohorts M1 and M2, as indicated in Table 9. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.
(l) PTEs will be collected from signing of ICF up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
[redacted]
(o) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the Day 10 visit is not necessary.
(p) Neurological exam to consist of light touch, power in limbs, and brief cranial nerve examination.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (non-routine/nonstandard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conforms to local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in local regulations, are met.
8. Obtain valid ICF from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entering into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Cerevance will collect and retain personal information of the Investigator, including their name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, and Japan), including the following:

- Cerevance, its affiliates, and licensing partners
- Business partners assisting Cerevance, its affiliates, and licensing partners
- Regulatory agencies and other health authorities
- IRBs and IECs
- Investigator's personal information may be retained, processed, and transferred by Cerevance and these other parties for research purposes, including the following:
- Assessment of the suitability of Investigator for the study and/or other clinical studies
- Management, monitoring, inspection, and audit of the study
- Analysis, review, and verification of the study results
- Safety reporting and pharmacovigilance relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication
- Inspections and investigations by regulatory authorities relating to the study
- Self-inspection and internal audit within Cerevance, its affiliates, and licensing partners
- Archiving and audit of study records
- Posting Investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites
- Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the Investigator's own country.
- Investigator acknowledges and consents to the use of their personal information by Cerevance and other parties for the purposes described above.

PROTOCOL

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects

Short Title: Phase 1 SAD/MAD Study of CVN766

Sponsor:	Cerevance Gamma, Inc. One Marina Park Drive, Suite 1410 Boston, MA 02210		
Study Number:	CVN766-101		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	CVN766		
Protocol Version:	4.0, Amendment 3		
Date:	01 June 2022		

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided for each site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Novotech
Medical Monitor (carries overall responsibility for the conduct of the study)	[redacted], MD
Responsible Medical Officer (medical advice on protocol and compound)	[redacted], MD

1.2 Approval

REPRESENTATIVES OF CEREVANCE

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations

SIGNATURES

Approved by: [redacted]

Signature __[redacted]__ Date 01-JUN-2022

[redacted], M.D.
Medical Monitor

INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation, E6 GCP: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Regulatory requirements for reporting serious adverse events (SAEs) are defined in **Section 9.9** of this protocol
- Terms outlined in the Clinical Study Site Agreement
- **Appendix B** – Responsibilities of the Investigator

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in **Appendix C** of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

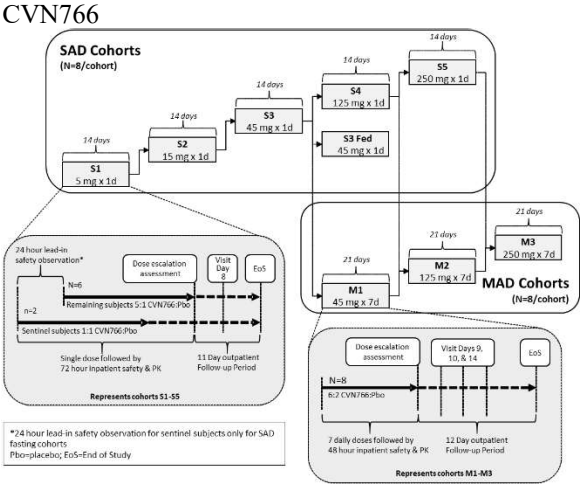
TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance, Inc.	**Compound:** CVN766 		
Title of Protocol: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of Escalating Single and Multiple Doses of CVN766 in Healthy Subjects	**IND No.:**	**EudraCT No.:** Not Applicable	
Study Number: CVN766-101	**Phase:** 1		

Study Design:

This is a Phase 1, randomized, double-blind, placebo-controlled, single- and multiple-dose ascending study in healthy subjects with concurrent PK sampling from blood plasma, urine, and cerebrospinal fluid. The overall study design is outlined below:

Part 1: Single-Dose Regimen and Fasted-Fed Crossover

For the single-dose regimen, approximately 40 healthy male or female subjects will be enrolled in 1 of 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. An optional 8 subject (Cohort S3a) may be added in parallel with Cohort S3. Cohort S3a dose level will be consistent with Cohort S3 (45 mg planned) in a fasted condition only and without lumbar puncture, aligned with the Schedule of Procedures (**Appendix A**) and other SAD Cohorts. Each cohort will consist of 8 subjects randomized to CVN766 or placebo. In each cohort, 6 subjects will receive a single oral dose of CVN766 suspension, and 2 subjects will receive a matching placebo suspension under overnight fasted conditions. Subjects will remain fasted for 4 hours post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 or placebo to the remainder of the subjects within the cohort. After blinded review by the Investigator of 24-hour post-dose adverse event listings (as applicable) from the sentinel group, the Investigator will advise the sponsor on the acceptability of enrolling the remaining 6 subjects in each cohort. In the event that a safety signal emerges in the sentinel group, a Safety Review Group (SRG) meeting may be required as requested by Investigator or Sponsor. To accommodate the lumbar puncture in the S3 fasted cohort, the remaining 6 subjects' dosing may be staggered every two days after the sentinel group. The planned dose levels will be 5, 15, 45, 125, and 250 mg CVN766. The SRG will review all available blinded safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and available pharmacokinetic (PK) data prior to all dose escalations and after the completion of all subjects in a cohort. If Cohort S3a (optional cohort) is enrolled and completed prior to Cohort 3, the SRG may determine dose escalation to Cohort S4 after evaluating data from Cohort 3a alone. Each following dose level may be higher, lower, or remain the same as the preceding cohort, dependent on the recommendation of the SRG.

Additional cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability

of CVN766. For example, if Cohort S5 is well-tolerated, additional cohorts with higher dose levels may be considered. Such additional cohorts will follow the same schedule of events as for Cohorts S1 through S5. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

To assess the effect of food on CVN766 bioavailability in suspension formulation, the single-dose administration will be repeated in a single cohort (S3) after ingestion of a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the Cohort S3 dose level has been assessed, the Cohort S3 subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives, has lapsed based on preliminary PK data, whichever is longer). They will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish at least approximately 85% of their breakfast within 30 minutes and receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

Subjects for all cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments. On Day 1, subjects will undergo safety monitoring and PK sampling from blood plasma through 72 hours post-dose and, for Cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. The total confinement period will be 4 nights unless extended at the discretion of the Investigator, e.g., for monitoring and/or management of AEs. Follow-up assessments will occur on approximately Days 8 and 14 and +21 and +28 for Cohort S3.

A summary of the single-dose regimen visit schedule is presented below:

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK, Safety and Lumbar Puncture Site Assessments (S3 fasted)	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. S3 subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required on Day -1.

(b) CSF collection will apply only to Cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal, clinically significant (CS) findings were observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 healthy male and female subjects aged 18 to 55 will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. The dose levels planned to be studied in the multiple-dose regimen are 45, 125, and 250 mg CVN766 for multiple-dose Cohorts M1 through M3, respectively. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily oral dose of CVN766, and 2 subjects will receive matching placebo for 7 days. Dosing will be administered in the fasting state; the SRG can change this if exposure is higher in the fed state. The planned dosing duration for the multiple-dose cohorts is 7 days. However, the duration may be increased to ≤14 days at the discretion of the SRG if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. For each dose on intensive PK sampling days (first and last days of dosing, e.g., Days 1 and 7), subjects will remain fasted for 4 hours post-dose. On other dosing days (Days 2-6), subjects will remain fasted for 1-hour post-dose. Consumption of water is permitted as desired except for 1 hour before and after administration of Study Drug. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 or Cohort S3a (minimally

including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of dose level may be modified by the SRG after the available blinded safety, tolerability, clinical laboratory results, and PK data in the preceding multiple-dose and corresponding single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose Cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in Cohort M1 only, from urine through 24 hours post-dose. Additionally, Cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7), subjects will undergo additional PK sampling from CSF via lumbar puncture at 3 hours post-dose. However, if the SRG determines additional PK sampling from CSF via lumbar puncture is not necessary for Cohort M2, the lumbar puncture may be omitted. Likewise, if needed to resolve questions arising from prior Cohorts' data, subjects in Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., $t_{½}$). The total confinement period will be 9 nights unless extended for additional dosing days or management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose.

A summary of the multiple-dose regimen visit schedule is presented below:

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g., Days 8-9)	3 days ±0 after last dose (e.g., Day 10) & 7 days ± 1 after last dose (e.g., Day 14)	14 days ±2 after last dose (e.g., Day 21)

(a) CSF sampling is planned on Day 7 in Cohorts M1 and M2 (CSF sampling for Cohort M2 may be omitted at the discretion of the SRG). Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or, if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal, clinically significant (CS) findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in Cohort M1.

Safety Review Group (SRG)

The SRG will comprise of the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for the ongoing review of safety, tolerability, clinical laboratory results, and available PK data and deciding:

1. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data, including at least 72 hours post-dose safety data and

clinical laboratory results from a minimum of 5 subjects in the current cohort),

2. Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data, including at least 48 hours post 7th dose safety data from a minimum of 5 subjects in the current cohort),
3. Add additional dose cohort(s) in either the single- or multiple-dose studies,
4. Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days,

In addition, if 2 or more subjects in a single cohort experience the same type of serious or medically significant event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

Primary Objective:

To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects and determine the recommended phase 2 dose (RP2D).

Secondary Objectives:

- To characterize the single-dose PK profile of CVN766 in plasma and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma and CSF
- To assess the effect of food on the bioavailability of CVN766

Exploratory Objectives:

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

[redacted]

Subject Population: Healthy male and female subjects 18 to 55 years old

Number of Subjects:	**Number of Sites:**
Each dose cohort: 8 subjects (6 active:2 placebo) Estimated total: 64 subjects (5 single-dose cohorts, 3 multiple-dose cohorts)	2 (Australia)
Dose Level(s): Planned single-dose levels are placebo, 5 mg, 15 mg, 45 mg, 125 mg, and 250 mg CVN766. Planned multiple dose levels are placebo, 45 mg, 125 mg, and 250 mg CVN766.	**Route of Administration:** Oral
Duration of Treatment: Single or daily oral doses for up to 7 days (+7 days as necessary to reach steady-state and as required by Safety Review Group).	**Period of Evaluation:** Screening Period: up to 28 days Treatment Period: 1-7 days (+7 days, as necessary). Food Effect washout period (for select cohort only): at least 14 days Follow-up Period: approximately 14 days Total Duration: • Single-dose cohorts: approximately 6 weeks • Food effect cohort: approximately 8 weeks • Multiple-dose cohorts: approximately 7 weeks

Main Criteria for Inclusion:

Healthy male and female subjects who are 18 to 55 years of age, inclusive and have a body mass index (BMI) between 18.0 and 32.0 kg/m^2 inclusive at Screening.

A complete list of inclusion criteria is provided in **Section 7.1**.

Main Criteria for Exclusion:

Subjects have a known hypersensitivity to any component of the formulation of CVN766. Subjects have evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, allergic skin rash, psychiatric disorder, or other abnormality that may impact the ability of the subject to participate or potentially confound the study results. Any finding in the subject's medical history, physical examination, or safety laboratory tests gives reasonable suspicion of a condition that might interfere with the conduct or interpretation of the study.

A complete list of exclusion criteria is provided in **Section 7.2.**

In addition, subjects may not use any excluded medications (including oral contraceptives as listed in Table 3), supplements, or food products. Concomitant medications and dietary products to be excluded are listed in Table 3.

Main Criteria for Evaluation and Analyses:

- Safety:

Safety parameters will include AEs, clinical laboratory results, vital signs, physical examinations, and electrocardiogram (ECG). AEs will be collected from signing the informed consent form (ICF) up until dosing on Day 1 as pretreatment events (PTEs), and any event that occurs from dosing until 14 days after the last dose will be captured as an AE. Vital signs will be recorded at Screening, Inpatient Check-in (Day -1), and throughout the dosing period. Vital signs will include tympanic body temperature measurement, blood pressure, respiration rate, and pulse (beats per minute [bpm]). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day -1) 15 minutes apart (the average will be used to determine eligibility). Heart rate and blood pressure will be measured after at least 5 minutes supine and again at 2 minutes after standing for all scheduled timepoints. Standard 12-lead ECGs will be recorded at Screening, Inpatient Check-in (Day -1), and periodically throughout the dosing period. Triplicate ECGs will be taken at each timepoint.

A complete list of safety assessments is provided in **Section 9.1**, and the full Schedule of Study Procedures is provided in **Appendix A**.

- PK:

The plasma PK parameters are used as PK endpoints to determine drug exposure at each dose and facilitate dose escalations.

Plasma samples will be collected for the determination of concentrations of CVN766 throughout the study as prescribed in the Schedule of Study Procedures (Appendix A). Cerebrospinal fluid (CSF) samples will be collected for the determination of concentrations of CVN766 as described in **Section 9.6** and the Schedule of Study Procedures (**Appendix A**). PK sampling timepoints may be modified or added based on emerging PK data to most appropriately characterize the PK profile of CVN766 as determined by the SRG.

PK parameters of CVN766 will be derived using noncompartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma: C_{max}, AUC from time 0 to the last quantifiable concentration (AUC_t), AUC from time 0 to infinity (AUC_∞), AUC from time 0 to 24 hours (AUC_{24}), time to reach C_{max} (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2z}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F). Multiple-dose PK will also include AUC over the dosing interval (AUC_{tau}), apparent clearance at steady state (CL/F_{ss}), apparent volume of distribution at steady state (Vz/F_{ss}), steady-state nadir concentrations, and accumulation ratios

The PK parameters to be determined from concentrations of CVN766 in CSF will include plasma: CSF ratio by time point.

- Pharmacogenomics:

One whole blood sample will be collected at pre-dose on Day 1 for pharmacogenomic analysis; this will only be collected once per subject. Two whole blood samples will be collected at pre-dose on Day 1 and at multiple timepoints post-dose for ribonucleic acid (RNA) pharmacogenomic analysis. The pre-dose RNA blood samples

should be collected under fasted conditions and prior to any other blood collection. The samples will be stored for no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from Cerevance. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personally identifying information, but key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; eligible subjects sign the ICF, which outlines the retention of pharmacogenomic and genotyping analysis in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

- Endpoints:

The primary endpoints of this study will be the following: percentage of subjects who experience at least one treatment-emergent adverse event (TEAE); percentage of subjects with abnormal and CS safety laboratory, vital signs, or ECG test results at least once post-dose.

The secondary endpoints will be the following plasma PK parameters of CVN766: C_{max}, AUC_{24}, AUC_{∞}, $t_{1/2z}$, AUC from time 0 to end of the dosing interval, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}.

The additional endpoints may include the following plasma PK parameters of CVN766: t_{max}, CL/F, V_z/F, CL/F_{ss}, Vz/F_{ss}, and plasma: CSF ratio.

Exploratory endpoints may include characterization of metabolic enzyme and transporter polymorphisms and/or

[redacted]

Statistical Considerations:

Safety:

AEs will be presented in listings, and TEAEs will be summarized. Individual results of laboratory tests (hematology, chemistry, and urinalysis) will be recorded at baseline and post-dose, and changes from baseline will be summarized using shift tables. Individual vital signs will be recorded, and observed values and changes from baseline will be summarized. Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed, and observed values and changes from baseline will be summarized. All summaries will be performed by placebo, each CVN766 dose level (fasted and fed separately), and CVN766 single-dose overall, and separately CVN766 multiple-dose cohorts overall. Placebo data will be pooled across single-dose cohorts and separately pooled across multiple-dose cohorts. Physical exam findings will be presented in data listings.

PK Measures:

Concentrations of CVN766 in plasma and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma and CSF concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically.

PK parameters of CVN766 will be summarized by dose using descriptive statistics. Dose proportionality will be assessed graphically and using a power model.

The concentrations of CVN766 in plasma and CSF will be compared.

Sample Size Justification:

The sample size chosen is considered sufficient for evaluating the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

3.0 STUDY REFERENCE INFORMATION

3.1 List of Abbreviations

λ_z	terminal elimination rate constant
AE	adverse event
[redacted]D	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUCt	area under the plasma concentration-time curve over the dosing interval (t)
BMI	body mass index
CL/F	apparent clearance after extravascular administration
CL/F_{ss}	apparent clearance after extravascular administration at steady state
[redacted]	[redacted]
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
CS	clinically significant
CSF	cerebrospinal fluid
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
[redacted]PD	[redacted]
FSH	follicle-stimulating hormone
FT4	free T4
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HED	human-equivalent dose
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee

INR	international normalized ratio
IRB	institutional review board
K_2EDTA	dipotassium ethylenediamine tetraacetic acid
LFT	liver function test
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRSD	maximum recommended starting dose
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
Ox1R	orexin 1 receptor
Ox2R	orexin 2 receptor
PK	pharmacokinetic
PRL	prolactin
PT	preferred term
PTE	pretreatment event
QTcB	QT interval with Bazett's correction method
QTcF	QT interval with Fridericia's correction method
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAD	single-ascending dose
SAP	statistical analysis plan
SOC	system organ class
SRG	Safety Review Group
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution after extravascular administration
V_z/F_{ss}	apparent volume of distribution after extravascular administration at steady state
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

The neuropeptide orexin, also known as hypocretin, is produced exclusively in the orexigenic neurons in the hypothalamus. There are two forms of orexin, Orexin-A, and orexin-B, alternatively spliced from the same gene, HCRT. There are two orexin receptors, orexin 1 receptor (Ox1R) and orexin 2 receptors (Ox2R), both of which are G-protein coupled receptors. Both orexin-A and orexin-B can bind to either receptor and in each case, agonist binding results in an increase in intracellular calcium levels. However, while orexin-A is equipotent at both receptors, orexin-B shows a 10-fold selectivity for Ox2R.

Ox1R is selectively expressed in key brain areas relating to psychiatric disorders. Ox1R-expressing neurons in the bed nucleus of the stria terminalis, amygdala, locus coeruleus, raphe nucleus, and the ventral tegmental area are important in regulating emotions of stress, anxiety, motivation, and reward. CVN766 is a potent and highly selective small-molecule Ox1R antagonist with no significant off-target activity. Nonclinical PK and toxicology studies with CVN766 and other Ox1R antagonists have established their pharmacological characteristics and probable safety profile.

Ox2R is expressed in some overlapping areas, including the raphe nucleus, and ventral tegmental area, but also in areas important to arousal and sleep regulation, including the tuberomammillary nucleus.

The widely used sleep aid suvorexant (Belsomra®), approved for use in Australia, is a dual Ox1R and Ox2R antagonist, but its sleep-inducing effects are generally attributed to its activity on Ox2R. A second dual Ox1R and Ox2R antagonist, lemborexant, appeared safe and effective in clinical studies, has been approved in many countries worldwide, and has been submitted for marketing authorization in Australia.

Clinical effects to be expected of a selective Ox1R antagonist remain uncertain. CVN766 has not yet been studied in humans. Other selective Ox1R antagonists have been reported in early-stage human clinical trials, notably JNJ-61393215 (ClinicalTrials.gov Identifier: NCT04080752; Salvadore *et al.*, 2020) and ACT-539313 (NCT01954589; Kaufmann *et al.*, 2020; Kaufmann et al., 2021). Both drugs were well tolerated and deemed safe for investigational use, the most common AEs being somnolence and mild headache.

4.2 Rationale for the Proposed Study

CVN766 is a highly selective orexin-1 receptor (Ox1R) antagonist and may have utility as a treatment for psychiatric disorders including schizophrenia, panic disorder and anxiety, and addiction. Its safety and PK profile have been preliminarily established in nonclinical toxicology studies. The present study will be the first conducted in humans with CVN766 and will examine the compound's safety, tolerability, and PK in healthy subjects.

Nonclinical pharmacology, toxicity, and pharmacokinetic (PK) studies support the proposed escalating single- and multiple-dose study of CVN766 in healthy subjects with a starting dose of 5 mg. **Section 6.2** outlines the justification for the planned dose ranges.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To characterize the safety and tolerability profile of escalating dose levels of CVN766 suspension when administered as a single oral dose or daily oral doses for 7 days in healthy subjects

5.1.2 Secondary Objectives

- To characterize the single-dose PK profile of CVN766 in plasma, and CSF
- To characterize the multiple-dose PK profile of CVN766 in plasma, and CSF
- To assess the effect of food on the bioavailability of CVN766 in the current formulation

5.1.3 Exploratory Objectives

- To explore possible drug metabolic enzyme and transporter polymorphisms that may contribute to variability in CVN766 PK, pharmacodynamics, or safety

5.2 Endpoints

5.2.1 Primary Endpoints

- Percentage of subjects who experience at least one treatment-emergent adverse event (TEAE)
- Percentage of subjects with abnormal and clinically significant (CS) safety laboratory test results at least once post-dose
- Percentage of subjects with abnormal and CS electrocardiogram (ECG) test results at least once post-dose
- Percentage of subjects with abnormal and CS vital sign measurements at least once post-dose

5.2.2 Secondary Endpoints

- Single-dose plasma PK parameters of CVN766, including time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from time 0 to 24 (AUC_{24}) and time 0 to infinity ($AUC\infty$), and terminal elimination half-life (t1/2z)

- Multiple-dose plasma PK parameters of CVN766 including C_{max}, AUC from time 0 to the end of the dosing interval, t1/2z, accumulation ratio, time to steady-state, steady-state C_{max}, and steady-state C_{min}
- Single-dose and multiple-dose CSF concentrations and CSF: plasma ratios of CVN766

5.2.3 Additional Endpoints

- Change from baseline in safety laboratory and ECG test results and vital signs
- Additional plasma PK parameters of CVN766, i.e., CL/F and V_z/F

[redacted]

- Characterization of metabolic enzyme and transporter polymorphisms

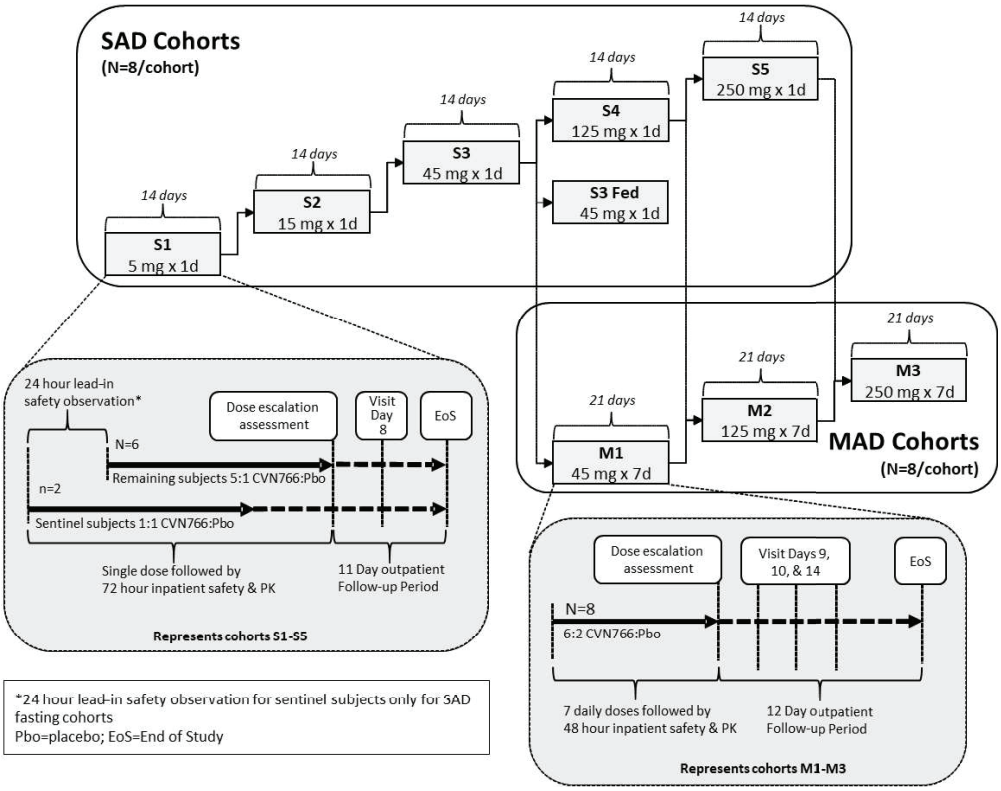
[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a Phase 1 ascending study in healthy subjects. Figure 1 provides a schematic illustration.

Figure 1 Study Schema



6.1.1 Part 1: Single-Dose Regimen and Fasted-Fed Crossover

Approximately 40 subjects will be enrolled in 1 of the 5 single-dose cohorts (designated as S1 through S5, respectively) in an ascending fashion. An optional Cohort 3a may be added in parallel to SC3 for additional safety and tolerability evaluation. Cohort S3a dose level will be consistent with Cohort S3 (45 mg planned) in a fasted condition only and without lumbar puncture, aligned with the Schedule of Procedures (**Appendix A**) and other SAD cohorts. Dose escalation will only occur after a fully blinded review of all available safety, tolerability, clinical laboratory results (minimally including samples collected from subjects through 72-hours post-dose), and available PK data, including at least a 72-hour follow-up from a minimum of 5 subjects of the most recent cohort.

The planned dose levels are provided in **Table 5**. Each cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a single dose of CVN766 and 2 subjects will receive a matching placebo under overnight fasted conditions.

Sentinel dosing (1 subject to receive CVN766 and 1 subject to receive placebo) will be used in each cohort to ensure adequate safety and tolerability evaluation prior to administering CVN766 to the remainder of the subjects within the cohort. After a blinded review of 24-hour post-dose safety and tolerability data, the remaining 6 subjects of each cohort may be dosed, provided that the adverse event (AE) profile of CVN766 in the first 2 subjects is considered acceptable.

Subjects for all cohorts (including optional Cohort S3a) will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments at least 72 hours after dosing. On Day 1, subjects will undergo safety monitoring (including labs, physical exam, neurological exam, cardia telemetry at 12-hours pre-dose), and PK sampling from blood plasma through 72 hours post-dose. In addition, for Cohort S3 (fasted) only, from CSF via lumbar puncture at 3 hours post-dose. For subjects participating in the SAD cohorts, the total confinement period will be 4 nights unless extended for management of AEs at the discretion of the Investigator. Follow-up assessments will occur on approximately Days 8 and 14.

To assess the effect of food on bioavailability of CVN766 in suspension formulation, single-dose administration will be repeated in a single cohort after ingestion of a standardized high-fat high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Once the safety of the S3 Cohort dose level has been assessed, the S3 Cohort subjects will return to the clinic (no sooner than 14 days after their prior dose, or at least 4 half-lives has lapsed based on preliminary PK data, whichever is longer) and will receive the same dose as before, administered after ingesting a standardized breakfast. Subjects will finish at least approximately 85% of their breakfast within 30 minutes and will receive an investigational product 30 minutes (± 5 minutes) after beginning the meal. Sentinel dosing will not be required for subjects returning to the clinic for the fed regimen. If the CVN766 PK parameters in the fasted S3 Cohort reveal poor absorption with inconclusive results, the fed cohort will be deferred until a higher dose level.

An outline of the single-dose study visit schedule is included in **Table 1**. A Schedule of Study Procedures is listed in **Appendix A**.

Table 1 Single-Dose Visit Schedule

Screening [a]	Inpatient Check-in	Dosing, PK, CSF & Safety Assessments [b]	Inpatient PK & Safety Assessments	Inpatient Discharge [c]	Follow-Up Outpatient Visit	Follow-Up Call [d]
Day -28 to -2	Day -1	Day 1	Day 2-4	Day 4	Day 8 ±1 day	Day 14 ±2 days

(a) Screening will occur at study entry. Subjects returning for the "Fed" repetition of the single-dose regimen will not undergo Screening assessments except as required at Day -1.

(b) CSF collection will apply only to Cohort S3 (fasted).

(c) Discharge from the clinic may be delayed if necessary to continue monitoring for resolution of AEs.

(d) The final follow-up assessment will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

6.1.2 Part 2: Multiple-Dose Regimen

For the multiple-dose regimen, approximately 24 subjects will be enrolled in 1 of the 3 multiple-dose cohorts (designated as M1 through M3, respectively) in an ascending fashion. Dosing will be administered in the fasting state; this can be changed by the SRG if exposure is found to be higher in the fed state. The dose levels planned to be studied in the multiple-dose regimen (M1 through M3) are provided in **Table 5**. Each multiple-dose cohort will consist of 8 subjects randomized to CVN766 or placebo, whereby 6 subjects will receive a daily dose of CVN766, and 2 subjects will receive matching placebo for 7 days. However, the duration may be increased to ≤14 days at the discretion of the safety review group (SRG) if preliminary PK data suggest steady-state will not be achieved within 6 days of daily dosing. Unlike the single-dose regimen, sentinel dosing within cohorts is not required in the multiple-dose regimen.

Subjects for all multiple-dose cohorts will be admitted to the study unit 1 day prior to dosing and remain in the unit for the duration of the dosing period and for at least 48 hours after the last dose for safety and PK assessments before discharge. On treatment Days 1 and 7, subjects will undergo safety monitoring and PK sampling from blood plasma through 48 hours post-dose and, in Cohort M1 only, from urine through 24 hours post-dose. In Cohorts M1 and M2, on treatment Day 7 (or last day of dosing, if extended beyond Day 7),. subjects will undergo additional PK sampling from CSF via lumbar puncture at 3 hours post-dose. If the SRG determines additional PK sampling from CSF via lumbar puncture is not necessary for Cohort M2, the lumbar puncture may be omitted. Likewise, if needed to resolve questions arising from prior Cohorts' data, subjects in Cohort, subjects in Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF via lumbar puncture, the choice of day (e.g., Day 1 or Day 7) and sampling time to be decided by SRG. Subjects in MAD cohorts may be asked to return to the clinic for an additional plasma PK sample 3 days after the last dose (e.g., Day 10) depending on emerging PK data, i.e., t½. The total confinement period will be 9 nights unless extended for additional dosing days or management of AEs. Follow-up assessments will occur approximately 7 and 14 days after the final dose. A summary of multiple-dose study visits is included in **Appendix A**.

Table 2 Multiple Dose Visit Schedule

Screening	Inpatient Check-in	Dosing, PK, CSF, & Safety Assessments [a,f]	PK / Safety Assessments & inpatient discharge [b]	Follow-Up Outpatient Visits [c]	Follow-Up Call [d]
Day -28 to -2	Day -1	Days 1-7 [e]	1 and 2 days after last dose (e.g. Days 8-9)	3 days ±0 after last dose (e.g. Day 10) & 7 days ± 1 after last dose (e.g. Day 14)	14 days ±2 after last dose (e.g. Day 21)

(a) CSF sampling is planned on Day 7 in Cohorts M1 and M2 (CSF sampling for Cohort M2 may be omitted at the discretion of the SRG). Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.

(b) Discharge from the clinic is planned for Day 9 but may be delayed for additional dosing days or if necessary, to continue monitoring for resolution of AEs.

(c) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the visit 3 days after the last dose (e.g., Day 10) may be omitted at Investigator's discretion.

(d) The Follow-up Visit will occur by telephone unless abnormal CS findings are observed upon discharge. In these cases, subjects must return to the clinic for re-evaluation.

(e) Dosing duration may be increased to ≤14 days at the discretion of the SRG based on preliminary PK and projected time to steady-state.

(f) Urine sampling will occur on Day1 and Day 7 in Cohort M1.

6.1.3 Dose Escalation

The SRG will comprise the Investigator, Medical Monitor, Cerevance Responsible Medical Officer and may include other Cerevance representatives. A pharmacokineticist and other subject matter experts may participate as needed. The SRG will be responsible for the ongoing review of safety, tolerability, clinical laboratory results, and available PK data and deciding to:

- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in single-dose cohorts (based on a review of available data, including at least 72 hours post-dose safety data and clinical laboratory results from a minimum of 6 evaluable subjects in the current cohort),
- Escalate to the next planned cohort or alternative dose levels (e.g., lower, intermediate, or higher) in multiple-dose cohorts (based on a review of available data, including at least 48 hours post 7th dose safety data from a minimum of 6 evaluable subjects in the current cohort),
- Add additional dose cohort(s) in either the single- or multiple-dose studies,
- Increase the duration of dosing in the multiple-dose cohorts from 7 days to ≤14 days

If 2 or more subjects in a single cohort experience the same type of serious or medically adverse event, further dosing will be withheld until the SRG investigates the events. Based on this assessment, the SRG will determine if the study should be terminated or continued and whether modification of planned dose levels and/or implementation of additional safety monitoring is indicated.

For each cohort (including sentinel subjects, where applicable), the SRG will carefully review the available blinded safety, tolerability, clinical laboratory results, and available PK data to determine whether dosing should stop or continue (and, if continued, at what dose, including whether to repeat the previous dose), whether additional sequential dosing should be implemented in future cohorts or whether the blind should be broken to identify whether the subjects received CVN766 or placebo. However, precautions must be taken not to unblind the study staff, including the Investigator.

If all doses are tolerated, then additional cohorts with higher doses may be considered. The actual choice of the subsequent dose level will occur after the full review of the available blinded safety, tolerability, clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the prior dose level. If necessary, additional cohort(s) may be added to fully characterize the safety and tolerability of CVN766.

Initiation of the multiple-dose regimen will only occur after a full blinded review of all available safety, tolerability, and clinical laboratory results for the fasting drug administration to single-dose Cohort S3 (minimally including samples collected through Day 4) and available PK data. For each multiple-dose cohort after the first, the actual choice of dose level may be modified by the SRG after a review of the available blinded safety, tolerability, and clinical laboratory results, and available PK data in the preceding multiple-dose and next-higher-dosage single-dose cohorts (i.e., multiple-dose Cohort M2 will not initiate until the data review for multiple-dose Cohort M1 and single-dose Cohort S4 is complete). Each subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Additional multiple-dose cohort(s) may be added if deemed necessary by the SRG to fully characterize the safety and tolerability of CVN766. Such additional cohorts will follow the same schedule of events as for prior multiple-dose cohorts. Additional/Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

All AEs reported during the Treatment Period, both within and across cohorts, up to the time of discharge, will be evaluated to assess the need for the subject and/or study termination in accordance with the prespecified criteria for discontinuation/termination (**Section 6.3.1**).

Additionally, the SRG may decide not to escalate the dose for a particular cohort but rather administer the same or a lower dose level to the next cohort. Additional/ Alternative PK timepoints may be implemented if the SRG determines this is necessary to fully characterize the PK profile of CVN766.

6.2 Justification for Study Design, Dose, and Endpoints

The study is double-blind and placebo-controlled to avoid subjective bias in assessing the safety and tolerability of CVN766. Dose escalation will be predicated on a review of available blinded safety, tolerability, and PK data from a minimum of evaluable 6 subjects from the prior Cohort.

The sponsor has selected the starting dose level considering the FDA Guidance for Industry (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, 06 July 2005) and providing additional safety factors to the initial calculations based on the principles outlined in the guidance. The toxicity profile of CVN766 after oral dosing was examined in repeat dosing studies in rats and dogs. Scaling based on body surface area was conducted by multiplying the NOAELs for the most sensitive animal species by the appropriate conversion factors. Based on these calculations and applying a 10-fold safety margin below the NOAEL human-equivalent dose (HED), the maximum recommended starting dose (MRSD) for this first-in-human study is 167 mg for a 60 kg subject. The selected starting dose level is 5 mg.

The study's multiple-ascending dose (MAD) portion seeks to prepare for subsequent repeat dosing studies in subjects. Each MAD dose level will have been studied or exceeded in the SAD portion of the study before its use in a MAD cohort.

Nonclinical toxicity study data provide a basis for calculating the maximum exposure level that can be presumed safe. Escalating to the HED of the NOAEL in the most sensitive animal species, the maximum dose for clinical use is 1670 mg/day.

The projected $t_{1/2z}$ in animal species ranged up to 6.5 hours, so sample collection through Inpatient Discharge 72 hours post-dose is expected to correspond to more than 5 half-lives and is anticipated to be adequate to document elimination of CVN766. The study design allows for collecting additional PK samples at later timepoints if preliminary emerging PK results are indicated.

AEs, physical exams, vital signs, ECG findings, and clinical laboratory results are used as safety assessments to determine dose tolerability and dose-limiting effects of CVN766. The plasma PK and CSF parameters and PK endpoints will help elucidate the pharmacology of CVN766.

Samples for DNA analysis will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless new information or other evaluation regarding the safety of the study medication indicates an adverse change in the risk profile for the compound, such that the SRG or Institutional Review Board (IRB) considers the risk is no longer acceptable for subjects participating in the study.

In addition, if any of the following occur, further dosing will be withheld until the SRG reviews the relevant data, including unblinded data (if deemed necessary by the SRG request), and will decide whether it is safe to suspend dosing or continue dosing at either the planned or alternative dose levels or decides to prematurely terminate the study:

1. Two or more subjects in any single cohort or across more than 1 cohort experience the same type of serious or medically significant event as defined by the Investigator
2. Two or more subjects in any single cohort or across more than 1 cohort experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limits of normal (ULN) in the absence of a concomitant bilirubin increase (see point 3 below)

3. One or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN in the presence of a total bilirubin increase >2 ×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., "Hy's Law cases")
4. Two or more subjects in any single cohort or across more than 1 cohort experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, is unable to ensure adequate study performance, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an IRB/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; applicable investigational sites will follow the procedure during the course of termination or study suspension.

7.0 SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days prior to randomization or first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the Investigator's opinion, the subject can understand and sign the Informed Consent Form and comply with all protocol requirements.
2. The subject is a healthy male or female adult who is 18 to 55 years of age, inclusive at the time of ICF.
3. Subject weighs at least 45 kg (99 lbs) and has a BMI between 18.0 and 32.0 kg/m^2, inclusive at Screening.
4. A male subject who is nonsterilized* and sexually active with a female partner of childbearing potential* agree to use two forms of adequate contraception* from signing the ICF throughout the study and for 90 days after the last dose.

*Definitions and acceptable methods of contraception are defined in **Section 9.1.13 Contraception and Pregnancy Avoidance Procedure**, and reporting responsibilities are defined in **Section 9.1.14** Pregnancy.

5. A female subject of childbearing potential who complies with contraception requirements* or a female with no childbearing potential, defined as the subject has been surgically sterilized (hysterectomy, bilateral oophorectomy) or who are postmenopausal (defined as continuous amenorrhea of at least 2 years and FSH>40 IU/L).

   Note: hormonal contraceptives are not permitted for female participants, as referenced in **Table 3**. Female partners of male participants can use hormonal contraceptives.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Subject has received any investigational compound within 30 days prior to the first dose of study medication or within 5 half-lives, whichever is greater.
2. Subject is a study site employee or an immediate family member of a study site employee.
3. Subject has evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, full-body allergic skin rash (including hives), psychiatric disorder, evidence of abnormal liver function test, evidence of abnormal renal function tests or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.

   Note: Healthy volunteers with pre-existing stable disease, defined as diseases not requiring significant change in therapy or hospitalization for worsening disease during the 6 wks before enrolment, may be included at the discretion of the Investigator.
4. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking CVN766 or a similar drug in the same class or that might interfere with the conduct of the study
5. Subject has a known hypersensitivity to any component of the formulation of CVN766.
6. Subject has a positive urine result for drugs of abuse at Screening or Inpatient Check-in (Day -1).
7. Subject has a history of a major psychiatric illness or currently receiving therapy for a psychiatric condition
8. Subject has a history of drug abuse or a history of alcohol abuse (more than 14 units/week) within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.
9. Subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table as listed in Table 3.

10. Male subjects who do not agree to all the following rules: when sexually active with a female partner(s) of childbearing potential during the study, and for 90 days after the last dose of study drug: a) must use two acceptable methods of birth control (condom combined with highly effective method of contraception as listed in **Section 9.1.13**). Female partners of male participants can use hormonal contraception, and this should be in place for at least 30 days prior to dosing. Male subjects must also agree to refrain from sperm donation during the study and until 90 days after the last dose of the study drug.
11. Female subjects who are pregnant or breastfeeding or plan to become pregnant or donate ova during the study or 30 days after the last dose of the study drug. Women of childbearing potential must agree to practice an acceptable method of birth control (e.g., intrauterine device, barrier, abstinence).

Note: hormonal contraceptives are not permitted for female participants, as referenced in Table 3. Female partners of male participants can use hormonal contraceptives.

*Definitions and acceptable methods of contraception are defined in **Section 9.1.13.** Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in **Section 9.1.14** Pregnancy.

12. Subject has previously had a seizure or convulsion (lifetime, with the exception of febrile seizures), including absence seizure.
13. Subject has current o recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (i.e., a history of malabsorption, any surgical intervention known to impact absorption [e.g., bariatric surgery or bowel resection], esophageal reflux, peptic ulcer disease, erosive esophagitis, or frequent [i.e., more than once per week] occurrence of heartburn).
14. Subject has a history of cancer or other malignancy, except for basal cell carcinoma or squamous cell carcinoma that has been in remission for at least 3 years prior to Day 1.
15. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or a human immunodeficiency virus infection at Screening.
16. Subject who regularly use nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum). The casual users (≤ 10 cigarettes/week) may participate but must agree to refrain from the time of Screening for the duration of the study or a positive urine cotinine test at Inpatient Check-in (Day -1).
17. Subject has poor peripheral venous access (defined as more than three failed attempts to cannulate.
18. Subject has donated or lost 450 mL or more of their blood volume (including plasmapheresis) or had a transfusion of any blood product within 45 days prior to Day 1.
19. Subject has an abnormal (CS) ECG at Screening or Inpatient Check-in (Day -1). Entry of any subject with an abnormal (NCS) ECG must be approved and documented by signature by the Investigator or medically qualified sub-Investigator.

20. Subject has a supine blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 40 to 90 mm Hg for diastolic, confirmed with repeat per PI discretion at the Screening Visit or Inpatient Check-in (Day -1).
21. Subject has a resting heart rate outside the range of 40 to 100 bpm, confirmed with repeat per PI discretion at the Screening Visit or Inpatient Check-in (Day -1).
22. Subject has a QT interval with Fridericia's correction method (QTcF) >450 ms (males) or >470 ms (females) or PR outside the range of 120 to 220 ms, confirmed with one repeat testing at the Screening Visit or Inpatient Check-in (Day -1) Visit.
23. Subject has abnormal Screening or Inpatient Check-in (Day -1) laboratory values that suggest a CS underlying disease or subject with the following lab abnormalities: ALT and/or AST >1.5 the ULN, confirmed with one repeat testing.
24. Subject has a risk of suicide according to the Investigator's clinical judgment or has made a suicide attempt in the previous 2 years.

7.3 Excluded Medications and Dietary Products

Use of the agents in Table 3 (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities

Table 3 Prohibited Medications and Dietary Products

28 days prior to Inpatient Check-in	14 days prior to Inpatient Check-in	7 days prior to Inpatient Check-in	72 hours prior to Inpatient Check-in	48 hours prior to Inpatient Check-in	24 hours prior to Inpatient Check-in
Nutraceuticals (e.g., St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Prescription medications [(d)](including hormonal contraceptives[(e)])	OTC medications, including antacids, proton-pump inhibitors, and H2 receptor antagonists [(a)]	Nicotine-containing products	Alcohol-containing products	Products containing caffeine or xanthine (e.g., tea or coffee)
Immunization/ Vaccines [(b)]		Vitamin supplements	Poppy seeds		
Known strong inhibitors/inducers of CYPs 3A4/5 [(c)]		Orexin receptor antagonists including suvorexant (Belsomra®), lemborexant (Dayvigo®), and related compounds			

CYP= cytochrome P-450, OTC=over the counter.

(a) Occasional use of acetaminophen (~1 g/day) and 400mg ibuprofen TDS when required or other medication as approved by the sponsor's Medical Monitor on a case-by-case basis is allowed except on Day 1

(b) Inclusive of but not limited to H1N1 and flu vaccinations. Subjects who have received the COVID-19 Vaccine between -10 and -28 days may participate, provided they did not experience any side effects of any description. COVID-19 vaccine doses may be administered 7 days post-study medication dosing.

(c) e.g., chloramphenicol, clarithromycin, ketoconazole.

(d) Certain prescription medications may be allowed on a case-by-case basis at the discretion of the Investigator and Sponsor.

(e) Hormonal contraceptives are not permitted for female participants, as referenced in Table 3. Female partners of male participants can use hormonal contraceptives.

Subjects must be instructed not to take any medications during study participation, including over-the-counter drug products, without first consulting with the Investigator.

7.4 Diet, Fluid, Activity Control

Subjects will be confined to the clinic for each of the dosing days as well as a period of time sufficient to collect additional post-dose PK samples and monitor for safety and tolerability (Day -1 through Day 4 for single-dose cohorts and Day-1 through Day 9 for multiple-dose cohorts). During confinement, subjects will be provided 3 standard meals and a snack per day, each containing approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be similar in nutritional content for each subject in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor following treatment. Breakfast will not be provided on dosing days until at least 4 hours after dose administration unless otherwise indicated (i.e., Days 2-6 for MAD cohorts). The meal start and stop times, and percentage of the meal consumed will be recorded in the source, and the appropriate electronic case report form (eCRF) for all meals served on dosing days.

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence, followed by the study procedure and then the meal.

Subjects will remain in bed at a semi-supine position for 4 hours following the dose administration, except as necessitated by the occurrence of an AE or study procedures (e.g., obtaining a 12-lead ECG). Subjects must refrain from strenuous exercise for 72 hours before Inpatient Check-in and until check-out.

On the dosing days where extensive PK and/or CSF sampling is indicated (i.e., single-dosing Day 1 and first and last multiple-dose days, e.g., days 1 and 7), CVN766 or placebo suspension will be administered with approximately 240 mL of water after a fast of at least 10 hours. Subjects will continue to fast for an additional 4 hours after dosing and eat lunch following the 4-hour PK blood and CSF collection. Subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration.

For the food effect cohort (S3), single-dose administration will be administered after ingesting a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Dec 2002). Subjects will finish at least approximately 85% of their breakfast within 30 minutes and will receive an investigational product 30 minutes (±5 minutes) after beginning the meal. The S3 (food effect) cohort meals may be staggered to ensure dosing occurs 30 minutes after the beginning of the meal.

Subjects will also fast for at least 10 hours prior to safety laboratory collection times as indicated. However, consumption of water as desired is permitted during this time, except for dosing days, as indicated above.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects**, Section 9.1.15**.

1. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver Function Test (LFT) Abnormalities

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests until a subject's laboratory profile has returned to normal/baseline status) if the following circumstances occur at any time during study medication treatment:

   – ALT or AST >8 × ULN, or
   – ALT or AST >5 × ULN and persists for more than 2 weeks, or
   – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or
   – ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. Significant protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic, and attempts to contact the subject were unsuccessful. Attempts to reach the subject must be documented.
5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal, and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE).

6. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The Investigator must discontinue a subject's study participation at any time during the study when the subject meets the study discontinuation criteria described in **Section 7.5**. In addition, a subject may discontinue their participation without giving a reason at any time during the study. Should a subject's involvement be terminated, the primary criterion for termination must be recorded by the Investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects may be replaced at the Sponsor's discretion.

Participants who withdraw from the study prior to dosing may be replaced. If a participant withdraws after the first dose of study medication or placebo, no replacement will occur.

8.0 CLINICAL TRIAL MANAGEMENT

8.1 Study Medication and Materials

This section contains information regarding all medication and materials provided directly by the sponsor and/or sourced by other means required by the study protocol, including important sections describing the management of clinical trial material.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

Study drug refers to CVN766 and matching placebo. Study drug will be provided in bulk supply. An unblinded pharmacist will manage and prepare doses as oral suspensions as needed throughout the study.

In this protocol, the term study medication refers to all or any of the drugs defined below.

8.1.1.1 Investigational Drug

CVN766 and Matching Placebo

CVN766 drug substance is supplied as a bulk powder to the clinical site and then compounded into oral suspensions. A matching placebo suspension containing all of the components of the active oral suspension with the exception of the drug substance will also be compounded by the site. Compounding instructions will be outlined in a separate pharmacy manual and provided by the sponsor. See **Table 4** for the composition of the drug product and matching placebo suspensions.

The oral suspensions will be labeled with the appropriate study information and caution statements.

Table 4 Composition of CVN766 Oral Suspension and Matching Placebo

Component	CVN766 Oral Suspension (individual dose)					Matching Placebo
CVN766 drug substance	5 mg	15 mg	45 mg	125 mg	250 mg	NA
Commercial suspending vehicle[a]	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL	10.0 mL

NA=Not applicable

[a] An off-the-shelf commercial suspending vehicle will be used, and the details of the vehicle will be provided in the Pharmacy Manual.

8.1.1.2 Ancillary Materials

Ancillary materials will be provided by either the clinical site and/or the sponsor based on availability.

Ancillary material details are provided in the pharmacy manual.

Unused ancillary materials, if provided by the sponsor, will be accounted for and disposed of as directed by the sponsor or their designee.

[redacted]

[redacted]

8.1.2 Drug Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until used or returned to the sponsor or designee for destruction.

All study medication must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

CVN766 drug substance is stored at room temperature. CVN766 oral suspension and matching placebo should be stored according to instructions in the Pharmacy Manual.

8.1.3 Dose and Regimen

The Investigator or Investigator's designee will instruct the subject on dosing procedures.

All dosing will occur while subjects are in the clinic under the supervision of the Investigator and in fed or fasting conditions as outlined in **Section 7.4**.

The exact time of dose will be recorded in the source documents and on the appropriate eCRF.

The planned dose levels to be studied are provided in **Table 5**. If the planned highest dose level does not reach the desired exposure, then additional cohorts with higher dose levels may be considered. If all planned dose levels are not tolerated in an earlier cohort, the following cohorts may study lower doses at the discretion of the Investigator and the SRG. The actual choice of the subsequent dose level will occur after a full review of the available blinded safety, tolerability, and clinical laboratory results, and available PK data in the preceding cohort. The subsequent dose level may be higher, lower, or remain the same as the preceding dose level.

Table 5 describes the treatment and medication type that would be provided for each cohort.

Table 5 Planned Single and Multiple Dose Levels by Cohort

Single-Dose Cohorts			
Cohort	**Planned Treatment***	**No. of Subjects**	**Medication Type**
S1	CVN766 5 mg	6	oral suspension
	Placebo	2	oral suspension
S2	CVN766 15 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fasted	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S3 Fed (Same 8 subjects as in the S3 FASTED cohort)	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
S4	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
S5	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension

Multiple Dose Cohorts

Cohort	Planned Treatment*	No. of Subjects	Medication Type
M1	CVN766 45 mg	6	oral suspension
	Placebo	2	oral suspension
M2	CVN766 125 mg	6	oral suspension
	Placebo	2	oral suspension
M3	CVN766 250 mg	6	oral suspension
	Placebo	2	oral suspension

* Dose (active or placebo) is in 10 mL of suspension.

8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to **Section 9.7.2**, PTEs and AEs.

Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure outlined in **Section 9.7.4**, Collection and Reporting of SAEs.

In the event of an overdose, supportive measures should be employed as needed, e.g., administration of supportive therapy as dictated by the subject's clinical status, removal of unabsorbed material from the gastrointestinal tract, or the initiation of additional clinical monitoring.

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive a unique randomization number.

The clinical site will use the unique identifier to facilitate the pre-labeling of PK samples. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory and will be used by the laboratory to report the subject data results. This unique identifier should only be used for the purposes described in this section. This identifier will be assigned upon randomization in the order in which subjects receive their first dose of the study drug.

8.3 Randomization Code Creation and Storage

The sponsor or their designee will generate the randomization schedule and provide a copy to the site pharmacist and bioanalytical laboratory prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind is maintained through a randomization schedule held by the dispensing pharmacist.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigative staff unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality assessments should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted to discuss the need for unblinding before the investigational drug blind is broken.

Unblinding envelopes will be supplied to the site prior to the first subject dosing and stored in a central and secure place to ensure access in the event of an emergency. Study staff will be trained on unblinding procedures.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information (except the time) must be recorded on the eCRF.

If any site personnel inadvertently become unblinded, the sponsor must be notified, and the SRG will determine whether to discontinue dosing or withdraw from the study of all affected subjects.

No change should be made to any assessment of the subject after unblinding.

Following assessment of the AE data and pre-defined criteria for study termination, dose escalation may be interrupted/stopped and the blind broken for further analysis. Based on a review of unblinded data, the sponsor, in consultation with the Investigator, will decide if and how it is appropriate for the study to proceed.

The Randomization schedule for all subjects will be released for analysis after the database for these cohorts is locked. The Investigator will be unblinded after database lock for all the cohorts if necessary.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or being destroyed.

The Investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document the appropriate use of study medication, the Investigator must maintain records of all study medication delivery to the site, site inventory used by each subject, and return to the sponsor or designee.

Upon receipt of study medication, the Investigator or designee must verify the contents of the shipments against the packing list, ensure the quantity is correct, and the medication is received within the labeled storage conditions. If quantity and conditions are acceptable, the Investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and send via email and per instructions provided on the form. If any discrepancies exist between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the Investigator's essential document file. The Investigator must maintain 100% accountability for all study medication received and dispensed during their entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The Investigator or designee must record the current inventory of all study medication on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of the Investigator, site identifier and number, description of study medication, expiry date, and amount dispensed, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction or destroyed at the site, as applicable. The Investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

The Investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The Schedule of Study Procedures is located in **Appendix A**.

9.1.1 Informed Consent Procedure

The requirements of the ICF are described in **Section 14.2**.

The ICF must be obtained prior to the subject entering the study and before any protocol-related procedures are performed.

A unique subject screening number (of the form xx-xxx), the first two numbers for the site, subsequent three numbers for subject identification will be assigned to each subject when the ICF is obtained. This subject ID will be used until the subject is assigned their 4-digit randomization number.

9.1.1.1 Pharmacogenomic and Cerebrospinal Fluid Informed Consent Procedure

Pharmacogenomics and cerebrospinal fluid informed consent is a component of the overall study ICF. The requirements are described in **Section 14.2**.

The pharmacogenomic and (for applicable cohorts) cerebrospinal fluid sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, ethnicity, race as described by the subject, smoking status, and caffeine consumption at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped at or prior to signing the ICF. Ongoing conditions are considered concurrent medical conditions (see **Section 9.1.7**).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days before signing ICF.

9.1.3 Physical Examination Procedure

A physical examination performed by the Investigator or medical officer consists of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal change from the baseline physical examination (Screening and Inpatient Check-in [Day -1]) must be assessed as not CS or CS by the Investigator and recorded in the source document and eCRF.

All CS findings/changes, as determined by the Investigator, from the baseline physical examination will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in **Section 9.8.1** or **Section 9.8.2**.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the investigational drug Inpatient Check-in (Day -1) must be assessed as not clinically significant (NCS) or CS by the Investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the Investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below:

Height is recorded centimeters without decimal places, and for weight, it is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $\text{BMI} = \text{weight (kg)}/[\text{height (m)}]^2$

Results for BMI will be expressed with 1 decimal place.

Example:

Height=176 cm (or 1.76 m), weight=79.2 kg; $\text{BMI}=79.2/1.76^2=25.57$ kg/m^2 captured as 25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs will include tympanic body temperature, respiration, pulse, and blood pressure and be collected at timepoints specified in the Schedule of Study Procedures (**Appendix A**). For eligibility determination, the pulse will not be derived from ECG. Pulse and blood pressure will be measured after at least 5 minutes supine and again after 2 minutes standing.

Vital signs should be measured at the same time (+/- 1 hour) of the day across visits if possible. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority, and vital signs will be obtained within approximately 0.25 hours before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from the signing of ICF through the end of the study), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at the signing of ICF. This includes CS laboratory, ECG, or physical examination abnormalities noted at Screening examination. The condition (i.e., diagnosis) should be described.

9.1.8 ECG Procedure

Standard 12-lead ECGs will be recorded at timepoints specified in the Schedule of Study Procedures (**Appendix A**). Triplicate ECGs will be taken at least 1-minute apart at each scheduled time. The average of the ECG measurements will be used for determining eligibility. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

When an ECG is scheduled at the same time as blood draws or vital signs, then the blood draws and vital signs will take priority, and the ECG will be obtained within 0.5 hour before or after the scheduled blood draw/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence, followed by the meal.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-minute rest period for ECG recordings. Should technical difficulties occur during the recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

ECGs will be read automatically, and also, the Investigator or sub-Investigator will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not CS, or abnormal and CS. Abnormal QTc readings will be manually recalculated and reported by the Investigator on the eCRF. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary. Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, and QTcF and QTcB (Fridericia's and Bazett's correction) intervals. Paper ECG traces will be recorded for 10 seconds at a standard paper speed of 25 mm/sec, and gain of 10 m/mV or digital recordings will be used.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

All ECGs will be recorded at the time points detailed in Appendix A.

9.1.9 Pharmacogenomic Sample Collection

Every subject must sign ICF/be consented to the sampling of whole blood for pharmacogenomic analysis to participate in the study.

One whole blood sample for DNA isolation and genotyping will be collected at time points specified in the Schedule of Study Procedures (**Appendix A**) into plastic dipotassium ethylenediamine-tetra acetic acid (K_2EDTA) spray-coated tubes and stored under frozen conditions. In addition, two whole blood samples will be collected at time points specified in the Schedule of Study Procedures (**Appendix A**) for ribonucleic acid (RNA) pharmacogenomic analysis. The pre-dose RNA blood samples should be collected under fasted conditions and prior to any other blood collection.

DNA may be evaluated for the genetic contribution to how the drug is broken down or affects the body. This is called a "pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to CVN766
- Finding out more information about how CVN766 works
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN766
- Identifying variations in genes related to the biological target of CVN766

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN766 and other study medications and for improving the efficiency, design, and study methods of future research studies.

The samples will be stored no longer than 15 years after completion of the CVN766 study and/or until the drug development of CVN766 is no longer actively pursued by the sponsor or its collaborators. No samples will be stored for longer than permitted by the applicable law, and samples will be destroyed upon notification from the sponsor. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; every subject must sign the ICF in order to participate in this study. DNA samples will be collected and may be used to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in the PK of CVN766. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA and RNA from the first sample was not successful or possible.

Samples will be frozen at -70°C or lower and shipped separately on dry ice prior to extraction and storage at -70°C or lower. Samples should not be allowed to thaw until processed.

Detailed instructions for the handling and shipping of samples are provided in a separate lab manual.

Genotyping on collected samples may be deferred until after the completion of the study's in-life activities.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the 4-digit randomization number.

9.1.10 PK Sample Collection

9.1.10.1 Collection of Blood for PK Sampling

Blood samples for analysis of CVN766 plasma concentrations will be collected into chilled Vacutainers containing K_2EDTA according to the schedule in **Appendix A**. Instructions for sample processing and shipment are provided in a separate lab manual.

In all single-dose cohorts, serial blood samples to determine CVN766 concentrations in plasma will be collected according to **Table 6**.

Table 6 Collection of Blood Samples for PK Analysis in Single-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24-, 36-, 48-, and 72-hours post-dose.

In all cohorts for Part 2, serial blood samples for determination of CVN766 concentrations in plasma will be collected according to **Table 7**.

Table 7 Collection of Blood Samples for PK Analysis in Multiple-Dose Cohorts

Sample Type	Dosing Day	Time Post-dose (hours).
Plasma	1	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, and 24 (Day 2 pre-dose) hours post-dose.
	3,4,5,6	Pre-dose (within 15 minutes prior to dosing)
	7	Pre-dose (within 15 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24, 36, 48, and 72 [(a)] hours post-dose.

(a) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the 72-hour timepoint is unnecessary.

The PK samples will be collected at the nominal time point; all other assessments will be collected, before or after, within the allowable windows. The actual time of sample collection will be recorded on the source document and eCRF.

Sampling time points may be adjusted or added based on the preliminary emerging PK data collected from prior cohort(s). Still, the total number of samples collected per subject should not exceed the planned number by more than 4.

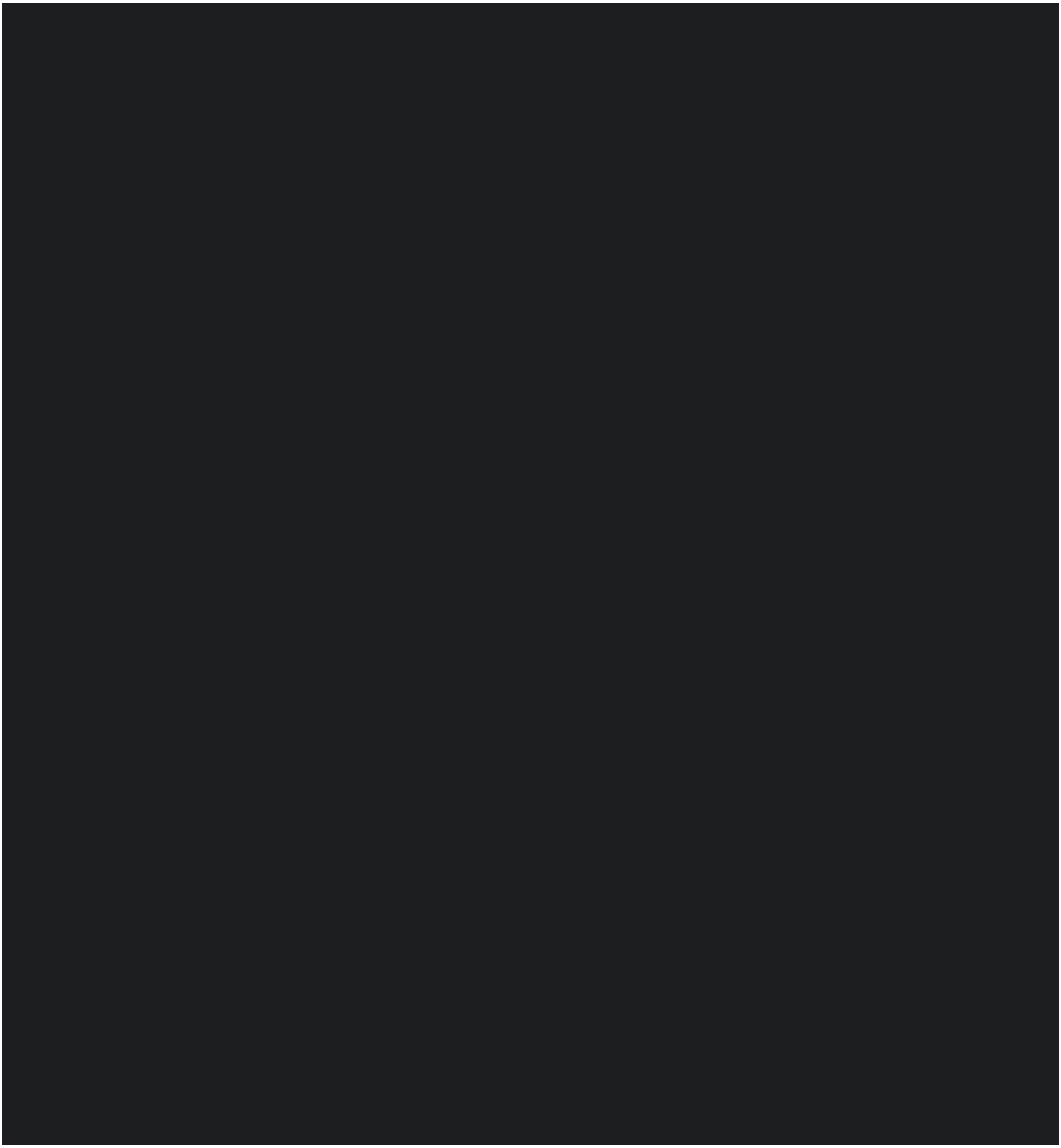
Placebo samples will not be analyzed by the bioanalytical laboratory except 2 samples per subject receiving placebo, 1 pre-dose, and the other around the expected time at which C_{max} occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional subjects could have been on active treatment.

[redacted]

[redacted]

[redacted]

[redacted]



9.1.11 PK Parameters

PK parameters of CVN766 will be derived using non-compartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be determined from concentrations of CVN766 in plasma and CSF:

Symbol/Term	Definition
Plasma	
AUC_t	Area under the plasma concentration-time curve from the time of dosing to the time of the last measurable concentration
AUC_∞	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_\infty=AUC_t+C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration.
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours, calculated using the linear trapezoidal rule.
AUC_τ	Area under the plasma concentration-time curve over the dosing interval (τ)
C_{max}	Maximum observed plasma concentration.
C_{min}	Minimum observed plasma concentration; pre-dose trough concentration
	Minimum observed plasma concentration at steady state, on last day of dosing
CL/F	Apparent clearance after extravascular administration, calculated as $Dose/AUC_\infty$ after a single dose.
CL/F_{ss}	Apparent clearance after extravascular administration at steady state, calculated as $Dose/AUC_{tau}$
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.
V_z/Fss	Apparent volume of distribution during the terminal phase after extravascular administration at a steady-state, calculated as $(CL/F_{ss})/\lambda_z$
CSF	
plasma: CSF ratio	ratio of the drug concentration in plasma vs. CSF

Additional PK parameters may be calculated as appropriate.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures on the days/times stipulated in the Schedule of Study Procedures (**Appendix A**).

Table 10 lists the tests that will be obtained for each laboratory specimen.

Table 10 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets PT/INR	ALT Albumin Alkaline phosphatase Lipase (d) AST Total bilirubin Direct bilirubin Total protein Creatinine BUN/Urea Creatine kinase GGT Potassium Sodium Glucose Chloride Bicarbonate Calcium	pH Specific gravity Protein Glucose Blood Nitrite Microscopic Analysis (only if positive dipstick results): RBC/high power field WBC/high power field Epithelial cells, casts etc.
Diagnostic Screening:		
Serum		**Urine/ Blood**
Serum hCG (a) FSH (b) Hepatitis panel, including HBsAg and anti-HCV (e) Human Immunodeficiency Virus (HIV) antibody		Drug screen including amphetamines (AMP), barbiturates (BAR), benzodiazepines (BZO), cannabinoids, cocaine (COC), opiates (OPI), alcohol, cotinine [c] methamphetamines, methadone (MET), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), tetrahydrocannabinol (THC) Urine Pregnancy Test (a) Alcohol (can be performed via breath test)

FT4= free T4, FSH= follicle-stimulating hormone, GGT=γ-glutamyl transferase, hCG= human chorionic gonadotropin, PT=prothrombin time, RBC=red blood cells, TSH= thyrotropin, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening, Urine Pregnancy Test will be done at Check-in (Day -1).
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.
(c) To be performed at Inpatient Check-in (Day -1).
(d) To be performed on SAD Day -1 and 24- and 48-hours post-dose; and MAD fasting lipase tests will be performed on Day -1, Days 2,7 and 8 (predose).

The local laboratory will perform all clinical laboratory tests. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing these results. All laboratory safety data will be transferred electronically to the sponsor or designee in the format requested by the sponsor. The Investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the Investigator or sub-Investigator, indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Subjects will be referred to their primary care physician for follow-up of any clinically significant findings or where the Investigator or medically trained sub-Investigator deems appropriate.

All CS laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A CS laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

(Please refer to **Section 7.5** for discontinuation criteria and **Section 9.8.3** for the appropriate guidance on Reporting of Abnormal LFT in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN).

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the Investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, and discussion of the relevant subject details, and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to **Section 9.8.3** Reporting of Abnormal LFT for reporting requirements).

9.1.13 Contraception and Pregnancy Avoidance Procedure

From the date of signing of ICF, throughout the duration of the study, and for 30 days after the last dose of study medication, females of childbearing potential* must use **two** acceptable methods of contraception and must agree not to donate eggs; Nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use **two** acceptable method(s) of contraception throughout the duration of the study, and for 90 days after the last dose of study medication. In addition, males must be advised not to donate sperm for 90 days after the last dose of study medication.

Females of childbearing potential are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal.

Menopause is defined as at least 2 years since the last regular menses with an FSH>40 IU/L or at least 5 years since the last regular menses, confirmed before any study medication is implemented. Male subjects with potentially postmenopausal partners who are under the age of 55 years must use condoms unless their partner's postmenopausal status has been confirmed by FSH level.

**Sterilized males should be at least 90 days post-vasectomy and confirm that they have obtained documentation of the absence of sperm in the ejaculate.

Acceptable and highly effective methods of contraception are:

Note: hormonal contraceptives are not permitted for female participants, as referenced in **Table 3**. Female partners of male participants can use hormonal contraceptives.

- Nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomised subject/partner with documented azoospermia 90 days after the procedure, if that partner is the sole sexual partner
- Same-sex intercourse, if used consistently for the duration of the study and post-dosing as specified above

Complete abstinence, defined as the complete avoidance of heterosexual intercourse - is an acceptable form of contraception if used consistently throughout the study and for the durations after dosing specified for males and females above. It is not necessary to use any other method of contraception when complete abstinence is elected. Females of childbearing potential who choose complete abstinence must continue to have pregnancy tests as per protocol. The reliability of sexual abstinence needs to be evaluated by the Investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Subjects will be provided with information on acceptable methods of contraception as part of the subject's informed consent process and will be asked to sign an ICF stating that they understand the requirements for avoidance of pregnancy, egg donation, and sperm donation during the study.

9.1.14 Pregnancy

Women who are pregnant or breastfeeding will not be included in this study.

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 90 days after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Visit 1 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in **Section 1.0**.

Should the pregnancy occur during or after administration of the blinded drug, the Investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the Investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the Investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to the final outcome using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted for 8 weeks.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign ICF. If the subject is not eligible at this visit, the Investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal
- Study termination
- Other

Subject numbers assigned to subjects who fail screening should not be reused.

If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were two separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is not eligible for randomization, the Investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The study-related procedures schedule for all evaluations is shown in **Appendix A** and is not duplicated in the following sections.

9.3.1 Screening

Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in **Section 7.0**. See **Section 9.1.15** for procedures for documenting screening failures. Subjects who are screening failures may be screened a second time if their reason for failing screening is thought to be resolved. Rescreened subjects will receive a new Screening number.

9.3.2 Inpatient Check-In

All subjects will be admitted to the study clinic the day prior to randomization and first dose. Subjects participating in the food effect cohorts will also check into the study clinic the day prior to the scheduled dosing.

9.3.3 Final Visit (discharge day from clinic)

Subjects will be confined to the study clinic for the duration of the treatment period to permit supervised dosing of study drug and repeat study assessments. Subjects participating in the single-dose study and food effect assessment will be discharged no sooner than 72 hours post-dose, and subjects participating in the multiple-dose study will be discharged no sooner than 48 hours following their last dose.

For all subjects receiving study medication, the Investigator must complete the End of Study eCRF page.

9.3.4 Early Termination

Subjects who discontinue dosing or decide to check out of the study clinic early will be advised to allow the Investigator (or authorized designees) to complete early termination assessments for safety purposes prior to discharge. The reason for discontinuation must be documented in the source document and eCRF.

For all subjects receiving study medication, the Investigator must complete the End of Study eCRF page.

9.3.5 Follow-up Visit

The Follow-up Visit will occur by telephone approximately 14 days (±2) after the final dose of study drug for the SAD cohorts and MAD cohorts unless abnormal CS findings were observed upon discharge or the SRG has determined additional PK sampling timepoints are indicated. In these cases, subjects must then be brought back to the clinic for re-evaluation per the Investigator's discretion.

9.4 Biological Sample Retention and Destruction

In all cohorts except S3 (fed), blood serum will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional retrospective analyses as needed. Samples will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law.

Blood specimens for genome/gene analysis will be collected as described in **Section 9.1.9**, Pharmacogenomic Sample Collection. After extraction and purification, the genetic material will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law. Blood and urine samples for PK analysis will be collected as described in **Section 9.1.10**, PK Sample Collection. Once PK analysis is complete, backup plasma and urine samples will be preserved and retained at a biorepository selected by the sponsor for up to, but not longer than, 15 years or as required by applicable law, to enable the conduct of exploratory, qualitative, metabolite identification studies or measurement of target related biomarkers, should the sponsor decide these are informative. The sponsor has put a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personally identifying information, but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

Subjects who consented and provided a pharmacogenomic sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. The Investigator will notify the sponsor of any subject who has withdrawn consent for the DNA and RNA analysis.

9.5 Blood Volume

Direct venipuncture or intravenous cannula is the preferred method of blood collection. Any other method will need to be approved by the sponsor. The maximum volume of blood on any single day is approximately 111 mL, with the maximum amount not to exceed 500mL for the duration of study participation.

9.6 CSF Volume

CSF will be collected by lumbar puncture, performed by a skilled and qualified individual. The maximum volume of CSF to be collected will be approximately 10 mL per subject.

9.7 Definitions

9.7.1 PTE

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed the ICF to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

9.7.2 AE

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., a CS abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

9.7.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs)
- Necessitate therapeutic intervention
- Require an invasive diagnostic procedure
- Require discontinuation or a change in dose of study medication or a concomitant medication
- Be considered unfavorable by the Investigator for any reason

- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be CS (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention
- If abnormal laboratory values or ECG findings are the results of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of the ICF) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays, etc.) should NOT be recorded as PTEs unless related to study procedures.
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy), any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious, or severe in nature; that is, Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., "worsening of…")
- If a subject has a concurrent degenerative condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…")

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE.

- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Changes in severity of AEs /Serious PTEs:
- If the subject experiences changes in the severity of an AE/serious PTE, the event should be captured once, with the maximum severity recorded

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF

9.7.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE-THREATENING

    - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization
4. Results in persistent or significant DISABILITY/INCAPACITY

5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT Is an IMPORTANT MEDICAL EVENT that may not result in death, be life-threatening or require hospitalization may be considered serious when, based on the appropriate medical judgment, satisfies any of the following:

    - May require intervention to prevent items 1 through 5 above
    - May expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization,

        - *Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.*

PTEs that fulfill 1 or more of the serious criteria above are also considered SAEs and should be reported and followed up in the same manner (see **Sections 9.8.1** and **9.8.2**).

9.7.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

9.7.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from the administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from the administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

9.7.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the Investigator considers that there is a reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

9.7.8 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

9.7.9 Stop Date

The stop date of the AE/serious PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

9.7.10 Frequency

Episodic AEs/serious PTE (e.g., vomiting) or those which repeatedly occur over a period of consecutive days are intermittent. All other events are continuous.

9.7.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE
- Dose not changed – the particular AE did not require stopping a study medication
- Unknown – only to be used if it has not been possible to determine what action has been taken
- Not Applicable – a study medication was stopped for a reason other than the particular AE, e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE

9.7.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/serious PTE
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/serious PTE with the condition remaining "recovering/resolving"
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms, or laboratory value on the last day of the observed study period had got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/serious PTE state remaining "Not recovered/not resolved."
- Resolved with sequelae – the subject recovered from an acute AE/serious PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis
- Fatal – the AEs/PTEs which are considered as the cause of death

- Unknown – the course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study

9.8 Procedures

9.8.1 Collection and Reporting of AEs

9.8.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication Day 1 or until screen failure. For subjects who discontinued prior to study medication administration, PTEs will be collected for the duration of study participation.

Collection of AEs will commence from the time that the subject is first administered study medication Day 1. Routine collection of AEs will continue until 14 days following last dose.

9.8.1.2 PTE and AE Reporting

At each study visit, the Investigator or designee will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not be followed up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date and time
3. Frequency
4. Severity
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs)
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
7. Action concerning study medication (not applicable for PTEs)

8. Outcome of event
9. Seriousness

9.8.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

An SAE form must be completed in English and signed by the Investigator immediately or within 24 hours of the first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study medication(s)
- Causality assessment

The SAE form should be transmitted within 24 hours to the attention of the contact listed in **Section 1.0.**

Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

9.8.3 Reporting of Abnormal LFT

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed by providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per **Section 9.8.2**. The Investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in **Section 9.1.8** must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the SAE form (as per **Section 9.8.3**).

9.9 Follow-up of SAEs

If information is not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee if requested.

All SAEs should be followed up until resuspension or the permanent outcome of the event. The timelines and procedures for follow-up reports are the same as those for the initial report.

9.9.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.0 STUDY-SPECIFIC COMMITTEES

The Safety Review Group (SRG) will be comprised of the Investigator, Medical Monitor, Cerevance Medical Officer and may include other sponsor representatives. A pharmacokineticist and other subject matter experts may participate as needed. The responsibilities of the SRG are outlined in **Section 6.1.3**.

11.0 DATA HANDLING AND RECORDKEEPING

AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary. All terms will be coded using the dictionary version available at the start of the study.

11.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change. Reasons for significant corrections should additionally be included.

The Investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure the accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without the written permission of the sponsor.

11.2 Record Retention

The Investigator agrees to keep the records stipulated in **Section 11.2** and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), an electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The Investigator should contact and receive written approval from the sponsor before disposing of such documents.

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of the subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A targeted data review will be conducted prior to unblinding of the subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

12.1.1 Analysis Sets

Safety Set

The Safety Analysis Set will consist of all subjects who are enrolled and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Set

The PK set will consist of all subjects who receive study drug and have at least 1 measurable plasma concentration.

If any subjects are found to be non-compliant in dosing schedule or with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis but will be presented in the subject listings.

12.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for pooled placebo, CVN766 dose level, CVN766 overall, and overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for pooled placebo, each CVN766 dose level, CVN766 overall, and overall. Individual subject demographic and baseline characteristics data will be listed.

Demographic variables of screen failure subjects and reasons for screen failures will be summarized overall for subjects who are screened but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

12.1.3 PK Analysis

The concentration of CVN766 in plasma and CSF will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual concentration data versus time will be presented in a data listing. Individual and mean plasma and CSF concentration data will be presented graphically. Descriptive statistics (arithmetic mean, SD, median, minimum and maximum) will be used to summarize the plasma and CSF PK parameters for CVN766. In addition, geometric mean and coefficient of variation will be computed.

The effect of fed/fasting state on PK and bioavailability of CVN766 will be characterized.

Plots of C_{max} and AUCs, as well as dose-normalized C_{max} and AUCs, versus doses, will be generated.

Dose proportionality will be tested for CVN766 C_{max} and AUCs using a power model.

A more detailed analysis will be presented in the SAP.

12.1.4 Safety Analysis

12.1.4.1 AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA. Treatment-emergent AEs with onset occurring within 30 days (onset date – last date of dose +1 ≤30) after study drug administration will be listed and included in the summary tables. Treatment-emergent AEs will be summarized by pooled placebo, each CVN766 dose level and CVN766 overall by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs. not-related), severity of AEs, and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs, including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs. All AEs will be listed.

12.1.4.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, and urinalysis that are abnormal and CS will be summarized and listed. Baseline, post-dose, and change from baseline to post-dose laboratory data will be summarized for pooled placebo, each CVN766 dose level, and CVN766 overall. All clinical laboratory data will be listed.

12.1.4.3 Vital Signs

Individual results of vital signs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from Baseline in vital sign measurements will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. All vital sign data will be provided in the data listings.

12.1.4.4 ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that are abnormal and CS will be summarized and listed. Baseline, post-dose, and changes from baseline in quantitative ECG parameters will be summarized by pooled placebo, each CVN766 dose level, and CVN766 overall. Shift tables may be generated for the Investigator's ECG interpretations that changed from baseline to the post-dose collections by the above groups. All ECG data will be provided in the data listings.

12.1.4.5 Other Variables

Physical exam findings and suicidal assessments will be presented in data listings.

12.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

12.3 Determination of Sample Size

The sample size chosen of 8 subjects per cohort (6 active: 2 placebo) is considered to be sufficient for the evaluation of the safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary, to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that require deviation from protocol-specified procedures, the Investigator should consult with the sponsor or

designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 12 defines the windows allowed for sample collections.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 11 Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 15 minutes pre-dose	0 hour
±5	immediately post-dose to ≤6 hours
±10	>6 hours to ≤12 hours post-dose
±15	>12 hours to ≤24 hours
±30	>24 hours

13.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of Australia (i.e., Therapeutic Goods Administration [TGA]) and foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all study documents as described in **Section 13.1.**

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each Investigator will conduct the study

according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in **Appendix B**. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

14.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICFs, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before the commencement of the study (i.e., before shipment of the sponsor-supplied drug or study-specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., ICF) reviewed; and state the approval date. The sponsor will ship the drug/notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from a competent authority to begin the trial. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence on participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without providing a reason and without prejudice to their other medical care.

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines they will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject or the subject's legally acceptable representative at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to the subject entering into the study; however, the sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and the subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

Subjects who consented and provided a pharmacogenomic sample for DNA analysis can withdraw

their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

14.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and the accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals, and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

The Investigator is obliged to provide the sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study, including data and information generated by the Investigator, without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

The sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator.

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, the sponsor will register this clinical trial on ClinicalTrials.gov (and possibly on other publicly accessible websites) before the start of study.

Sponsor contact information, along with the Investigator's city, state, country, and recruiting status, will be registered and available for public viewing. Once subjects receive the Investigator contact information, they may call the site and request enrollment into the trial. The investigative site(s) are encouraged to handle such trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

14.4.3 Clinical Trial Results Disclosure

If required at the conclusion of the study, the sponsor will post the results on ClinicalTrials.gov or other publicly accessible websites, as required by applicable national and local laws and/or regulations.

14.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the Investigator has questions regarding this policy, they should contact the sponsor or sponsor's designee.

15.0 REFERENCES

FDA Guidance for Industry: Food-effect bioavailability and fed bioequivalence studies (Dec 2002).

FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 06 July 2005. Publication No. 5541.

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Kaufmann P, Ort M, Golor G, Kornberger R, Dingemanse J. Multiple-dose clinical pharmacology of the selective orexin-1 receptor antagonist ACT-539313. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Jun 8;108:110166. doi: 10.1016/j.pnpbp.2020.110166.

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Appendix A: Schedule of Study Procedures

SAD Cohorts 1, 2, 3a*,4, 5	Screening	Check-in	Dosing & Observation			Discharge (a)	Outpatient Visit	Early Termination	Follow-up
Study Day:	-28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 8		Day 14 (±2) (b)
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Demographics and medical history	X								
Medication history	X								
Neurological Exam (o)		X	X	X	X	X			
Physical examination	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X	
Urine drug screen	X	X							
Cotinine screen		X							
Concomitant medications (e)	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X								
FSH (g)	X								
Serum Pregnancy test (hCG)	X								
Urine Pregnancy test		X							
CV Telemetry (n)			X	X					
ECG (h)	X	X	X	X	X	X	X	X	
PGx DNA sample collection (i)			X						
PGx RNA collection (j)			X						
PK blood collection (k)			X	X	X	X		X	

SAD Cohorts 1, 2, 3a*,4, 5	**Screening**	**Check-in**	**Dosing & Observation**			**Discharge (a)**	**Outpatient Visit**	**Early Termination**	**Follow-up**
Study Day:	**-28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**		**Day 14 (±2) (b)**
Standardized pre-dose meal (S3 fed cohorts only)			X						
Study drug dosing			X						
PTE assessment (l)	X	X	X						
AE assessment (m)			X	X	X	X	X	X	X

PGx=pharmacogenomic.(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the Investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) Whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples for PK analyses will be collected at time points indicated in Table 6.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) CV telemetry should be recorded at least 12 hours prior to dosing, and up to 24 hours after dosing
(o) Neurological exam to consist of light touch, power in limbs, and brief cranial nerve examination.

Cohort 3 SAD Fasted-Fed Crossover	**Screening**	**Dosing and Observation Inpatient**				**D/C**		**Inpatient** No sooner than +14 days or 4 half-lives of Day 8 visit					**+4 days post D/C**	**E/T**	**F/U**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**			**Day 14 (±2) (b)**
Informed consent	**X**														
Inclusion/exclusion criteria	X	X													
Admitted to the Clinic		X													
Demographics and medical history	X														
Medication history	X							X							
Neurological Exam (o)		X	X	X	X	X		X	X	X	X	X			
Physical examination	X	X				X	X	X				X	X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight, height, and BMI (d)	X	X				X	X	X				X	X	X	
Urine drug screen	X	X						X							
Cotinine screen		X													
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X						X							
Clinical laboratory tests (f)	X	X	X	X	X	X	X		X	X	X	X	X	X	
Hepatitis panel and HIV antibody test	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X														
Urine Pregnancy test		X						X							
CV Telemetry (n)			X	X				X	X	X					
ECG (h)	X	X	X	X	X	X	X		X	X	X	X	X	X	
PGx DNA sample collection (i)			X												
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X			X	X	X	X		X	

Cohort 3 SAD Fasted-Fed Crossover	**Screening**	**Dosing and Observation Inpatient**				**D/C**		**Inpatient** No sooner than +14 days or 4 half-lives of Day 8 visit					**+4 days post D/C**	**E/T**	**F/U**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**			**Day 14 (±2) (b)**
Lumbar puncture & CSF collection (k)			X												
Standardized pre-dose meal									X						
Study drug dosing			X						X						
PTE assessment (l)	X	X	X					X	X						
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X
Discharged from Clinic						X						X		X	

*S3 Cohort will return no sooner than Day 14 or 4 half-lives (whichever is greater) after Day 8 for the Fed portion. The Fed portion will commence on Day -1 will all the same schedule of events with the exception of **dosing will be post-meal.**

PGx=pharmacogenomic.
(a) Events listed as occurring at "Inpatient Discharge" visit will occur prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 14 (±2) unless abnormal CS findings were observed during previous visits. In these cases, subjects must then be brought back to the clinic for re-evaluation per the Investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours through 72 hours post-dose, and at Outpatient Visit Day 8, or Early Termination (if applicable) and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Day 1, Days 2 through 4, Day 8, Early Termination (if applicable), and as appropriate at the follow up visit Fasting lipase tests will be collected at Day -1, 24 hours and 48 hours post-dose. An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Day 1 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), and then every 12 hours until 48 hours post-dose, Day 4, Day 8, Early Termination (if applicable) .
(i) One blood sample will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) Whole blood samples will be collected on Day 1 (pre-dose, 8-, and 24-hours post-dose) for RNA pharmacogenomic analysis. Samples will also be collected during the food effect period.
(k) Blood samples for PK analyses will be collected at time points indicated in Table 6.
CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in selected cohorts as indicated in Table 9.
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) CV telemetry should be recorded at least 12 hours prior to dosing, and up to 24 hours after dosing
(o) Neurological exam to consist of light touch, power in limbs, and brief cranial nerve examination.

Multiple-Dose Regimen Cohorts	**SCR**	**Check -in**	**Inpatient Dosing & Observation**								**Inpatient Discharge (a)**	**Outpatient Visit**		**E/T**	**Follow-up**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**(model for additional dosing days) Day 6**	**Day of last dose (e.g. Day7)**	**1 day after last dose (e.g. Day 8)**	**2 days after last dose (e.g. Day 9)**	**3 days ±0 after last dose (e.g. Day 10) (o)**	**7 days ±1 after last dose (e.g. Day 14)**		**14 days ±2 after last dose (e.g. Day 21 ±2) (b)**
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics and medical history	X														
Medication history	X														
Neurological exam (p)		X	X						X		X		X	X	
Physical examination	X	X	X						X		X		X	X	
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X		X	X	
Weight, height, and BMI (d)	X	X	X						X		X		X	X	
Urine drug screen	X	X													
Cotinine screen		X													
Concomitant medications (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X	X													
Clinical laboratory tests (f)	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hepatitis panel and HIV antibody test	X														
FSH (g)	X														
Serum Pregnancy test (hCG)	X														
Urine Pregnancy Test		X													
ECG (h)	X	X	X	X	X	X	X	X	X	X	X		X	X	

Multiple-Dose Regimen Cohorts	**SCR**	**Check -in**	**Inpatient Dosing & Observation**								**Inpatient Discharge (a)**	**Outpatient Visit**		**E/T**	**Follow-up**
Study Day:	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**(model for additional dosing days) Day 6**	**Day of last dose (e.g. Day7)**	**1 day after last dose (e.g. Day 8)**	**2 days after last dose (e.g. Day 9)**	**3 days ±0 after last dose (e.g. Day 10) (o)**	**7 days ±1 after last dose (e.g. Day 14)**		**14 days ±2 after last dose (e.g. Day 21 ±2) (b)**
[redacted]															
PGx DNA sample collection (i)			X												
PGx RNA collection (j)			X						X						
PK blood collection (k)			X	X	X	X	X	X	X	X	X	X		X	
[redacted]															
Study drug dosing			X	X	X	X	X	X	X						
PTE assessment (l)	X	X	X												
AE assessment (m)			X	X	X	X	X	X	X	X	X	X	X	X	X

PGx=pharmacogenomic (a) Events listed as occurring at "Inpatient Discharge" visit will occur on that day prior to formal "Inpatient Discharge" but not necessarily at the time of Discharge.
(b) The Follow-up Visit will occur by telephone on Day 21 (±2) unless abnormal CS findings are observed upon discharge. In these cases, subjects must then be brought back to the clinic for re-evaluation per Investigator's discretion.
(c) Vital signs (tympanic body temperature, respiration, pulse, and blood pressure) will be obtained at Screening, Inpatient Check-in (Day -1), Day 1 and Day 7 (pre-dose [within 1 hour and 30 minutes prior to dosing], and at 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Day 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 14 (±2 days). Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded at baseline (Check-in Day-1) 15 minutes apart.
(d) Height and BMI will be collected at Screening only.
(e) Record all ongoing medications from Screening and throughout the study.
(f) Fasting clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening, Day -1, prior to dosing on Days 1 through 8, Day 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days). Fasting lipase tests will be collected at Day -1, Days 2, 7, and 8 (pre-dose). An additional tube (for blood serum) will be obtained on Day -1 and Day 2, and the collected serum will be stored at -70C to enable additional, retrospective analyses as needed.
(g) A FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile).
(h) Triplicate standard 12-lead ECG will be recorded at Screening, Inpatient Check-in (Day -1), Days 1 and 7 (pre-dose [within 1 hour prior to dosing], and at 0.5, 1, 2, 4-, 6-, 8-, and 12-hours post-dose), Days 2 through 6 (pre-dose and 12 hours post-dose), Days 8 and 9, Early Termination (if applicable), and as appropriate at the Follow-up Visit Day 21 (±2 days).
(i) One blood sample will be collected for pharmacogenomic analysis prior to dosing on Day 1; this will only be collected once per subject.
(j) Whole blood samples will be collected on Day 1 and Day 7 (pre-dose, 8- and 24-hours post-dose) for RNA pharmacogenomic analysis.
(k) Blood samples for PK analyses will be collected at time points indicated in Table 7. CSF samples (up to 10 mL) will be collected at 3 h post-dose by lumbar puncture only in Cohorts M1 and potentially M2, as indicated in Table 9. Cohort M3 also may, at SRG discretion, undergo PK sampling from CSF, the choice of day and sampling time to be decided by SRG.
(l) PTEs will be collected from signing of ICF up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.
(n) 24-hour urine collection is only done for Cohort M1, predose on Day 1, and at three separate time points post-dose: 0-6h, 6-12h, and 12-24h on Day 1 and Day 7 Cohort(o) If emerging PK data indicate the CVN766 $t_{½}$ is 15 hours (or less), the Day 10 visit is unnecessary.
(p) Neurological exam consists of light touch, power in limbs, and brief cranial nerve examination.

Appendix B: Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study-specific (non-routine/nonstandard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conforms to local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in local regulations, are met.
8. Obtain valid ICF from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entering into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C: Investigator Consent to Use of Personal Information

Cerevance will collect and retain personal information of the Investigator, including their name, address, and other personally identifiable information. In addition, Investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, and Japan), including the following:

- Cerevance, its affiliates, and licensing partners
- Business partners assisting Cerevance, its affiliates, and licensing partners
- Regulatory agencies and other health authorities
- IRBs and IECs
- Investigator's personal information may be retained, processed, and transferred by Cerevance and these other parties for research purposes, including the following:
- Assessment of the suitability of Investigator for the study and/or other clinical studies
- Management, monitoring, inspection, and audit of the study
- Analysis, review, and verification of the study results
- Safety reporting and pharmacovigilance relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication
- Inspections and investigations by regulatory authorities relating to the study
- Self-inspection and internal audit within Cerevance, its affiliates, and licensing partners
- Archiving and audit of study records
- Posting Investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites
- Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the Investigator's own country.
- Investigator acknowledges and consents to the use of their personal information by Cerevance and other parties for the purposes described above.