16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Note to File 21 October 2022
Note to File 20 October 2022
Note To File 30 September 2022
Final Protocol 30 August 2022

cerevance

NOTE TO FILE

To: Cerevance 424-102 Study Trial Master File

From: [redacted] Consultant to Cerevance

Date: 21Oct2022

Study: CVN424-102

Re: Protocol Clarifications

The following are clarifications for the CVN424-102 protocol version 1.0 dated 30Aug2022.

- 9.1.5 Vital Sign Procedure
  - Clarifying that respiration rate is not needed in triplicate
  - Clarifying that the triplicate measurements at the "initial post-dose" timepoint are to be collected from 1-3 hours post administration of the study drug
    - Subsequent post-dose measurements (i.e., 24-, 48-, 72-, and 96- hours) are not needed in triplicate

Signed,

[redacted]

[redacted]

Consultant
Cerevance

cerevance

NOTE TO FILE

To: Cerevance 424-102 Study Trial Master File

From: [redacted], Consultant to Cerevance

Date: 20Oct2022

Study: CVN424-102

Re: Protocol Clarifications

The following are clarifications for the CVN424-102 protocol version 1.0 dated 30Aug2022.

The language in section 9.7.3 Reporting of Abnormal LFT, is to be updated as follows below. The rationale for the change is to better align with section 7.4 Criteria for Discontinuation or Withdrawal of a Participant.

Existing language:
~~If a participant is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE at the discretion of the PI. 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 participant 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 9.7.2. The Investigator must contact the Medical Monitor to discuss the relevant participant 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 will be at the discretion of the Investigator.~~

To be replaced with:
If a participant is noted to have ALT or AST elevated >2 ×ULN at any point, the abnormality should be recorded as an AE.

If a participant is noted to have

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (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 appearance of fatigue, nausea, vomiting, right upper quadrant

pain or tenderness, fever, rash and/or eosinophilia (>5%)

the event should be recorded as an SAE (note the reason for Seriousness: medically important event) and reported as per Section 9.7.2. The Investigator must refer to section 7.4 Criteria for Discontinuation or Withdrawal of a Participant for guidance as to the appropriate next steps.

Signed,

DocuSigned by:
[redacted] 10/26/2022
[redacted] MD
Chief Medical Officer
Cerevance

cerevance

NOTE TO FILE

To: Cerevance 424-102 Study Trial Master File

From: [redacted], Consultant to Cerevance

Date: 30Sep2022

Study: CVN424-102

Re: Protocol Clarifications

The following are clarifications for the CVN424-102 protocol version 1.0 dated 30Aug2022.

- Randomization: clarifying that Celerion will serve as designee for the randomization generation
- Physical Assessment at follow-up visit: clarifying that this is to be a symptom driven physical examination
- Vital signs: clarifying that temperature is not needed in triplicate
- Appendix A: Schedule of Study Procedures
  - Follow-Up:
    - Overall Study Day # to be update to 42
  - Randomization:
    - To be moved from first Check-in to first Dosing day
  - Pregnancy Test:
    - Add assessment to Day 5 of Period 3
  - C-SSRS:
    - Remove assessment from Day 1 of Periods 2 and 3 as well as from Follow-Up visit
  - Physical Examination:
    - Add assessment to Day 2 of each Period for 24-hours post-dose
  - Vital Signs (footnote 3):
    - Update to include Respirations
    - Respirations should also be added to the Study Summary (page 11)
  - Urinalysis (footnote 5)
    - Update to include statement that Predose labs do not need to be reviewed prior to dosing
  - Clinical laboratory tests (footnote 7):
    - Partial list should be removed as Table 4 in section 9.1.11 indicates the full list of tests
  - ECG (footnote 11):
    - Study days to be updated to 0, 14, and 28
    - 3 hours post-dose window to be updated to +/- 30 minutes

Signed,

DocuSigned by:
[redacted]
[redacted] MD
Chief Medical Officer
Cerevance

PROTOCOL

A Randomized, Open-Label, Single Oral Dose, Three-Way Cross-Over Trial to Evaluate the Relative Bioavailability of CVN424 Suspension and Tablet Formulations Including an Assessment of the Effect of Food on the Tablet Formulation in Healthy Adult Volunteers

Short Title: Relative Bioavailability and Food Effect Study of CVN424

Sponsor:	Cerevance Beta, Inc. One Marina Park Drive, Suite 1410 Boston, MA 02210		
Study Number:	CVN424-102		
IND Number:	138119	**EudraCT Number:**	Not Applicable
Compound:	CVN424		
Version:	Protocol 1.0		
Date:	30 August 2022		

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Contact Type / Role	Contact
Serious adverse events and pregnancy reporting	Celerion
Medical Monitor (carries overall responsibility for the conduct of the study)	ProPharma Representative
Responsible Medical Officer (medical advice on protocol and compound)	[redacted] M.D. [redacted] Email: [redacted]

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[R2] Good Clinical Practice (GCP): Integrated Addendum to E6[R1].
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Approved by:

Signature [redacted] Date [redacted]

[redacted] M.D.
Responsible Medical Officer
Cerevance, Inc.

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 participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation, E6 [R2]; GCP Integrated Addendum to E6 [R1]
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 9.7 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/Province)

Location of Facility (Country)

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LIST OF IN-TEXT TABLES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance Beta, Inc.	**Compound:** CVN424	
Title of Protocol: A Randomized, Open-Label, Single Oral Dose, Three-Way Cross-Over Trial to Evaluate the Relative Bioavailability of CVN424 Suspension and Tablet Formulations Including an Assessment of the Effect of Food on the Tablet Formulation in Healthy Adult Volunteers	**IND No.:** 138119	**EudraCT No.:** Not applicable
Study Number: CVN424-102	**Phase:** 1	
Study Design: This is a Randomized, Open-Label, Single Oral Dose, Three-Way Cross-Over Trial to Evaluate the Relative Bioavailability of CVN424 Suspension and Tablet Formulations in Healthy Volunteers Under Fasted and Fed Conditions. The overall study design is outlined below:		

Sequence	Dosing #1 (Period 1 Day 1)		Dosing #2 (Period 2 Day 1)		Dosing #3 (Period 3 Day 1)
1 (n=5)	Suspension (fasted)		Tablet (fasted)		Tablet (fed)
2 (n=6)	Tablet (fasted)		Tablet (fed)		Suspension (fasted)
3 (n=5)	Tablet (fed)	Washout	Suspension (fasted)	Washout	Tablet (fasted)
4 (n=5)	Suspension (fasted)		Tablet (fed)		Tablet (fasted)
5 (n=5)	Tablet (fasted)		Suspension (fasted)		Tablet (fed)
6 (n=6)	Tablet (fed)		Tablet (fasted)		Suspension (fasted)

32 healthy male or female participants will be enrolled in 1 of 6 sequences (designated as 1 through 6, respectively) in an ascending fashion. Sequences 1, 3, 4, and 5 will have 5 participants each, and Sequences 2 and 6 will have 6 participants each.

Each sequence will proceed through the three cross-overs (suspension-fasted, tablet-fed, and tablet-fasted) according to the schematic above, with dosing to occur on Days 1 of Periods 1, 2, and 3. Participants in the fasted portion of each sequence will be dosed under overnight fasted conditions and will remain fasted for 4 hours post-dose. Water consumption is permitted as desired except for 1 hour before and after administration of the Study Drug.

To assess the effect of food on CVN424 bioavailability in tablet formulation, the single dose will be administered after ingestion of a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Jun 2022).

<table>
<tr><td colspan="2">Participants for all sequences will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and pharmacokinetics (PK) assessments through 96 hours post-dose. The total confinement period will be 5 nights for each period unless extended at the discretion of the Investigator, e.g., for monitoring and/or management of adverse events (AEs).

Once 96-hour post-dose PK has been collected, participants will be discharged from the unit for the remainder of the washout period and return the day prior to their next scheduled dosing period.</td></tr>
<tr><td colspan="2">Primary Objective:
To determine the relative bioavailability of 150 milligrams (mg) of CVN424 administered in a single dose of suspension formulation compared to 150 mg tablet.</td></tr>
<tr><td colspan="2">Secondary Objectives:
To establish the effects of food on the rate and extent of absorption of CVN424 150 mg tablet when administered in fed conditions compared to administration under fasting conditions.
To assess the tablet's safety under fast and fed conditions and suspension under fasted conditions.</td></tr>
<tr><td colspan="2">Exploratory Objectives:
To explore serum/plasma (e.g., potential characterization of drug metabolites) that may contribute to variability in CVN424.
To assess urine concentrations and volumes to enable calculation of urine PK parameters where possible.</td></tr>
<tr><td colspan="2">Participant Population:
Healthy male and female participants 18 to 55 years old (inclusive)</td></tr>
<tr><td>Number of Participants:
Estimated total: 32 participants
(4 sequences of 5 and 2 sequences of 6)</td><td>Number of Sites:
1 (United States)</td></tr>
<tr><td>Dose Level(s):
Participants to receive a single-dose level of 150 mg CVN424 in either tablet or suspension formulation</td><td>Route of Administration:
Oral</td></tr>
<tr><td>Duration of Treatment:
Single oral dose on Day 1 of Periods 1, 2, & 3 (Study Days 0, 14, & 28)</td><td>Period of Evaluation:
• Screening Period: up to 28 days
• 5 days of inpatient confinement from Check-In until after the 96-hour post-dose blood draw on Day 5
• 9 additional days of washout (Days 6-13)
• To be repeated for the subsequent two Periods
• Total Duration: Approximately 10 weeks</td></tr>
<tr><td colspan="2">Main Criteria for Inclusion:
Healthy male and female participants, 18 to 55 years of age, inclusive, and have a body mass index (BMI) between 18.0 and 35 kg/m^2 inclusive at Screening.
A complete list of inclusion criteria is provided in Section 7.1.
Main Criteria for Exclusion:
Participants are vegan, vegetarian, lactose intolerant, or follow a Kosher diet. Participants have a known hypersensitivity to any component of the formulation of CVN424. Participants have evidence of clinically significant [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 participant to participate or potentially confound the study results. Any finding in the participant’s medical history, physical examination, or safety laboratory tests gives reasonable suspicion of a condition</td></tr>
</table>

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, participants may not use any excluded medications, supplements, or food products. Concomitant medications and dietary products to be excluded are listed in Table 2.

Main Criteria for Evaluation and Analyses:

- Safety assessments:

Safety parameters will be collected from the signing of the informed consent form (ICF) until final charge and include AEs, clinical laboratory results, vital signs, physical examinations, and electrocardiogram (ECG).

- Vital signs will include body temperature measurement, blood pressure, and heart rate (beats per minute [bpm]).
- Orthostatic vital signs (blood pressure and heart rate) will be recorded
- Standard 12-lead ECG will be recorded. Clinical laboratory data collected will include hematology, chemistry, and urinalysis.
- Physical exams

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:

Plasma PK parameters will be used to determine the relative bioavailability of CVN424 suspension to tablet.

Plasma and urine samples will be collected for the determination of concentrations of CVN424 throughout the study as prescribed in the Schedule of Assessments (Appendix A).

PK parameters of CVN424 will be derived using noncompartmental analysis methods from the concentration-time data for all evaluable participants. 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 CVN424 in plasma: maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), time taken for drug to appear in systemic circulation following administration (T_{lag}), area under plasma concentration-time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), and truncated AUC from time 0 to 96 hours (AUC_{0-96h}), AUCinf, terminal elimination half-life ($t_{1/2}$), apparent clearance after extravascular administration (CL/F), apparent volume of distribution after extravascular administration (V_z/F) where possible

- Endpoints:

The primary endpoints of this study will be the following: the relative bioavailability of the CVN424 solution and CVN424 tablet formulation in the fasted state based on Cmax, Tmax, AUC_{inf}, and AUC_{0-96h}.

Additionally, the ratio of the PK parameters between CVN424 solution and tablet in the fasted state will be calculated and summarized descriptively. An analysis of variance (ANOVA) on log-transformed PK parameters (AUC_{0-t}, AUC_{0-96}, C_{max}) will be performed. Ratios of geometric means and 90% confidence intervals will be calculated. T_{max} will be compared between the CVN424 solution and the CVN424 tablet.

The secondary endpoints will be the following: The ratio of the PK parameters between CVN424 tablets in the fed and fasted state will be calculated and summarized descriptively. In addition, an ANOVA on log-transformed PK parameters (AUC0-t, AUC0- 96h, Cmax) will be performed. Ratios of geometric means and 90% confidence intervals will be calculated. Tmax will be compared between CVN424 tablets in the fed and fasted state.

The additional endpoints may include the following plasma PK parameters of CVN424: AUC∞ and t1/2z

Exploratory endpoints may include characterization of metabolic enzyme and transporter polymorphisms and/or qualitative metabolite identification in plasma and/or urine. Exploratory endpoints may also include renal PK parameters; cumulative amount of unchanged drug excreted into the urine (Ae), fraction of unchanged drug excreted in

the urine (fe), and renal clearance (CL_R).

Safety assessments will be measured by treatment-emergent adverse events (TEAEs), and tolerability will be measured by discontinuation (D/C) due to AE.

Statistical Considerations:

The proportion of participants administered CVN424 in tablet formulation who achieved at least an 80 percent relative bioavailability compared to CVN424 administered in suspension formulation as calculated by comparing the plasma drug concentration-time curves (AUC - area under the curve).

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 each sequence (suspension and table fasted and tablet fed separately), and CVN424 suspension versus tablet overall, and separately each of the 6 CVN424 sequences overall. Physical exam findings will be presented in data listings.

PK Analysis:

Noncompartmental pharmacokinetic (PK) calculations include C_{max}, T_{max}, and $AUC_{0\text{-}96h}$ active ingredients.

Sample Size Justification:

It is planned to enroll 32 male or female participants for participation. Based on previous PK studies with CVN424, it was determined 28 participants would be needed to show bioequivalence, assuming an intra-participant CV of 16% and an expected ratio of 1:10. 32 participants will be enrolled to ensure at least 28 evaluable participants.

3.0 STUDY REFERENCE INFORMATION

3.1 List of Abbreviations

λ_z	terminal elimination rate constant
AE	adverse event
Ae	cumulative amount of unchanged drug excreted into the urine
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
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
BDI	Beck Depression Inventory
BMI	body mass index
bpm	beats per minute
CGI	Clinical Global Impression Scale
CL/F	apparent clearance after extravascular administration
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CNS	central nervous system
COMT	catechol-O-methyl transferase
CRP	c-reactive protein
CRU	clinical research unit
CS	clinically significant
CSF	cerebrospinal fluid
DBS	deep brain stimulation
D/C	discontinuation
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
fe	fraction of unchanged drug excreted in the urine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen

hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
ICF	informed consent form
ICH	International Council on Harmonisation
INR	international normalized ratio
IRB	institutional review board
K_2EDTA	dipotassium ethylenediamine tetraacetic acid
LFT	liver function test
MAO-B	monoamine oxidase B
MedDRA	Medical Dictionary for Regulatory Activities
MSN	medium spiny neuron
NCS	not clinically significant
PGI	Patient Global Impression
PK	pharmacokinetic
PT	preferred term
QTcB	QT interval with Bazett's correction method
QTcF	QT interval with Fridericia's correction method
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{lag}	time taken for drug to appear in systemic circulation following administration
t_{max}	time to reach C_{max}
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
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
WOCBP	woman of childbearing potential

4.0 INTRODUCTION

4.1 Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system (CNS) caused by the gradual loss of the dopaminergic neurons of the substantia nigra pars compacta that project to the striatum (Wichmann, 2011). PD afflicts >1 million individuals in the United States of America and >10 million worldwide (APDAparkinson.org, accessed 26 Jan 2018), causing cardinal symptoms of tremor, bradykinesia, rigidity, and postural instability. Motor fluctuations refer to a decline in the usual benefit from levodopa and develop gradually after several years of successful treatment. Most patients will eventually experience motor fluctuations as their disease progresses. There are several types of motor fluctuations, including wearing off, morning off, partial on, delayed on, dose failure, and unpredictable off. As PD progresses and there is a continuous loss of dopamine neurons, the peaks and troughs of the levodopa levels become more problematic and result in motor fluctuations. Changes in the gastrointestinal tract due to PD can slow the absorption of levodopa and, thus, the rate at which it reaches the brain, and this also contributes to motor fluctuations. Current treatments for motor fluctuations include levodopa dose changes and medications that delay the breakdown of dopamine, including catechol-O-methyl transferase (COMT) inhibitors and monoamine oxidase B (MAO-B) inhibitors. Dopamine agonists may also be prescribed. Apomorphine rescue, levodopa gel delivered to the small intestine, and deep brain stimulation may also be employed (APDAparkinson.org, April 2017). The financial burden of PD is significant.

GPR6 is an orphan G-protein coupled receptor that is selectively expressed in the brain and is a nondopaminergic target for the treatment of PD. In the brain, GPR6 is predominantly localized to striatopallidal medium spiny neurons (MSNs) that also express dopamine D2 receptors (Lein et al. 2007; also, Cerevance data on file). GPR6 is a constitutively active Gs-coupled receptor that functionally opposes the Gi-coupled D2 receptor in indirect MSNs. Pharmacological intervention to inhibit the GPR6 pathway using an inverse agonist is predicted to exert antiparkinsonian effects by reducing overactivity of striatopallidal output neurons in the indirect pathway without activating the dopamine D1-receptor-expressing MSNs of the direct (striatonigral) pathway.

CVN424 is a potent and selective inverse agonist of GPR6. Two studies have been completed with CVN424 in human participants.

A first-in-human safety study of CVN424 in 64 healthy volunteers has been completed (NCT03657030); the study findings are summarized in the Investigator's Brochure. In brief, CVN424 was safe and well tolerated when administered to healthy participants as a single oral dose of between 1 milligram (mg) and 225 mg or when administered as 7 daily oral doses of between 25 mg and 150 mg. Study drug-related adverse events (AEs) were reported by 2 of 40 participants (5.0%) overall in the single-dose cohorts (feeling hot; headache). Study drug-related AEs were reported by 2 of 24 participants (8.3%) overall in the multiple-dose cohorts (dysphagia; chills). With one exception, all AEs were mild in severity; dysphagia of moderate severity led to treatment discontinuation in one participant after their third daily dose (75 mg). There were no severe or serious AEs, and all AEs resolved by the end of the study. Administration of the first dose of CVN424 was associated with an elevation in group mean and median body temperature.

These changes were detectable at 1 hour (h) post-dose (the earliest scheduled post-dose assessment), increased further by 6 h post-dose, and spontaneously returned to baseline by 24 h post-dose. The increases tended to be larger at higher doses but did not appear strictly dose proportional. A trend of increased heart rate while standing was also observed with a similar time course and relationship to dosage. These trends were not considered clinically significant, and no individual vital sign measurement was reported as an AE. In the multiple-dose cohorts, elevations in body temperature and heart rate were observed only after the first dose of CVN424, not following subsequent doses. No other trends in vital sign measurements were noted. No treatment-related trends were observed in the clinical laboratory results or 12-lead electrocardiogram (ECG) measurements. In the healthy volunteer study, CVN424 in suspension was rapidly absorbed after oral administration in the fasted state; peak plasma concentration was usually attained between 1 and 3 h post-dose (median 1.5 h). When CVN424 was administered after a meal, the peak plasma concentration was delayed and decreased while total exposure was minimally increased compared to the same dose level administered under fasted conditions. With repeated once-daily dosing, trough plasma concentrations usually reached a steady-state level by Day 4, with a terminal elimination half-life of approximately 33 h. Accordingly, CVN424 pharmacokinetics (PK) is appropriate for once-daily oral dosing, with or without food.

In the Phase 2 study, exposure to CVN424 increased with dose level from 50 to 150 mg. The increase in exposure with dose was slightly less than dose-proportional. After CVN424 50 mg dosing, there was a trend for higher exposure in females compared with males. There were no apparent differences between females and males after CVN424 150 mg dosing, and PK parameters were comparable. After CVN424 50 mg dosing, maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 6 h (AUC_6) were slightly higher in the < median weight group compared with the ≥ median weight group. Exposure parameters were generally comparable between weight groups after CVN424 150 mg dosing.

In a Phase 2 study of CVN424 in patients diagnosed with Parkinson's disease with motor fluctuations (NCT04191577), 136 patients were in the primary efficacy analysis safety analysis set. After Screening, to establish baseline safety and efficacy assessments, patients were randomized in a 1:1:1 ratio into 1 of 3 study groups to receive once-daily low-dose (50 mg) CVN424, high-dose (150 mg) CVN424, or matching placebo on Day 0/Visit 1. Patients not randomized to placebo-initiated treatment with 50mg CVN424 on Day 1 (Visit 2). Thereafter, the low-dose group continued to receive 50mg per day, while the high-dose cohort increased their dosage to 150 mg CVN424 per day beginning on Day 8± 2 days (Visit 3) and continued this dose thereafter. The study drug was self-administered each morning on an outpatient basis as an oral suspension. Efficacy and safety evaluations were made throughout the study on Visit 1 through Visit 7, inclusive according to the Schedule of Study Procedures (Appendix A). Follow-up safety and efficacy assessments occurred on Day 35/Visit 7, approximately 7 days after the final study drug dose was taken on Day 27 ± 1. The primary efficacy endpoint for the study was OFF time.

Treatment with CVN424 was associated with a statistically significant and clinically meaningful improvement (relative to placebo) in OFF time with the 150 mg dose. This reduction in OFF time was accompanied by numerical improvements in ON time without troublesome dyskinesia compared with placebo. Treatment with CVN424 150 mg reduced the average daily hours of OFF time relative to placebo at Day 27 in the Primary Efficacy Analysis Set. Thus, this study met its

primary efficacy endpoint with the CVN424 150 mg dose and combined CVN424 dose groups. On Day 27, the LS mean (± SE) for average daily hours of OFF time for the CVN424 150 mg vs placebo comparison was -1.30 (± 0.56) h; P = 0.0418 (Dunnett) and P = 0.0225 (MMRM). However, the CVN424 50 mg vs placebo comparison was not statistically significant at Day 27 (P = 0.3302 [Dunnett]; P = 0.1985 [MMRM]). At Day 27, the LS mean (± SE) for the combined CVN424 vs placebo comparison was -1.02 (± 0.50) h; P = 0.0410 (MMRM). Analysis of the Secondary Efficacy Analysis Set and a sensitivity analysis yielded results similar to the Primary Efficacy Analysis Set. Treatment with CVN424 50 mg and CVN424 150 mg was associated with a non-statistically significant numerical increase in ON time without troublesome dyskinesia on Day 15 and Day 27 vs. placebo. ON time with troublesome dyskinesia was generally constant throughout the course of the trial; changes from baseline to Day 27 were less than 12 minutes. In the CVN424 150 mg group, ON time with dyskinesia was generally constant throughout the study; the change from baseline was less than 6 minutes on Day 27. Treatment with CVN424 50 mg and CVN424 150 mg was associated with an increase in ON time on Day 15 and Day 27; however, the differences between the CVN groups and placebo were not statistically significant.

Treatment with CVN424 did not demonstrate significant benefit on Unified Parkinson's Disease Rating Scale (UPDRS) Part I, Part III, Part IV Section A, and Part IV Section B scores. Treatment with CVN424 150 mg was associated with a clinically meaningful numerical improvement on the UPDRS Part II scores (motor experiences of daily living) vs. placebo, but the difference compared to placebo did not reach statistical significance due to the small size of the study. Treatment with CVN424 did not demonstrate significant benefit on the Clinical Global Impression Scale (CGI) or the Patient Global Impression (PGI) scores. On Day 15 and Day 27, numerically higher percentages of CVN424-treated patients were considered CGI responders compared with the placebo group, but this difference did not reach statistical significance. On Day 15 and Day 27, numerically higher percentages of CVN424-treated patients were considered PGI responders compared with the placebo group, but this difference did not reach statistical significance. Treatment with CVN424 150 mg led to numeric improvement in the Epworth Sleepiness scores from baseline, with numerical improvement compared to placebo on Day 15, Day 27, and Day 35 (statistically significant difference on Day 15 only).

At Day 15, there were statistically significant differences for the CVN424 150 mg vs placebo comparison (LS mean [± SE] = -1.35 [± 0.68]; P = 0.0493) and for the CVN424 50 mg vs CVN424 150 mg comparison (LS mean = 1.72 [± 0.67]; P = 0.0119). CVN424 50 mg vs. placebo favored the CVN424 50 mg group for reducing OFF time in the following subgroup population: age ≥ median. CVN424 150 mg vs. placebo favored the CVN424 150 mg group for reducing OFF time in the following subgroup populations: age ≥ median; females; weight < median; no dopamine agonist; no monoamine oxidase or catechol-o-methyl transferase inhibitor; no amantadine; baseline UPDRS Part II Total Score < median and ≥ median; baseline UPDRS Part III Total Score ≥ median; baseline ON time ≥ median; response rate defined as patients with ≥30% decrease in OFF time was significantly increased in the CVN424 150 mg group compared to placebo. On Day 27, 33.3%, 36.8%, and 56.8% of patients in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively, achieved the definition of responder. The P value for the CVN424 150 mg vs. placebo comparison was statistically significant (P = 0.0310). Analysis of the Secondary Efficacy Analysis Set and a sensitivity analysis yielded results similar to the Primary Efficacy

Analysis Set. There were no significant differences for any treatment comparison in any analysis set for the percentage of patients meeting ascending OFF time reduction thresholds (≥0.5 hour, ≥1 hour, ≥1.5 hours, ≥2 hours, ≥2.5 hours).

The primary endpoint of the study was safety. During the study (overall), there was a higher incidence of treatment-emergent adverse events (TEAE) and treatment-related TEAEs among patients treated with CVN424 (both dose groups) compared to placebo. Overall, there was a higher incidence of TEAEs in the CVN424 150 mg than in the CVN424 50 mg group; however, treatment-related TEAEs had a similar incidence in the 50 mg and 150 mg CVN424 dose groups. There were no treatment-related serious adverse events (SAE) in this study, and there was 1 SAE unrelated to the study treatment. The SAE unrelated to study treatment was an event of cardiac arrest in 1 (2.1%) patient in the CVN424 150 mg group, leading to study drug discontinuation and death. Overall, the most common TEAEs (preferred terms) were headache and nausea. A total of 6 patients developed headaches (1 [2.3%] patient, 1 [2.2%] patient, and 4[8.5%] patients in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively). A total of 6 patients developed nausea (1 [2.3%] patient, 2 [4.4%] patients, and 3 [6.4%] patients in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively). Overall, treatment-related TEAEs were more common in the CVN424 groups than in the placebo group (9.1%, 17.8%, and 19.1% of patients in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively). Nausea was the most common treatment-related TEAE, with a total of 4 (2.9%) patients experiencing 5 treatment-related events (0 [0%] patients, 2 [4.4%] patients, and 2 [4.3%] patients in the placebo, CVN424 50mg, and CVN424 150 mg groups, respectively). Hallucinations, somnolence, confusion, orthostatic hypotension, and dyskinesia were each observed in fewer than 2 CVN424-treated patients. Overall, approximately 67% of treatment-related TEAEs were mild in severity; the remainder were moderate in severity. There were no severe treatment-related TEAEs. There was a higher incidence of moderate treatment-related TEAEs in the CVN424 150mg group (8.5%) than in the CVN424 50 mg (2.2%) and placebo groups (4.5%). Overall, 6 (4.4%) patients discontinued study drug due to a TEAE: 2 (4.5%), 1 (2.2%), and 3 (6.4%) patients in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively.

Of these, 4 patients who received CVN424, 2 patients (1 each in the CVN424 50 mg and 150 mg groups) discontinued the study drug due to nausea. During the study, no medically significant treatment-related TEAEs (as defined in the protocol) occurred. There were no notable changes in laboratory parameters, physical examinations, electrocardiograms (ECGs), and Beck Depression Inventory (BDI) scores during the study. However, patients receiving CVN424 did experience transient increases in blood pressure and pulse rate on Day 1 and Day 8. Treatment with CVN424 did not impact impulsivity as assessed by the Questionnaire for Impulsive-Compulsive Disorders (QUIP) with the exception of sex on Day 15. No statistically significant correlations were identified between 3-hour post-dose CVN424 concentration and ECG or vital signs parameters on Days 1 and 8 for the 50 mg or 150 mg dose levels.

Cerevance conducted additional post-hoc analyses on the PD diary data, conforming to the Food and Drug Administration (FDA) standardized analysis for the PD diary. The PD diary was normalized to a 16-hour waking day, required 44/48 entries per day, required having both days of diaries, and only included participants with at least one post-baseline data. This post-hoc analysis was first conducted for the full analysis set and confirmed the result of the primary analysis, with

greater numeric improvement compared to placebo on the reduction in OFF time (CVN424 150 had a 1.45-hour benefit compared to placebo; nominal p=0.01) and improvement in ON time without troublesome dyskinesia (CVN424 had a 0.96-hour benefit compared to placebo; p=0.098).ON time with troublesome dyskinesia was comparable to the primary analysis. A second post-hoc analysis was conducted using FDA standards for the PD diary analysis, excluding patients with a Baseline OFF time of 2-3 hours. Previous studies in PD patients with motor fluctuations with drugs proven effective have demonstrated that patients with 2-3 hours of OFF time do not show improvement. A minimum OFF time of 3 hours or more is standard for clinical trials in PD patients with motor fluctuations and will be the cutoff for the adequate and well-controlled trial of CVN424 in PD patients with motor fluctuations. This analysis showed a more robust effect of CVN424 on reduction in OFF time (1.78-hour improvement vs. placebo for the 150 mg dose; nominal p=0.005) and improvement in ON time without troublesome dyskinesia (1.30-hour improvement vs. placebo for the 150 mg dose; nominal p=0.042). ON time with troublesome dyskinesia was similar to the primary analysis.

CVN424 is expected to be a pharmacological treatment for PD participants, as monotherapy or adjunctive to dopaminergic therapy, to elicit sustained improvement of motor activity with a reduced risk of troublesome dyskinesia compared with dopaminergic therapies. As a novel, first-in-class, non-dopaminergic drug for the symptomatic treatment of PD, CVN424 may become a significant addition to neurologists' clinical armamentarium

4.2 Rationale for the Proposed Study

Non-invasive treatments typically reduce OFF time by approximately one hour with similar improvement in ON time without troublesome dyskinesias. The majority of approved treatments directly stimulate the dopamine receptor or increase levodopa bioavailability. As a result, these treatments have high rates of dopaminergic treatment-emergent adverse events and perpetuate the underlying cause of motor complications. Non-invasive treatments have limited efficacy, and patients continue to have OFF time that poorly impacts quality of life. Approved interventional procedures include deep brain stimulation (DBS) and intrajejunal levodopa. Both are highly effective but require an invasive procedure and risk serious and significant short-term and long-term AEs and device complications. Thus, additional non-invasive treatments are needed that can provide greater efficacy benefits with low rates of dopaminergic AEs.

The efficacy of CVN424 in animal models of PD and a prior phase 2a with PD patients supports its further investigation into the comparison of the *in vivo* performance of solution to tablet formulation.

A safety and pharmacokinetic (PK) study previously performed in 64 healthy volunteers supports the selected dose levels of CVN424 in this study. Section 6.2 outlines the justification for the planned dosages.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

Objectives	Endpoints
Primary	Primary
• To determine the relative bioavailability of 150 mg of CVN424 administered in a single dose of suspension formulation compared to 150 mg tablet.	• The relative bioavailability of the CVN424 solution and CVN424 tablet formulation in the fasted state based on maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and area under the plasma concentration-time curve from time 0 to 96 hours (AUC_{0-96h}). • The ratio of the PK parameters between CVN424 solution and tablet in the fasted state will be calculated and summarized descriptively. In addition, an analysis of variance (ANOVA) on log-transformed PK parameters (AUC_{0-t}, AUC_{0-96h}, C_{max}) will be performed. Ratios of geometric means and 90% confidence intervals will be calculated. T_{max} will be compared between CVN424 solution and CVN424 tablet.
Secondary	Secondary
• To establish the effects of food on the rate and extent of absorption of CVN424 150mg tablet when administered in fed conditions compared to administration under fasting conditions. • To assess the safety of the tablet under fast and fed conditions and suspension under fast conditions.	• The ratio of the PK parameters between CVN424 tablets in the fed and fasted state will be calculated and summarized descriptively. In addition, an analysis of variance (ANOVA) on log-transformed PK parameters (AUC_{0-t}, AUC_{0-96h}, C_{max}) will be performed. Ratios of geometric means and 90% confidence intervals will be calculated. T_{max} will be compared between CVN424 tablets in the fed and fasted state. T_{max} and T_{lag} will be compared between CVN424 tablets in the fed and fasted state. • Assessment of safety as measured by TEAEs and tolerability as measured by discontinuations (D/Cs) due to AE.
Exploratory	Exploratory
• Explore serum/plasma (e.g., potential characterization of drug metabolites) that may contribute to variability in CVN424. • Assessment of urine concentrations and volumes to enable calculation of urine PK parameters where possible.	• Potentially characterize metabolic enzyme and transporter polymorphisms. • Urine concentrations and volumes of CVN424 tablet formulation at pre-dose and 0-12, 12-24, 24-48, 48-96 hours post-dose. Urine PK parameters (cumulative amount of unchanged drug excreted into the urine [Ae], fraction of unchanged drug excreted in the urine [fe], and renal clearance [CL_R]) to be determined where possible.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a randomized, open-label, single-oral dose, three-way cross-over study under fasted and fed conditions, study in healthy participants.

Table 1 Study Schema

Sequence	Dosing #1 (Period 1 Day 1)		Dosing #2 (Period 2 Day 1)		Dosing #3 (Period 3 Day 1)
1 (n=5)	Suspension (fasted)		Tablet (fasted)		Tablet (fed)
2 (n=6)	Tablet (fasted)		Tablet (fed)		Suspension (fasted)
3 (n=5)	Tablet (fed)	Washout	Suspension (fasted)	Washout	Tablet (fasted)
4 (n=5)	Suspension (fasted)		Tablet (fed)		Tablet (fasted)
5 (n=5)	Tablet (fasted)		Suspension (fasted)		Tablet (fed)
6 (n=6)	Tablet (fed)		Tablet (fasted)		Suspension (fasted)

6.1.1 Single Oral Dose, Three-Way Cross-Over

32 healthy male or female participants will be enrolled in 1 of 6 single-dose, three-way cross-over sequences (designated as 1 through 6, respectively) in an ascending fashion. Sequences 1, 3, 4, and 5 will have 5 participants each, and Sequences 2 and 6 will have 6 participants each.

Each sequence will proceed through three cross-overs (suspension-fasted, tablet-fed, tablet-fasted) according to the schematic above, with dosing to occur on Day 1 of each of the three Periods. Participants in the fasted portion of each sequence will be dosed under overnight fasted conditions and will remain fasted for 4 hours post-dose. Water consumption is permitted as desired except for 1 hour before and after administration of Study Drug.

To assess the effect of food on CVN424 bioavailability in tablet formulation, the single-dose administration will be administered after ingestion of a standardized high-fat, high-calorie meal according to FDA Guidance for Industry (Food-effect bioavailability and fed bioequivalence studies, Jun 2022).

Participants for all sequences will be admitted to the study unit 1 day prior to dosing and remain in the unit for safety and PK assessments through 96 hours post-dose. The total confinement for each period will be 5 nights per sequence (15 days total) unless extended at the discretion of the Investigator, e.g., for monitoring and/or management of AEs.

Once 96-hour post-dose PK has been collected, participants will be discharged from the clinical research unit (CRU) for the remainder of the washout period and return the day prior to their next dose.

An outline of the study visit schedule is included in Appendix A.

6.2 Justification for Study Design, Dose, and Endpoints

This is a randomized, open-label, single-oral dose, three-way crossover study under fasted and fed conditions in healthy participants. The selected dose level (150 mg) is expected to provide a high level of GPR6 occupancy in brain tissue even at its steady-state nadir plasma concentration.

Based on the Phase 2 data (see Section 4.1) and a previous healthy volunteer study, the planned dose of CVN424 is within the dose range previously shown to be safe and well-tolerated.

AEs, physical exams, vital signs and weight, ECG findings, and clinical laboratory results are used as safety assessments to determine the relative bioavailability of the CVN424 suspension and tablet formulations. The plasma PK parameters will further elucidate the pharmacology of CVN424 in the intended participant population.

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 Sponsor or Institutional Review Board (IRB) considers the risk is no longer acceptable for participants participating in the study.

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 and is unable to ensure adequate study performance or otherwise permitted by the contractual agreement.

If the Sponsor, IRB, or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the Sponsor; applicable investigational sites will follow the procedure during termination or trial suspension.

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

If the Sponsor, IRB, 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 PARTICIPANT POPULATION

Screening for eligible participants will be performed within 28 days prior to randomization.

7.1 Inclusion Criteria

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

1. In the Investigator's opinion, the participant can understand and sign the Informed Consent Form (ICF) and comply with all protocol requirements.
2. The participant is male or female adult who is 18 to 55 years of age, inclusive at the time of Screening.
3. Participant weighs at least 45 kilograms (kg) (99 pounds [lbs]) and has a BMI between 18.0 and 35.0 kg/m2, inclusive at Screening.
4. The participant is medically healthy with no clinically significant (CS) or relevant abnormalities in medical history, physical exam, vital signs, ECG, and laboratory evaluations (hematology, chemistry, and urinalysis) as assessed by the Investigator.
5. Female participants of childbearing potential and male participants with female partners of childbearing potential must agree to either remain abstinent or use two methods of adequate and reliable contraception (see Section 9.1.12) throughout the study and at least 12 weeks after the last dose of study drug has been taken.

7.2 Exclusion Criteria

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

1. Vegetarian, Vegan, Lactose intolerant, or follows a Kosher diet.
2. Evidence of clinically significant neurologic or other disorder or impairment that, in the opinion of the Investigator, is reasonably expected to impact the ability of the participant to participate or confound the study results.
3. A current or 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]). Note, history of cholecystectomy is permitted if there is no evidence of malabsorption per the Investigator.
4. A history of cancer or other malignancy, with the exception of low-grade cervical intraepithelial neoplasia, low-grade (low-risk) prostate cancer, or 5-year cancer-free survivors of basal or squamous cell carcinoma or higher-grade cervical intraepithelial neoplasia or prostate cancer.
5. A positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or a human immunodeficiency virus (HIV) infection at Screening.
6. Any clinically significant abnormalities in labs: biochemistry (including liver function test [LFT], estimated glomerular filtration rate [eGFR], and glucose), standard

hematology with white blood cell (WBC) differential, c-reactive protein (CRP), coagulation tests, lipase, amylase, albumin, and calcium.

7. A supine blood pressure outside the ranges of 80 to 160 mm Hg for systolic and 50 to 100 mm Hg for diastolic, confirmed with up to two repeat tests at the Screening Visit; or symptomatic orthostatic hypotension, in the opinion of the Investigator.
8. A resting heart rate outside the range of 40 to 100 beats per minute (bpm) confirmed with up to two repeat tests at the Screening Visit. Note that 40-50 and 90-100 bpm may be permitted only at the discretion of the Investigator.
9. Positive urine result for illegal drugs at Screening and Check-In, or history of illicit drug use or alcohol abuse within 1 year prior to the Screening Visit.
10. Received any investigational compound (defined as a drug that has not been FDA-approved) within 30 days prior to the first dose of study medication or within 5 half-lives of the investigational compound, whichever is greater.
11. Within 14 or 28 days prior to randomization, ingested any of the following excluded medication, supplements, or food products: St. John's wort, ginseng, kava, Ginkgo biloba, Chinese herbs, and melatonin, or known strong inhibitors/inducers of cytochrome P-4503A4/5, including rifampin, clarithromycin, ketoconazole, itraconazole. For full list of prohibited medications and dietary products, (See Table 2).
12. Regularly uses 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; however, they must agree to refrain from 30 days before Day 0 (Inpatient Check-in) for the duration of the study or a positive urine cotinine test at Inpatient Check-in.
13. Known history of coronary artery disease and hospitalization for myocardial infraction, ischemic heart disease, or congestive heart failure within the 2 years prior to the screening visit.
14. Any clinically significant medical, psychiatric, or laboratory abnormality that, in the judgment of the Investigator, is likely to interfere with study participation
15. A history of major depression or risk of suicide according to the Investigator's clinical judgment or has made a suicide attempt.
16. Is a study site employee or an immediate family member of a study site employee.

Table 2 Prohibited Medication and Dietary Products

Use of the agents in Table 2 (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

The following table defines the prohibited medications and dietary products:

Prohibited Medication and Dietary Product
Within 30 days before Randomization:
• Nicotine-containing products
Within 28 days before Randomization:
• St. John's wort, ginseng, kava, ginkgo biloba, Chinese herbs, and melatonin • Known strong inducers of cytochrome P-4503A4/5 or p-gp, including rifampin • Immunization vaccines: Inclusive of but not limited to H1N1 and flu vaccinations. Participants 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.
Within 14 days before Randomization:
• Known strong inhibitors of cytochrome P-4503A4/5, including clarithromycin, ketoconazole, itraconazole • All prescription and non-prescription medications, herbal remedies, or vitamin supplements. Medication listed as part of acceptable birth control (Section 9.1.12), hormone replacement therapy, and thyroid hormone replacement therapy medication will be allowed without dose changes during the study.
Potential exceptions:
• 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 • Certain prescription medications may be allowed on a case-by-case basis at the discretion of the Investigator and Sponsor

7.3 Diet, Fluid, and Activity Control

Participants will refrain from the consumption of food and beverages containing the following:

- Xanthines/caffeine: 24 hours prior to each dosing and until last PK sample in each period (small amounts of caffeine derived from normal foodstuffs, e.g., 250 mL/8 oz/ 1 cup decaffeinated coffee or other decaffeinated beverage per day, except for espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction).
- Alcohol: 48 hours prior to each dosing and until last PK sample in each period.
- Grapefruit/Seville orange: 14 days prior to first dosing and until the last pk sample in Period 3.

Participants will be confined to the clinic on three separate sequences for approximately 5 days which will allow dosing sufficient time to collect additional post-dose PK samples and monitor for safety and tolerability (Check-in through Day 5 for each of the three Periods). During confinement, with the exception of the dosing day (See Section 7.3.1), participants will be provided 3 standard meals and a snack per day, each containing approximately 30% fat (relative to the total calories). Each meal and/or snacks served at the CRU will be standardized, similar in caloric content and composition, and taken at approximately the same time in each period. When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, participants will be required to fast from all food and drink except water between meals and snacks.

The study menu should be recorded and submitted to the study file, with a copy provided to the Sponsor following treatment. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

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.

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

7.3.1 On Dosing Days:

For the Suspension (fasted) and Tablet (fasted) portions: Breakfast will not be provided on dosing days. Participants must fast for a minimum of 4 hours after dose administration unless otherwise indicated. CVN424 will be administered with approximately 240 mL of water after a fast of at least 10 hours. Participants will continue to fast for an additional 4 hours after dosing and eat lunch following the 4-hour PK blood collection. Participants may consume water ad libitum except for 1 hour before and 1 hour after drug administration.

For the Tablet (fed) portion (food effect): CVN424 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, June 2022). Participants will finish their breakfast in its entirety within 30 minutes and will receive an investigational product 30 minutes (±5 minutes) after beginning the meal. 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.

7.4 Criteria for Discontinuation or Withdrawal of a Participant

Participants are free to withdraw from the study at any time upon request. The Investigator may remove a participant from the study if, in the Investigator's opinion, it is not in the best interest of the participant to continue the study. Participants may be discontinued due to the following (not inclusive):

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

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

   – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (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 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 participant failed to meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the participant's health.
4. Lost to follow-up. The participant did not return to the clinic and attempts to contact the participant were unsuccessful. Attempts to reach the participant must be documented.
5. Voluntary withdrawal. The participant (or participant's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
   Note: Attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (e.g., withdrawal due to an AE; withdrawal due to relocation).
6. The Sponsor, IRB, or regulatory agency terminates the study.
7. Other.

The primary reason for discontinuation or withdrawal of the participant from the study or study medication should be recorded in the eCRF using the following categories. For screen failure participants, refer to Section 9.1.14.

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

7.5 Procedures for Discontinuation or Withdrawal of a Participant

The Investigator must discontinue a participant's study participation at any time during the study when the participant meets the study discontinuation criteria described in Section 7.4. In addition, a participant may discontinue their participation without giving a reason at any time during the study. Should a participant'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 participants may be replaced at the Sponsor's discretion. Participants who withdraw from the study prior to dosing may be replaced.

8.0 CLINICAL TRIAL MATERIAL 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 CVN424 in both suspension and tablet formulations.

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

8.1.1.1 Investigational Drug

CVN424 Suspension:

The oral suspension drug product will be compounded by an accredited compounding pharmacy, e.g., Infuserve America Inc.

CVN424 oral suspension is prepared by suspending CVN424 drug substance in 2% Methocel, E15 Premium LV Hydroxypropyl Methylcellulose (HPMC)/0.5% Tween 80 vehicle. CVN424 oral suspension is supplied to the clinical site in bottles with contents clearly labeled, along with the appropriate study information and caution statements.

CVN424 Tablet:

Patheon Milton Park UK will manufacture the bulk drug product (150 mg tablets) and bottle it, and Patheon Allentown, US, will perform labeling and distribution of the study drug.

The components of the CVN424 tablet include the CVN424 API, Colloidal Silicon Dioxide, Croscarmellose Sodium, Hydroxypropylcellulose, Magnesium Stearate, Mannitol, and Microcrystalline Cellulose.

The tablets will be packaged in a high-density polyethylene (HDPE) bottle with an induction seal and a child-resistant cap; each bottle will contain 30 tablets.

Ancillary Materials:

Ancillary materials will be provided by either the clinical site and/or the Sponsor based on availability. Unused ancillary materials provided by the Sponsor will be accounted for and disposed of as directed by the Sponsor or their designee.

8.1.2 Drug Storage

All study drug stored at the investigative site must be kept in an appropriate, limited-access, secure place until it is used or returned to the Sponsor or designee for destruction. All study drug 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; short excursions are allowed but must be evaluated by the Sponsor.

8.1.3 Dose and Regimen

Prior to dosing initiation, the Investigator or Investigator's designee will instruct the participant on dosing procedures.

All dosing will occur while participants are in the clinic under the supervision of the Investigator or designee and in fed or fasting conditions as outlined in Section 7.3.

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

The planned sequences to be studied are provided in Table 3.

Table 3 Three-Way Cross-Over Sequences

Sequence	Dosing #1 (Period 1 Day 1) (Study Day 0)		Dosing #2 (Period 2 Day 1) (Study Day 14)		Dosing #3 (Period 3 Day 1) (Study Day 28)
1 (n=5)	Suspension (fasted)		Tablet (fasted)		Tablet (fed)
2 (n=6)	Tablet (fasted)		Tablet (fed)		Suspension (fasted)
3 (n=5)	Tablet (fed)	Washout	Suspension (fasted)	Washout	Tablet (fasted)
4 (n=5)	Suspension (fasted)		Tablet (fed)		Tablet (fasted)
5 (n=5)	Tablet (fasted)		Suspension (fasted)		Tablet (fed)
6 (n=6)	Tablet (fed)		Tablet (fasted)		Suspension (fasted)

8.1.4 Overdose

An overdose is defined as a known, deliberate, or accidental administration of an investigational drug, to or by a study participant, at a dose above that assigned to that individual participant 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 9.7.1.

Serious adverse events (SAEs) associated with an overdose should be reported according to the procedure outlined in Section 9.7.2.

In the event of an overdose, supportive measures should be employed as needed, e.g., administration of supportive therapy as dictated by the participant'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

Participants will be assigned to receive a unique randomization number. Study drug will be dispensed to participants as either tablets or suspensions. The tablets must be stored at controlled room temperature, and the suspensions must be stored refrigerated. See Pharmacy Manual for specifics.

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.

8.4 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 before 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 participants 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 participant, 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 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 participant 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, participants 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 13.2.

A properly signed ICF must be obtained prior to the participant entering the study and before any protocol-related procedures are performed.

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 participant, smoking status, and caffeine consumption at Screening.

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases that stopped at or prior to signing the ICF. Ongoing conditions are considered concurrent medical conditions (see Section 9.6.2).

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 designee 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 must be assessed as not clinically significant (NCS) or clinically significant (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 AE eCRF described in Section 9.7.1.

9.1.4 Weight, Height, and BMI

A participant 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 centimeter (cm) (or 1.76 m), weight=79.2 kg; BMI=79.2/1.76^2=25.57 kg/m^2 captured as 25.5 kg/m^2.

9.1.5 Vital Sign Procedure

Orthostatic vital signs will be measured after the participant has been at rest in a supine position for at least 3 minutes. Vital signs include blood pressure (BP), pulse rate, respiration rate, and body temperature. Triplicate measurements will be taken at pre-dose, initial post-dose, and final study assessment to ensure accuracy unless values are unexpected and additional measurements are clinically indicated for confirmation. Additionally, abnormal or unexpected measurements are to be rechecked manually.

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 15 minutes 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 participant over the counter. Concomitant medication is not provided by the Sponsor. At each study visit, participants 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. 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.

9.1.7 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

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 participant 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 30 minutes 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. Participants should be in a supine position following an approximate 5-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 interpreted by qualified personnel. The Investigator or sub-Investigator will categorize the ECG findings using 1 of the following categories: within normal limits, abnormal but not CS, or abnormal and CS. 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 method) intervals.

9.1.9 PK Sample Collection

9.1.9.1 Collection of Blood for PK Sampling

Blood samples for analysis of CVN424 plasma concentrations will be collected into chilled Vacutainers containing K_2EDTA.

Instructions for sample processing and shipment are provided in a separate lab manual.

In all sequences, serial blood samples to determine CVN424 concentrations in plasma will be collected according to the Schedule of Study Procedures (Appendix A).

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 sequence(s).

9.1.9.2 Collection of Urine for PK Sampling

In Tablet (fasted) sequences only, urine samples for analysis of CVN424 (or its metabolites) concentration in urine will be collected: pre-dose (within 12 hours prior to dosing), 0-12, 12-24, 24-48, and 48-96-hours post-dose. Volume of urine collected is to be recorded. Instructions for sample processing and shipment are provided in a separate lab manual.

9.1.9.3 Bioanalytical Methods

Plasma and urine concentrations of CVN424 will be measured by high-performance liquid chromatography with tandem mass spectrometry using validated (for plasma) and qualified (for urine) assays.

Plasma and urine samples will be archived for potential analysis of metabolites and/or target-related biomarkers, if appropriate.

9.1.10 PK Parameters

PK parameters of CVN424 will be derived using non-compartmental analysis methods from the concentration-time data for all evaluable participants. 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 CVN424 in plasma.

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
$AUC_{0\text{-}96h}$	Area under the plasma concentration-time curve from time 0 to 96 hours
C_{max}	Maximum observed plasma concentration.
T_{max}	Time to reach C_{max}.

Additional PK parameters may be calculated as appropriate.

9.1.11 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures.

Table 4 lists the tests that will be obtained for each laboratory specimen.

Table 4 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC WBC with differential (% and absolute) Hemoglobin Hematocrit Platelets PT/INR	ALT Albumin Alkaline phosphatase Amylase AST Total bilirubin Direct bilirubin Total protein Coagulation Creatinine CRP BUN/Urea Creatine kinase GGT eGFR Lipase 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 FSH		Drug screen including amphetamines (AMP), barbiturates (BAR), benzodiazepines (BZO), cannabinoids, cocaine (COC), opiates (OPI),

Hepatitis panel, including HBsAg and anti-HCV Human Immunodeficiency Virus (HIV) antibody	alcohol, methamphetamines, methadone (MET), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), tetrahydrocannabinol (THC) Cotinine Urine Pregnancy Test Alcohol (may be performed via breath test or urine)

The in-house 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. Participants 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 an AE in the participant'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 participants experience ALT or AST >3 ×ULN, follow-up laboratory tests at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase (GGT), and international normalized ratio (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 7.4 for discontinuation criteria and Section 9.7.3 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 participant details, and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 9.7.3 for reporting requirements).

9.1.12 Contraception and Pregnancy Avoidance Procedure

From the date of signing of ICF, throughout the duration of the study, and for 12 weeks 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 participants 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 12 weeks after the last dose of study

medication. In addition, males must be advised not to donate sperm for 12 weeks after the last dose of study medication.

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

Menopause is defined as at least 1 years since the last regular menses with a follicle-stimulating hormone (FSH)>40 IU/L or at least 5 years since the last regular menses, confirmed before any study medication is implemented. Male participants 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 120 days post-vasectomy and confirm that they have obtained documentation of the absence of sperm in the ejaculate.

Participants in a same-sex relationship must use a barrier form of birth control (for example, condom or diaphragm) to protect against the transfer of the study drug in any bodily fluids for 12 weeks after the last dose of study medication.

Acceptable and highly effective methods of contraception are:

- Abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The investigator will assess the reliability of abstinence concerning the duration of the clinical trial and the preferred and usual lifestyle of the participant.
- Intrauterine device (IUD)
- Surgical sterilization or postmenopausal
- Condom, diaphragm, or cervical cap with spermicide
- Hormonal contraception, including oral, injectable, transdermal, or implantable methods
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (if the partner is the sole sexual partner of the woman of childbearing potential [WOCBP] participant and the vasectomized partner has received medical assessment of the surgical success)

Participants will be provided with information on acceptable methods of contraception as part of the participant'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.

9.1.13 Pregnancy

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

If any participant 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 participant during the study or for 90 days after the last dose, should also be recorded following authorization from the participant's partner.

If the pregnancy occurs during administration of active study medication, e.g., after Period 1 or within 90 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.

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

All reported pregnancies will be followed up to final outcome using the pregnancy form and you may be asked to report the outcome. An evaluation after the birth of the child will also be conducted.

9.1.14 Documentation of Screen Failure

Investigators must account for all participants who sign ICF. If the participant 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:

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

Participant numbers assigned to participants who fail Screening should not be reused.

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

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

2. Rescreened participants should be assigned a new participant number and treated as a stand-alone participant.

9.1.15 Documentation of Randomization

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

If the participant is not eligible for randomization, the Investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Participant Treatment Compliance

Study medication will first be administered while participants 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 participant's source document records or equivalent. The exact dose time of consecutive participants 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.

9.3.1 Screening

Participants will be screened within 28 days prior to randomization. Participants will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.14 for procedures for documenting screening failures. Participants who are screening failures may be screened a second time if their reason for failing Screening is thought to be resolved. Rescreened participants will receive a new Screening number.

9.3.2 Inpatient Check-In

Following Screening and Baseline assessments, eligible participants will be randomized to one of the 6 sequences at the time of the first administration of study drug (Period 1 Day 1). Additionally, all participants will be admitted to the study clinic the day prior to subsequent dosing days, See Schedule of Study Procedures (Appendix A).

9.3.3 Dosing

Participants will be dosed according to the schema (See Table 1) on Day 1 of Periods 1, 2, and 3.

9.3.4 Washout and Discharge

Participants will be discharged after 5 consecutive days for a 14-day washout period (following 96-hour post-dose blood draw).

9.3.5 Final Visit (discharge day from clinic)

Participants will be confined to the study clinic for the first 96 hours of each washout period to permit supervised dosing of study drug and repeat study assessments.

The Investigator must complete the End of Study eCRF page for all participants.

9.3.6 Early Termination

If a participant withdraws from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last study drug treatment and the reason for withdrawal. If the participant is withdrawn due to an AE, the Investigator will follow the participant until the AE has resolved or stabilized. In all cases, the reason for and date of withdrawal must be recorded in the eCRF and in the participant's medical records. Efforts will be made to perform all early termination procedures for safety purposes prior to discharge. The early termination visit should be performed 2 weeks after the last dose if agreed to by the participant.

The Investigator must complete the End of Study eCRF page for all participants receiving study medication.

9.3.7 Follow-up Visit

The Follow-up Visit will occur by telephone 14 days (±2) after the final dose of study drug unless abnormal CS findings are observed upon discharge. In these cases, participants must be brought back to the clinic for re-evaluation per the Investigator's discretion.

9.4 Biological Sample Retention and Destruction

Blood and urine samples for PK analysis will be collected as described in Section 9.1.9. 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 participants' 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 participant may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

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 Definitions

9.6.1 AE

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug whether or not considered drug-related (CFR Title 21, Part 312.32(a)); 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.

A treatment-emergent adverse event (TEAE) is an AE than begins on or after administration of the first dose of trial medication or an increase in severity or frequency on or after administration of the first dose of trial medication.

9.6.2 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 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
- AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as an 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 an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be 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 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 AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays, etc.) should NOT be recorded unless related Study Procedures (Appendix A).
- If a participant has a pre-existing episodic condition (e.g., asthma, epilepsy), any occurrence of an episode should only be captured as an 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 participant has a concurrent degenerative condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an 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 AEs:

- If the participant experiences a worsening or complication of an AE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE.
- If the participant 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 participant experiences changes in the severity of an AE, the event should be captured once, with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) scheduled prior to the signing of the ICF are not considered 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 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 participant's medical condition should not be recorded as AEs but should be documented in the participant'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 AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

9.6.3 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 participant 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/CONGENITAL DISABILITY
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 participant 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.*

AEs 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 Section 9.7.1 and Section 9.7.2).

9.6.4 Severity of AEs

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

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

9.6.5 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.

9.6.6 Relationship to Study Procedures

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

9.6.7 Start Date

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

9.6.8 Stop Date

The stop date of the AE is the date at which the participant recovered, the event resolved but with sequelae, or the participant died.

9.6.9 Frequency

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

9.6.10 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 participant died, dosing with study medication was already stopped before the onset of the AE

9.6.11 Outcome

- Recovered/Resolved – Participant returned to first assessment status with respect to the AE
- 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 baseline; the participant died from a cause other than the particular AE 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 participant died from another cause with the particular AE/ state remaining "Not recovered/not resolved."
- Resolved with sequelae – the participant recovered from an acute AE/ but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis)
- Fatal – the AEs which are considered as the cause of death
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study

9.7 Procedures

9.7.1 Collection and Reporting of AEs

9.7.1.1 AE Collection Period

Collection of AEs will commence from the time the participant signs the informed consent to participate in the study and continue until 14 days following last dose.

9.7.1.2 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. Participants may report AEs occurring at any other time during the study. Participants experiencing an AE 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. All AEs will be documented on the 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)
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
7. Action concerning study medication
8. Outcome of event

9. Seriousness

9.7.2 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
- Participant identification number
- Investigator's name
- Name of the study medication(s)
- Causality assessment

The SAE form should be transmitted within 24 h 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.

9.7.3 Reporting of Abnormal LFT

If a participant is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE at the discretion of the PI. 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 participant 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 9.7.2. The Investigator must contact the Medical Monitor to discuss the relevant participant 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 will be at the discretion of the Investigator.

9.8 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 procedure for follow-up reports are the same as those for the initial report.

9.8.1 Safety Reporting to Investigators, IRBs, 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, 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 their IRB in accordance with national regulations.

10.0 DATA HANDLING AND RECORDKEEPING

AEs, 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.

10.1 CRFs (Electronic)

Completed eCRFs are required for each participant 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, the 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 participant'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.

10.2 Record Retention

The investigator agrees to keep the records stipulated in Appendix B and those documents that include (but are not limited to) the study-specific documents, the identification log of all participants, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, participant 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 participant'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 the 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.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of the participant'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 participant's treatment assignment. This review will assess the accuracy and completeness of the study database, participant evaluability, and appropriateness of the planned statistical methods.

11.1.1 Analysis Sets

Safety Set

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

PK Set

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

If any participants are found to be non-compliant with the 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 participant listings.

11.1.2 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) CVN424 dose level, CVN424 overall, and overall. The number and percentage of participants in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for each CVN424 formulation, CVN424 overall, and overall. Individual participant demographic and baseline characteristics data will be listed.

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

11.1.3 PK Analysis

The concentration of CVN424 in plasma will be summarized by treatment over each scheduled sampling time using descriptive statistics. Individual concentration data versus time will be presented in a data listing. Individual and mean plasma concentration data will be presented graphically. Descriptive statistics (arithmetic mean, SD, median, minimum and maximum) will be used to summarize the plasma PK parameters for CVN424. In addition, geometric mean and coefficient of variation will be computed.

The effect of formulation on PK and bioavailability of CVN424 will be assessed.

The effect of fed/fasting state on PK and bioavailability of CVN424 will be characterized.

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

A more detailed analysis will be presented in the SAP.

11.1.4 Safety Analysis

11.1.4.1 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 each CVN424 formulation, if in the fed or fasted state, and CVN424 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, TEAEs, AEs leading to study drug discontinuation, and SAEs. All AEs will be listed.

11.1.4.2 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 each CVN424 dose level and CVN424 overall. All clinical laboratory data will be listed.

11.1.4.3 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 each CVN424 dose level and CVN424 overall. All vital sign data will be provided in the data listings.

11.1.4.4 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 each CVN424 dose level and CVN424 overall. Shift tables may be generated for the Investigator's ECG interpretations that changed from baseline to the post-dose collections by the above sequences. All ECG data will be provided in the data listings.

11.1.4.5 Other Variables

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

11.2 Interim Analysis and Criteria for Early Termination

Two interim analyses are planned, after dosing in the 2nd and 3rd periods.

11.3 Determination of Sample Size

It is planned to enroll up to 32 male or female participants for participation in this study.

Based on previous PK studies with CVN424, it was determined 28 participants would be needed to show bioequivalence, assuming an intra-participant CV of 16% and an expected ratio of 1.10. 32 participants will be enrolled to ensure at least 28 evaluable participants.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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.

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, participant medical records, informed consent documentation, documentation of participant 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.

12.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary, to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that require deviation from protocol-specified procedures, the Investigator should consult with the Sponsor or designee (and IRB, 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 participant'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 participant, 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 1 defines the windows allowed for sample collections.

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

Table 5 Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
±5	immediately post-dose to ≤6 hours
±10	>6 hours to 12 hours post-dose
±15	>12 hours to 24 hours
±30	>24 hours

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site 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. 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 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., participants) 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.

13.1 IRB Approval

IRBs 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. If any member of the IRB 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 for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICFs, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and participant 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 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. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by participants, local safety reporting requirements, reports, and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the Investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the Sponsor or designee.

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRB and Sponsor.

13.2 Participant Information, Informed Consent, and Participant 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, participant authorization form (if applicable), and

participant information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study. The ICF and the participant 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 participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

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

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

The participant, or the participant'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 participant, or the participant's legally acceptable representative, determines he or she will participate in the study, then the ICF and participant authorization form (if applicable) must be signed and dated by the participant, or the participant's legally acceptable representative, at the time of consent and prior to the participant entering into the study. The participant or the participant'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 participant authorization (if applicable) at the time of consent and prior to participant 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, participant authorization form (if applicable), and participant information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed ICF, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

All revised ICFs must be reviewed and signed by relevant participants or the relevant participant'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 participant's objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that they are 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, IRB approval of the ICF and, if applicable, the participant authorization form. The ICF, participant authorization form (if applicable), and participant information sheet (if applicable) must be approved by the IRB and the Sponsor prior to use

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

The participant, or the participant's legally acceptable representative, must be given medical record, and the participant should receive a copy of the revised ICF.

13.3 Participant Confidentiality

The Sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant'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 participant attributes, such as sex, age, or date of birth, and participant initials may be used to verify the participant and the accuracy of the participant'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 to review the participant'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 participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process (see Section 9.1.1).

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

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 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 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.

13.4.2 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 the study.

Sponsor contact information, along with the Investigator's city, state, country, and recruiting status, will be registered and available for public viewing. Once participants receive the Investigator's 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 participant screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the Sponsor.

13.4.3 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.

13.5 Insurance and Compensation for Injury

Each participant in the study must be insured in accordance with the regulations applicable to the site where the participant 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 participants. Refer to the Clinical Study Site Agreement regarding the Sponsor's policy on participant compensation and treatment for an injury. If the Investigator has questions regarding this policy, they should contact the Sponsor or designee.

14.0 REFERENCES

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Appendix A: Schedule of Study Procedures

Overall Study Day #	**-28 to -2**	**-1**	**0**	**1-4**	**5-12**	**13**	**14**	**15-18**	**19-26**	**27**	**28**	**29-32**	**33 +/- 2**
Period			**1**				**2**				**3**		
Day		**0**	**1**	**2-5**	**6-13**	**14**	**1**	**2-5**	**6-13**	**14**	**1**	**2-5**	**15 +/- 2**
				Washout				**Washout**					
			Inpatient				**Inpatient**				**Inpatient**		
	Screening	**Check-in**	**Dosing**			**Check-in**	**Dosing Day**			**Check-in**	**Dosing**		**Follow-Up/ET[1]**
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Review ICF and I/E	X	X				X				X			
Demographics and Medical History	X												
Randomization[2]		X											
Concomitant medications	X	X	X	X		X	X	X		X	X	X	X
Participant Admission to CRU		X				X				X			
Vital signs[3]	X	X	X	X		X	X	X		X	X	X	X
Weight, height, and BMI[4]	X												X
Urinalysis[5]	X		X	X			X	X			X	X	X
Urine Drug Screen	X	X				X				X			
Cotinine Screen		X				X				X			

[1] Assessments to be completed on final in-patient day and will be repeated if AE requires in-person follow-up
[2] Once eligibility has been confirmed by Screening assessments
[3] Assessments to include HR, BP, and temperature
[4] Height only at screening
[5] Part of safety assessments (Pre and 24h post-dose)

Physical Examination[6]	X		X				X				X		X
Hepatitis panel and HIV antibody test	X												
Clinical laboratory tests[7]	X	X	X	X			X	X			X	X	X
Pregnancy Test[8]	X	X		X		X		X		X			X
FSH[9]	X												
C-SSRS[10]	X	X		X		X	X	X		X	X	X	X
ECG[11]	X		X				X				X		X
PK Blood Collection[12]			X	X			X	X			X	X	
PK Urine[13]			X	X			X	X			X	X	
Overnight Fasting		X[14]				X[15]				X[16]			
CVN424 Dosing[17]			X				X				X		
AE Assessment		X	X	X		X	X	X		X	X	X	X

[6] Full PE at Screening, Medical Assessment pre-dose (within 24 hours prior to dosing) and 24-hours post-dose
[7] Pre and Post dose Safety Labs, standard hematology with WBC differential, CRP, coagulation tests, lipase, amylase, albumin, and calcium. Predose labs do not need to be reviewed prior to dosing. Post dose to be done at 48 hours and EOT. Unscheduled as clinically indicated.
[8] Serum pregnancy test at Screening and urine pregnancy test at subsequent discharge and check-ins
[9] FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile)
[10] Screening, Check-in, 24 and 96-hour post dose
[11] Triplicate standard 12-lead ECG will be recorded at Screening and on Days 0, 10, and 20 pre-dose [within 1 h prior to dosing] and 3h (+/-15 minutes) post-dose. Triplicate standard 12-lead ECG will also be recorded at Early Termination (if applicable)

[12] Plasma Sampling: Predose (within 15 minutes prior to dosing; 60 minutes for the fed treatments), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 84 and 96h
[13] For tablet fasted sequence: Predose (for bioanalysis), 0-12, 12-24, 24-48, 48-96h. Volume of urine collected needs to be recorded
[14] Sequences 1, 2, 4, 5
[15] Sequences 1, 3, 5, 6
[16] Sequences 2, 3, 4, 6
[17] Sequences 1, 4 will be dosed with suspension; 2,3,5,6 will be dosed with tablet per figure 1

Appendix B: Responsibilities of the Investigator

Clinical research studies Sponsored by the Sponsor are participant 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 participants, 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 that conforms to local regulatory requirements.
6. Ensure that the IRB will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB 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 participant who participates in the study and document the date of consent in the participant's medical chart. Valid informed consent is the most current version approved by the IRB. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a participant authorization, then the Investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered 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
- 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 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.

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Reason for signing: Approve	Name: [redacted]MD Role: Principal Investigator Date of signature: 08-Sep-2022 17:23:17 GMT+0000

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