PROTOCOL

A Phase II, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of CVN424 in Parkinson's Disease Patients with Motor Fluctuations

Short Title: Phase 2 Study of CVN424

Sponsor:	Cerevance Beta, Inc. One Marina Park Drive, Suite 1410 Boston, MA 02210		
Study Number:	CVN424-201		
IND Number:	138119	**EudraCT Number:**	Not Applicable
Compound:	CVN424		
Version/Date:	Protocol 4.0	14 July 2021	

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Contact Type / Role	Contact
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1.2 Approval

REPRESENTATIVES OF CEREVANCE

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

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

SIGNATURES

Approved by:

Signature DocuSigned by: David Margolin 31772E8F24AB481... Date 7/14/2021

David H. Margolin, MD PhD
Senior Vice President
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 subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council on Harmonisation, E6 GCP: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 9.6 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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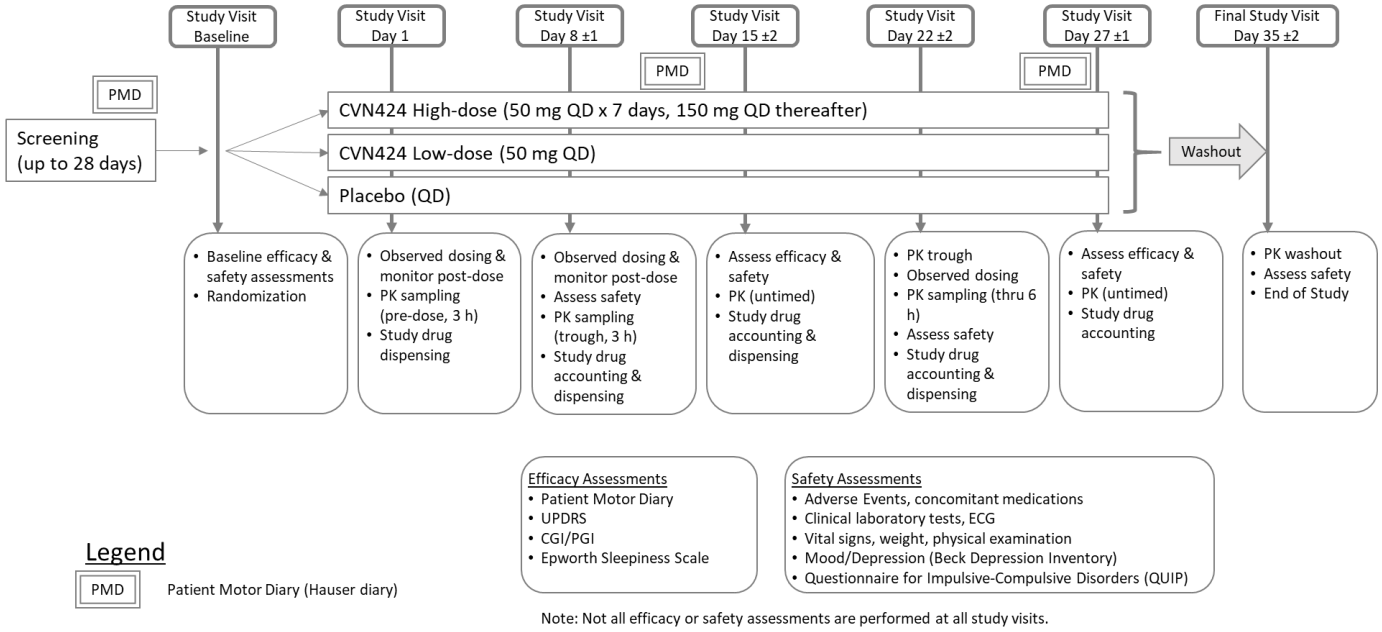
2.0 STUDY SUMMARY

Name of Sponsor(s): Cerevance Beta, Inc.	**Compound:** CVN424	
Title of Protocol: A Phase II, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of CVN424 in Parkinson's Disease Patients with Motor Fluctuations	**IND No.:** 138119	**EudraCT No.:** Not applicable
Study Number: CVN424-201	**Phase:** 2	

Study Design:

This is a phase 2 study, randomized, double-blind, placebo-controlled, multicenter study of oral CVN424 at two dose levels (low-dose 50 mg, high-dose 150 mg) in Parkinson's disease (PD) patients with motor fluctuations. The overall study design is depicted and described below:



Note: Not all efficacy or safety assessments are performed at all study visits.

Approximately 135 male and female subjects with Parkinson's disease, on a stable dosage of levodopa but with an average of ≥ 2 h total OFF time/day and not less than 1 h per day, will be enrolled. Following baseline safety and efficacy assessments, subjects will be randomized to receive once-daily doses of either low-dose CVN424, high-dose CVN424, or matching placebo. The planned low-dose and high-dose levels will be 50 and 150 mg CVN424 per day, respectively. All subjects not randomized to placebo will initiate treatment with 50 mg CVN424 on Day 1; the low-dose arm will continue to receive 50 mg per day, while the high-dose arm will increase their daily dosage to 150 mg CVN424 beginning on Day 8 ±2 days and continuing thereafter. Investigator or their delegate will manage incident AEs according to their medical judgment. Study drug will be self-administered each morning as an oral suspension. Subjects will continue their other PD medications.

Subjects will follow the study schedule presented below. Dosing on Day 1, Day 8, and Day 22 visits will be observed at the study site by Investigator or their delegate. For Visit Days 8 and 22, dosing of study drug (but not subjects' other medications) will be deferred until after collection of a blood sample for determination of the study drug "trough" concentration.

Screening [a]	Baseline & Random-ization	Treatment [b]	Follow-up [c]

Consent, Eligibility	Patient Motor Diary at Home	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit	Final Study Visit
Days -28 to -1	Days -2 & -1	Day 0	Day 1 [d]	Day 8 ±2 days	Day 15 ±2 days	Day 22 ±2 days	Day 27 ±1 day	Day 35 ±2 days

(a) Screening activities must occur within 28 days of randomization, but may be completed in fewer than 28 days. Screening days are nominally called Day -28 to Day -1 but will not necessarily correspond numerically to the calendar days prior to the Baseline Visit. By the same convention, the Patient Motor Diary will be recorded at home over 2 consecutive days during screening, but not necessarily on the 2 days immediately prior to the Baseline visit.

(b) Study drug supply will be dispensed (as suspension in amber colored bottles) on Day 1 and at subsequent weekly study visits. Subjects will return empty and unused bottles to site. Study drug will be self-administered each morning as an oral suspension. For Visit Days 8 and 22, dosing of study drug (but not subjects' other medications) will be deferred until after collection of a blood sample for determination of the study drug "trough" concentration.

(c) Subjects who have abnormal, clinically significant (CS) findings at the Final Study Visit may be asked to return to the clinic subsequently to ensure appropriate safety follow-up.

(d) By convention, Day 1 will be the first day of treatment. It will not necessarily occur on the calendar day following the baseline and randomization visit.

Follow-up assessments will occur approximately 7 days after the final (Day 27 ±1 day) dose.

Study committees:

None. (Review of incident and cumulative safety data and findings is the responsibility of the Medical Monitor and sponsor's Responsible Medical Officer.)

Safety stopping rules:

If any of the following occur, the Medical Monitor and Sponsor's Responsible Medical Officer will review the relevant data, including unblinded data if deemed necessary, and decide whether it is safe to suspend dosing or continue dosing at either the planned or alternative dose levels or decides to prematurely terminate the study:

1. Four or more subjects receiving CVN424 experience the same type of serious or Medically Significant event deemed related to study drug.
2. Three or more subjects receiving CVN424 experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase (see below).
3. One or more subjects receiving CVN424 experience ALT and/or AST elevations >3 ×ULN in the presence of a total bilirubin increase >2 ×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., "Hy's Law cases").
4. Two or more subjects receiving CVN424 experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

Primary Objective:

To assess the safety and tolerability of CVN424 when administered as daily oral doses for 28 days, adjunctive to levodopa, in subjects with Parkinson's disease and motor fluctuations.

Secondary Objectives:

- To assess potential efficacy of CVN424 adjunctive to levodopa in alleviating symptoms of PD
- To assess CVN424 multiple-dose PK in blood of PD subjects

Exploratory Objectives:

- To explore possible serum/plasma, DNA and/or RNA markers (e.g., drug metabolic enzyme and transporter polymorphisms) that may contribute to variability in CVN424 PK, safety or efficacy

Subject Population:

Male and female subjects, ages 30 to 80 years old, with idiopathic Parkinson's disease and motor fluctuations on stable doses of levodopa

Target Number of Subjects:	**Number of Sites:**
45 subjects per arm (total n=135 subjects)	Approximately 30 in the United States of America
Dose Level(s): Planned dose levels are placebo, 50 mg, and 150 mg CVN424. Study drug dispensed as CVN424 suspension (or matching placebo) in amber colored bottles suitable for self-administered dosing.	**Route of Administration:** Oral
Duration of Treatment: Daily oral doses for 28 days.	**Period of Evaluation:** Screening Period: up to 28 days Treatment Period: 28 days Follow-up Period: approximately 7 days Total Duration: Approximately 9 weeks

Main Criteria for Inclusion:

1. Male or female adult who is 30 to 80 years of age inclusive at study entry.
2. Has idiopathic Parkinson's disease, Hoehn and Yahr stages 2-4, and is on a stable dosage of levodopa. (Stable is defined as a dosage unchanged in the 30 days prior to randomization and, in the opinion of the investigator, able to continue the current regimen throughout the month-long study without undue inconvenience or harm.)
3. Experiences an average of at least 2 h total OFF time/day, and at least 1 h each day, per Patient Motor Diary over 2 days during Screening assessment.
4. The subject signs and dates a written informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures.

Main Criteria for Exclusion:

1. Has atypical parkinsonism, severe disabling dyskinesia, or severe motor fluctuations that the investigator considers likely to interfere with study participation or assessments, or history of implant for Deep Brain Stimulation.
2. Poor concordance (<75%) of self-report with site rater on in-clinic Screening period Patient Motor Diary. Subjects with low concordance may be retested after further instruction, at investigator's discretion.
3. Screening period Patient Motor Diary scored at-home over 2 days demonstrates unacceptable quality of the diary, with more than 4 errors per day. (Assistance from caregivers is permitted if they also will be providing assistance with home Patient Motor Diary entries for Day 15 and 27 efficacy assessments.) Subjects with more than 4 errors per day may be retested after further instruction, at investigator's discretion.
4. Body mass index (BMI) at Screening <18.0 or >35.0 kg/m^2, inclusive.
5. Subject has evidence of CS neurologic or other disorder or impairment that, in opinion of Investigator, is reasonably expected to impact the ability of the subject to participate or to confound the study results.
6. Subject has 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]).

7. Subject has 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, higher-grade cervical intraepithelial neoplasia or prostate cancer.
8. Has a history of human immunodeficiency virus (HIV) infection.
9. Subject has 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.
10. Subject has a resting heart rate outside the range 50 to 100 bpm, confirmed with up to two repeat tests, at the Screening Visit.
11. Positive urine result for illegal drugs (except cannabis) at Screening, or history of illegal drug use (except cannabis) or alcohol abuse within 1 year prior to the Screening Visit.
12. Subject has 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.
13. Subject has, within the prior month, ingested any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table as listed in Table 2.
14. Male subjects who do not agree to all the following rules: when sexually active with female partner(s) of childbearing potential during the study and for 12 weeks after the last dose of study drug: a) use an acceptable method of birth control (condom with spermicide or surgical sterilization) and b) refrain from sexual activity with female partners who do not use an acceptable method of birth control. Barrier contraception (condom with spermicide) must be used by all male subjects who were not surgically sterilized at least 90 days prior to screening. Male subjects must also agree to refrain from sperm donation during the study and until 12 weeks after the last dose of study drug.
15. Female subjects who are pregnant or breastfeeding or plan to become pregnant or donate ova during the study or for 30 days after the last dose of study drug. Women of childbearing potential (WOCBP) also must be practicing an adequate method of birth control (e.g., oral or parenteral contraceptives, intrauterine device, barrier, abstinence).

    *Definitions and acceptable methods of contraception are defined in Section 9.1.9, Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities are defined in Section 9.1.10, Pregnancy.

16. Risk of suicide according to the investigator's clinical judgment or has made a suicide attempt in the previous 3 years.
17. Subject is a study site employee or an immediate family member of a study site employee.

In addition, subjects may not use any excluded medications, supplement, or food product as listed in Table 2 during the study.

- Safety assessments:

Safety assessments will include AEs, clinical laboratory results, vital signs and weight, physical examinations, electrocardiogram (ECG), Questionnaire for Impulsive-Compulsive Disorders (QUIP), and Beck Depression Inventory. AEs will be collected from signing of ICF. AEs with onset or exacerbation up until dosing on Day 1 will be scored as pretreatment events (PTEs), and AEs that occur from first dosing until 30 days after the last dose will be captured as a treatment-emergent AE (TEAE). Vital signs will be recorded at Screening and at least once at each Study Visit. On Day 1 and Day 8, vital sign assessments will be conducted pre-dose [within 90 minutes prior to dosing], and at least hourly through 3 h post-dose. Vital signs will include oral temperature, blood pressure, respiration rate and heart rate. Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded 15 minutes apart at baseline. Orthostatic vital signs (non-triplicate) will be recorded pre-dose and at 3 h post-dose on Visit Days 1 and 8. Heart rate and blood pressure will be measured after at least 5 minutes supine and (when orthostatic vital signs are specified) again after 2 minutes standing. Additional monitoring of vital signs and ECGs may continue beyond 3 h post-dose at the discretion of Investigator.

Standard 12-lead ECGs will be recorded in triplicate at Screening and on Visit Days 1, 8, 27, and 35.

A description of safety assessments is provided in Section 9.1 and the full Schedule of Study Procedures is provided in Appendix

A.

- Efficacy assessments:

Efficacy assessments will include Patient Motor Diary (Hauser diary), Unified Parkinson's Disease Rating Scale (UPDRS), Epworth Sleepiness Scale, Clinical Global Impression (CGI), and Patient Global Impression (PGI).

- Determination of CVN424 concentration in plasma:

Plasma samples will be collected for the determination of concentrations of CVN424 as described in Section 9.1.13, PK Sample Collection.

PK parameters of CVN424 will be derived from the concentration-time data for evaluable subjects. The following PK parameters will be determined from concentrations of CVN424 in plasma: C_{min} at steady state (trough level on Day 22), C_{max} on Day 22, time to reach C_{max} on Day 22 (t_{max}), AUC from time 0 to 6 h (AUC_6), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2z}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F).

- Pharmacogenomics:

One whole blood sample will be collected at Baseline for pharmacogenomic analysis; this will only be collected once per subject. A whole blood sample will be collected at pre-dose and 3 h post-dose on Day 1 for ribonucleic acid (RNA) pharmacogenomic analysis. The samples will be stored for no longer than 15 years after completion of the CVN424 study and/or until the drug development of CVN424 is no longer actively pursued by Cerevance or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Cerevance. "Stored samples" in this context are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; every subject must sign the ICF in order to participate in this study. DNA samples can be used to identify markers (e.g., potential metabolites, or drug metabolic enzyme and transporter polymorphisms) that may contribute to variability in CVN424 PK, pharmacodynamics, or safety. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Endpoints:

The primary endpoint of this study will be:

- Percentage of subjects with TEAE related to study drug

The secondary endpoints will include:

- Percentages of subjects with abnormal and clinically significant (CS) safety laboratory test results, ECG test results, or vital sign measurements at least once post-dose
- Change from baseline in 2-day average OFF time at Day 27 as recorded in the Patient Motor Diary over the two days prior to each visit

Additional and Exploratory endpoints will include:

- Change from baseline in UPDRS Part I at Day 27
- Change from baseline in UPDRS Part II at Day 27
- Change from baseline in UPDRS Part III at Day 27
- Change from baseline in UPDRS Part IV question 32 at Day 27
- Change from baseline in UPDRS Part IV question 33 at Day 27
- Change from baseline in CGI and PGI at Day 27

- Change from baseline in Epworth Sleepiness Scale at Day 27
- Change from baseline in 2-day average ON time without troublesome dyskinesia at Day 27
- Change from baseline in efficacy measures at Days 15 and 27
- Plasma PK parameters
- Possible characterization of plasma metabolites, or metabolic enzyme and transporter polymorphisms.

Statistical Considerations:

Safety:

Safety will be assessed among all subjects who receive at least one dose of study drug, classified according to the treatment actually received. AEs will be presented in listings, and TEAEs will be summarized as number of distinct events and the number and percentage of subjects experiencing a given class of AE as defined by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Individual results of laboratory tests (e.g., hematology, chemistry, urinalysis, and endocrine) will be listed and observed values and change from baseline will be summarized. Individual results of vital signs and weight will be listed and observed values and changes from baseline will be summarized. Individual results of quantitative ECG parameters from the 12-lead safety ECGs will be listed and observed values and changes from baseline will be summarized. All summaries will be performed by placebo, by CVN424 dose level, and for CVN424 overall. Subgroup analyses will assess the influence of selected demographic and disease-related characteristics. Physical exam findings will be presented in data listings.

Efficacy:

Efficacy will be assessed among all subjects who were eligible, randomized, and received at least one dose of study drug, classified according to the treatment actually received. Secondary tests of efficacy will assess subjects who were eligible, randomized, and judged compliant with treatment and follow-up as classified prior to breaking the blind. Serial assessments of average daily hours of OFF time as recorded in the Patient Motor Diary over the two days prior to each visit will be using mixed model for repeated measures (MMRM). The model will include fixed terms for treatment, visit, treatment x visit interaction and baseline measurement with subject-level unstructured covariance among repeated measurements. Other covariance structures may be used in case the model do not converge using unstructured covariance structure. Additional covariates may be included based on review prior to breaking the blind. The primary estimand of efficacy for each active dose vs. placebo will be the treatment-dependent difference in change from baseline to Day 27 and will be tested using linear contrasts of least-square means. Each comparison will test for significance at one-tailed $p < 0.1$ to control the overall type 1 error rate at 20% based on Dunnett's method for comparing two treatments to the same control. Additional contrasts will be used to test for a dose-dependent effect of treatment and to estimate dosage-dependent differences in change from baseline at all other visits. Additional and exploratory efficacy endpoints will be analyzed in the same model and using the same estimands. Subgroup analyses will assess the influence of selected demographic and disease-related characteristics.

PK Measures:

Concentrations of CVN424 in plasma will be summarized by dose level and by gender (if possible) over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing.

PK parameters of CVN424 will be summarized by dose and by gender (if possible) using descriptive statistics.

Sample Size Justification:

The safety and tolerability of single- and repeated (7 daily) administration of CVN424, including doses higher than in the present study, were previously demonstrated in a study with 64 healthy volunteers (NCT03657030). The target sample size of 45 subjects per treatment arm (total N=135) is considered to be sufficient for the preliminary evaluation of CVN424 safety, tolerability and efficacy in a PD population. The study will have 90% power to detect at least one instance of any TEAE with an expected incidence of 0.10 per participant exposed at a given dosage of CVN424.

When the true effect of both dosages is zero, the study will have an 80% probability of declaring neither dosage of CVN424 significantly better than placebo at reducing OFF time based on the one-tailed $p < 0.1$ criterion, allowing 20% non-evaluable (e.g., loss to follow-up, incomplete data) and assuming a standard deviation (SD) of 3 h for the change in OFF time from baseline

to 27 days. When the true effect of a dosage is a reduction in average OFF time of at least 1.5 h, the study will have an 80% probability of declaring at least one dosage of CVN424 significant based on the one-tailed $p < 0.1$ criterion. By this construction, the study has 80% power to detect whether CVN424 does not reduce OFF time and 80% power to detect whether CVN424 at one or both of the two dosages tested reduces OFF time by at least 1.5 h.

3.0 STUDY REFERENCE INFORMATION

3.1 List of Abbreviations

λ_z	terminal elimination rate constant
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_6	area under the plasma concentration-time curve from time 0 to 6 hours
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
BCRP	breast cancer resistance protein
BMI	body mass index
CGI	Clinical Global Impression Scale
CL/F	apparent clearance
cm	centimeter
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CS	clinically significant
D2	dopamine receptor, type 2
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GPR	G-protein coupled receptor
h	hour(s)
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
K_2EDTA	dipotassium ethylenediamine tetraacetic acid
LFT	liver function test

m	meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MSN	medium spiny neuron
N	number
NCS	not clinically significant
ng	nanogram
Occ_{50}	50% receptor occupancy
Occ_{90}	90% receptor occupancy
PD	Parkinson's disease
PGI	Patient Global Impression Scale
Pgp	P-glycoprotein 1
PK	pharmacokinetic
PTE	pretreatment event
QD	once daily
OATP	organic-anion-transporting polypeptide
QTcB	QT interval with Bazett's correction method
QTcF	QT interval with Fridericia's correction method
QUIP	Questionnaire for Impulsive-Compulsive Disorders
RNA	ribonucleic acid
RO	receptor occupancy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
V_z/F	apparent volume of distribution
WOCBP	women 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 (APDA.org, accessed 26 Jan 2018), causing cardinal symptoms of tremor, bradykinesia, and postural instability. 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 G_s- coupled receptor that functionally opposes the G_i-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. The efficacy of CVN424 has not previously been studied in humans, but has been demonstrated in various animal models of PD. It was dose-dependently effective as monotherapy in reversing immobility in rats with bilateral 6-OHDA lesions. It dose-dependently blocked D2 antagonist induced (indirect pathway dependent) catalepsy in rats. Safety studies of CVN424 conducted in rodents, dogs, and monkeys have demonstrated minimal toxicity, with the primary dose-limiting effect of body weight loss or reduced body weight gain. All toxicity findings demonstrated dose-dependency and reversibility of effects.

A first-in-humans 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 subjects as a single oral dose of between 1 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 subjects (5.0%) overall in the single-dose cohorts (feeling hot; headache). Study drug-related AEs were reported by 2 of 24 subjects (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 subject after their third daily dose (75 mg). There were no severe or serious AEs, and all AEs had 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 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 to be strictly dose-proportional. A trend of increase in 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 PK is appropriate for once-daily oral dosing, with or without food.

CVN424 is expected to be a pharmacological treatment for PD subjects, 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

Although available medications and implanted deep brain stimulation can often treat the motoric symptoms of PD, many patients with PD have motor fluctuations despite treatment and may not experience improvement in non-motor symptoms. Moreover, current treatments are fraught with side-effects (e.g., drug induced dyskinesia), and their efficacy diminishes as the disease progresses. Therefore, novel therapies are needed to improve the quality of life for patients with PD. The efficacy of CVN424 in animal models of PD supports its investigational use in PD patients.

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. This will be the first study conducted with CVN424 in patients with PD, and will examine the safety, tolerability, efficacy, and plasma PK of the compound in PD patients.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To assess the safety and tolerability of CVN424 when administered as daily oral doses for 28 days, adjunctive to levodopa, in subjects with Parkinson's disease and motor fluctuations.

5.1.2 Secondary Objectives

- To assess potential efficacy of CVN424 adjunctive to levodopa in alleviating symptoms of PD
- To assess CVN424 multiple-dose PK in blood of PD subjects

5.1.3 Exploratory Objectives

- To explore possible serum/plasma, DNA and/or ribonucleic acid (RNA) markers (e.g., drug metabolic enzyme and transporter polymorphisms) that may contribute to variability in CVN424 PK, pharmacodynamics, safety or efficacy

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint of this study will be:

- Percentage of subjects with treatment-emergent adverse events (TEAE) related to study drug

5.2.2 Secondary Endpoints

The secondary endpoints will include:

- Percentages of subjects with abnormal and clinically significant (CS) safety laboratory test results, ECG test results, or vital sign measurements at least once post-dose
- Change from baseline in 2-day average OFF time at Day 27 as recorded in the Patient Motor Diary

5.2.3 Additional and Exploratory Endpoints

Additional and Exploratory endpoints will include:

- Change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) Part I at Day 27
- Change from baseline in UPDRS Part II at Day 27
- Change from baseline in UPDRS Part III at Day 27
- Change from baseline in UPDRS Part IV question 32 at Day 27

- Change from baseline in UPDRS Part IV question 33 at Day 27

Change from baseline in Clinical Global Impression Scale (CGI) and Patient Global Impression (PGI) at Day 27

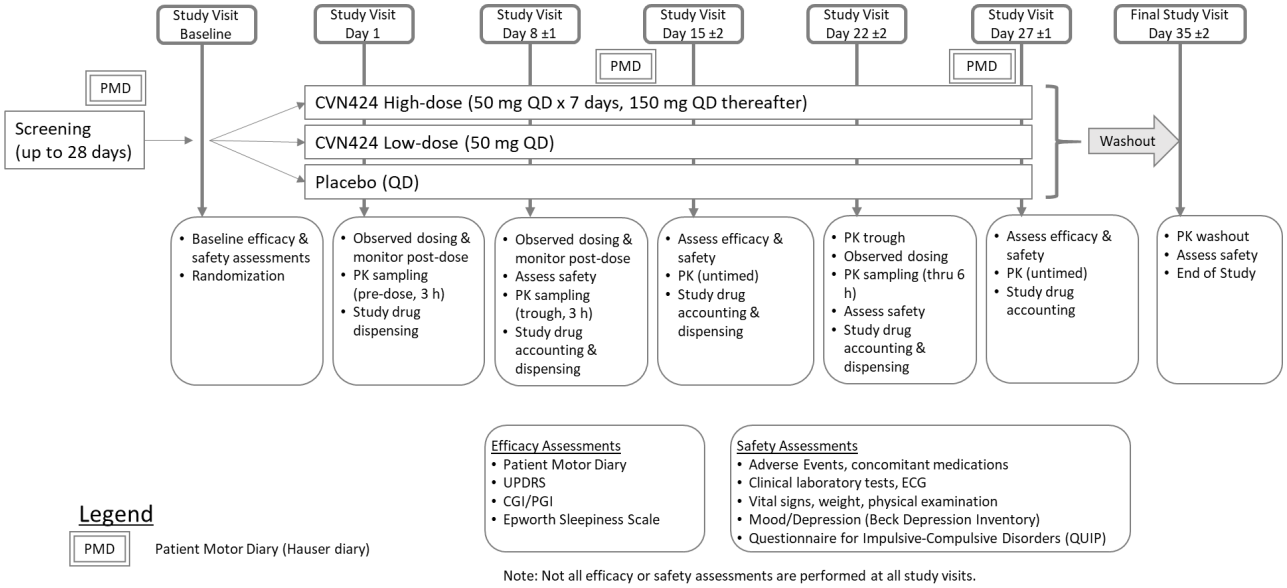
- Change from baseline in Epworth Sleepiness Scale at Day 27
- Change from baseline in 2-day average ON time without troublesome dyskinesia at Day 27 as recorded in the Patient Motor Diary
- Change from baseline in efficacy measures at Days 15 and 27
- Plasma PK parameters
- Possible characterization of plasma metabolites, or metabolic enzyme and transporter polymorphisms via pharmacogenomic analyses

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2, randomized, double-blind, placebo-controlled, multicenter study of two dose levels of oral CVN424 (low-dose 50 mg, high-dose 150 mg) in Parkinson's disease (PD) patients with motor fluctuations. The overall study design is depicted in Figure 1.

Figure 1. Schematic design of study



Approximately 135 subjects with Parkinson's disease will be enrolled. Following baseline safety and efficacy assessments, subjects will be randomized in a 1:1:1 ratio into one of 3 study arms to receive low-dose CVN424, high-dose CVN424 or matching placebo. The planned low-dose and high-dose levels will be 50 and 150 mg CVN424 per day, respectively, as shown in Table 3.

Subjects not randomized to placebo will initiate treatment with 50 mg CVN424 on Day 1. Thereafter, the low-dose arm will continue to receive 50 mg per day, while the high-dose cohort will increase their dosage to 150 mg CVN424 per day beginning on Day 8 ±2 days and continuing thereafter. This step-wise increase is intended to limit the changes that the first dose of CVN424 may elicit in vital signs (notably, increased temperature and heart rate, which were dose-dependent and not clinically significant in a healthy volunteer study). Investigator or their delegate will manage incident AEs according to their medical judgment.

Study drug supply will be dispensed (as suspension in amber colored bottles) on Day 1 and at subsequent weekly study visits. Study drug will be self-administered each morning on an outpatient basis as an oral suspension. Dosing on Day 1, Day 8 and Day 22 visits will be observed at the study site by Investigator or their delegate. For Visit Days 8 and 22, dosing of study drug (but not subjects' other medications) will be deferred until after collection of a blood sample for determination of the study drug "trough" concentration.

Following dosing on days 1 and 8, subjects will remain on site until at least 3 h after dosing for safety and PK assessments. Investigator or their delegate will manage any incident AEs.

The study visit schedule is summarized in Table 1. Follow-up assessments will occur approximately 7 days after the final (Day 27 or 28) dose. A summary of activities scheduled at each study visit is included in Section 9.3. A Schedule of Study Procedures is listed in Appendix A.

Table 1 Subject Visit Schedule

Screening [a]		Baseline & Random-ization	Treatment [b]					Follow-up [c]
Consent, Eligibility	Patient Motor Diary at Home	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit	Study Visit	Final Study Visit
Days -28 to -1	Days -2 & -1	Day 0	Day 1 [d]	Day 8 ±2 days	Day 15 ±2 days	Day 22 ±2 days	Day 27 ±1 day	Day 35 ±2 days

(a) Screening activities must occur within 28 days of randomization but may be completed in fewer than 28 days. Screening days are nominally called Day -28 to Day -1,but will not necessarily correspond numerically to the calendar days prior to the Baseline Visit. By the same convention, the Patient Motor Diary will be recorded at home over 2 consecutive days during screening, but not necessarily on the 2 days immediately prior to the Baseline visit.

(b) Study drug supply will be dispensed (as suspension in amber colored bottles) on Day 1 and at subsequent weekly study visits. Subjects will return empty and unused bottles to site. Study drug will be self-administered each morning as an oral suspension. For Visit Days 8 and 22, dosing of study drug (but not subjects' other medications) will be deferred until after collection of a blood sample for determination of the study drug "trough" concentration.

(c) Subjects who have abnormal, clinically significant (CS) findings at the Final Study Visit may be asked to return to the clinic subsequently to ensure appropriate safety follow-up.

(d) By convention, Day 1 will be the first day of treatment. It will not necessarily occur on the calendar day following the baseline and randomization visit.

6.1.1 Study Committees

None.

Review of incident and cumulative safety data and findings during study is the responsibility of the Medical Monitor and sponsor's Responsible Medical Officer.

6.2 Justification for Study Design, Dose, and Endpoints

The study is double-blind and placebo-controlled to avoid subjective bias in the assessment of the safety, tolerability, and efficacy of CVN424.

The selected dose levels are predicted to achieve potentially therapeutic concentrations of drug exposure. The lower dose (50 mg per day) may attain CNS exposure at the low end of the therapeutic range, while the higher dose (150 mg per day) is expected to provide a high level of GPR6 occupancy in brain tissue even at its steady-state nadir plasma concentration.

CVN424 is a potent inverse agonist of GPR6 (half maximal effective concentration [EC_{50}] = 8.5 nM to 27 nM) in mice, rats, dogs, and humans. The minimum target for a potentially therapeutic drug exposure in plasma and CSF was informed by (*i*) plasma concentrations yielding half maximal effectiveness (EC_{50}) in rodent models of PD; (*ii*) plasma concentrations yielding 50% receptor occupancy (Occ_{50}) in mouse brain; and (*iii*) estimation of the ratio of CVN424 concentration in brain (mice) or CSF (monkeys) versus unbound in plasma; and (*iv*) the similar % binding of CVN424 to plasma proteins in rodents and humans (approximately 2%), which implies a similar proportion across these species of unbound drug in plasma available to enter the CNS. CVN424 has high cellular membrane permeability and is not a substrate for various transporter proteins (P-glycoprotein 1 [Pgp], breast cancer resistance protein [BCRP], or organic-anion-transporting polypeptide [OATP]), so CNS penetration in humans is expected to be similar to that in nonhuman species.

The EC_{50} for influencing motor function in unlesioned rodents ranged from 4 to 13 ng/mL in plasma with predicted CNS receptor occupancy (RO) between 39 to 76%. Supporting this prediction, direct measurement showed that brain Occ_{50} was achieved at plasma concentrations of 6.0±0.9 ng/mL to 7.4 ± 0.9 ng/mL. However, correcting motor impairments in 6-OHDA lesioned rats required 10-fold higher plasma concentrations, likely corresponding to approximately CNS Occ_{90}.

Assuming Parkinson's disease subjects will require a CNS exposure closer to that of 6-OHDA lesioned rats than to that of unlesioned rats, the minimum plasma level for a potentially therapeutic level of drug exposure is predicted to be between approximately 50 ng/mL and 150 ng/mL, corresponding to CSF drug concentrations between 1 ng/mL and 3 ng/mL. Based on observations in the phase 1 study, the low-dose in the present study (50 mg) is expected to yield a steady-state trough plasma drug concentration of approximately 150 ng/mL, corresponding to the minimum potentially therapeutic drug exposure. The high-dose (150 mg) will achieve a higher plasma level, and higher CNS RO, to maximize the likelihood of detecting an efficacy signal.

Importantly, the planned low- and high-dose levels of CVN424 are both within the dose range that has been previously shown to be safe and well-tolerated in healthy volunteers.

In the phase 1 multiple-dosing cohorts, the trough plasma concentration ($C_{min)}$ of CVN424 typically reached steady state by day 4, so trough sample collection on Visit Days 8 and 22 in the present study will adequately measure steady state trough concentrations. The terminal elimination half-life of CVN424 is approximately 33 h. Therefore, with dosing ending on Day 28, sample collection on Day 35 (i.e., washout over approximately 5 half-lives) will be adequate to document substantial elimination of CVN424.

AEs, physical exams, vital signs and weight, ECG findings, and clinical laboratory results are used as safety assessments to determine dose tolerability and dose limiting effects of CVN424. The efficacy of CVN424 in symptomatic treatment of PD will be explored using scales and methods that are standard in studies of this indication. The plasma PK parameters will further elucidate the pharmacology of CVN424 in the intended subject population.

Samples collected for serum/plasma, DNA and/or RNA analysis will be used to evaluate markers (e.g., DNA polymorphisms; RNA expression profile) that may contribute to variability in CVN424 PK, pharmacodynamics, efficacy or safety.

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

If any of the following occur, the Medical Monitor and Sponsor's Responsible Medical Officer will review the relevant data, including unblinded data if deemed necessary, and decide whether it is safe to suspend dosing or continue dosing at either the planned or alternative dose levels or decides to prematurely terminate the study:

1. Four or more subjects receiving CVN424 experience the same type of serious or Medically Significant event deemed related to study drug.
2. Three or more subjects receiving CVN424 experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase.
3. One or more subjects receiving CVN424 experience ALT and/or AST elevations >3 ×ULN in the presence of a total bilirubin increase >2 ×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (i.e., "Hy's Law cases").
4. Two or more subjects receiving CVN424 experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

In addition, the study may be terminated at the discretion of the Sponsor.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SUBJECT POPULATION

Screening for eligible subjects will be performed within 28 days prior to randomization. Subjects may be re-screened if their reason for failing screening is thought to be resolved.

7.1 Inclusion Criteria

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

1. Male or female adult who is 30 to 80 years of age inclusive at study entry.
2. Has idiopathic Parkinson's disease, Hoehn and Yahr stages 2-4, and is on a stable dosage of levodopa. (Stable is defined as a dosage unchanged in the 30 days prior to randomization and, in the opinion of the investigator, able to continue the current regimen throughout the month-long study without undue inconvenience or harm.)
3. Experiences an average of at least 2 h total OFF time/day, and at least 1 h each day, per Patient Motor Diary over 2 days during the Screening assessment.
4. The subject signs and dates a written informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures.

7.2 Exclusion Criteria

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

1. Has atypical parkinsonism, severe disabling dyskinesia, or severe motor fluctuations that the investigator considers likely to interfere with study participation or assessments, or history of implant for Deep Brain Stimulation.
2. Poor concordance (<75%) of self-report with site rater on in-clinic Screening period Patient Motor Diary. Subjects with low concordance may be retested after further instruction, at investigator's discretion.
3. Screening period Patient Motor Diary scored at-home over 48 h demonstrates unacceptable quality of the diary, with more than 4 errors per day. (Assistance from caregivers is permitted if they also will be providing assistance with home Patient Motor Diary entries for Day 15 and 27 efficacy assessments.) Subject with more than 4 errors per day may be retested after further instruction, at investigator's discretion.
4. Body mass index (BMI) at Screening <18.0 or >35.0 kg/m^2, inclusive.
5. Subject has evidence of clinically significant (CS) neurologic or other disorder or impairment that, in opinion of Investigator, is reasonably expected to impact the ability of the subject to participate or to confound the study results.
6. Subject has 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].

7. Subject has 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.
8. Has a history of human immunodeficiency virus (HIV) infection.
9. Subject has 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.
10. Subject has a resting heart rate outside the range 50 to 100 bpm, confirmed with up to two repeat tests, at the Screening Visit.
11. Positive urine result for illegal drugs (except cannabis) at Screening, or history of illegal drug use (except cannabis) or alcohol abuse within 1 year prior to the Screening Visit.
12. Subject has 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.
13. Subject has, within the prior month, ingested any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table as listed in Table 2: Excluded Medications and Dietary Products.
14. Male subjects who do not agree to all the following rules: when sexually active with female partner(s) of childbearing potential during the study and for 12 weeks after the last dose of study drug: a) use an acceptable method of birth control (condom with spermicide or surgical sterilization) and b) refrain from sexual activity with female partners who do not use an acceptable method of birth control. Barrier contraception (condom with spermicide) must be used by all male subjects who were not surgically sterilized at least 90 days prior to screening. Male subjects must also agree to refrain from sperm donation during the study and until 12 weeks after the last dose of study drug.
15. Female subjects who are pregnant or breastfeeding or plan to become pregnant or donate ova during the study or for 30 days after the last dose of study drug. WOCBP also must be practicing an adequate method of birth control (e.g., oral or parenteral contraceptives, intrauterine device, barrier, abstinence).

*Definitions and acceptable methods of contraception are defined in Section 9.1.9, Contraception and Pregnancy Avoidance Procedure, and reporting responsibilities are defined in Section 9.1.10, Pregnancy.

16. Risk of suicide according to the investigator's clinical judgment or has made a suicide attempt in the previous 3 years.
17. Subject is a study site employee or an immediate family member of a study site employee.

7.3 Excluded Medications 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.

Table 2 Prohibited Medications and Dietary Products

Within 28 days prior to randomization
Nutraceuticals (e.g., St. John's wort, ginseng, kava, ginkgo biloba, Chinese herbs, and melatonin)
Known strong inhibitors/inducers of cytochrome P-450 3A4/5, including rifampin, clarithromycin, ketoconazole, itraconazole

The following medications are not prohibited prior to or during the study, but should only be used if medically necessary because they may (theoretically) diminish CVN424 bioavailability:

- Proton pump inhibitors (e.g., omeprazole, pantoprazole, lansoprazole)
- Histamine H2-receptor antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine)
- Antacids taken within 4 hours of dosing.

All concomitant medications, including proton pump inhibitors and H2-receptor antagonists, will be documented. Subjects will be instructed not to take any new medications without first consulting with the Investigator or their delegate.

7.4 Diet and Fluid Control

CVN424 suspension (10 mL) will be administered with approximately 120-240 mL (one-half to one cup) of water. Diet and fluid intake are not otherwise specified by protocol and may be consumed ad libitum per subject's routine.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The following represent criteria that require discontinuation of study drug and/or withdrawal from the study. The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the electronic case report form (eCRF). For screen failure subjects, refer to Section 9.1.15.

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

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

- ALT or AST >8 × ULN, or
- ALT or AST >5 × ULN and persists for more than 2 weeks, or
- ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or
- ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: 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).
5. The sponsor, IRB, IEC, or regulatory agency terminates the study.

   Additionally, the Investigator should consider discontinuation of study drug and/or withdrawal from the study for subjects with a major protocol deviation, including violation of protocol entry criteria, such that continuation on study poses an unacceptable risk to the subject's health or to the study's scientific objectives.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

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

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the terms "study medication", "study drug", and "investigational drug" refer to CVN424 and/or matching placebo. Study drug will be supplied to sites in bottles with contents and label individualized per randomization assignment.

8.1.1.1 Investigational Drug

CVN424 and Matching Placebo

CVN424 drug substance is manufactured at Aptuit or Pharmaron.

The oral suspension drug products 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. The placebo does not contain CVN424 drug substance, and is comprised of the same suspending liquid plus calcium carbonate, an insoluble excipient safe to humans (it is the main ingredient in the antacid brand, Tums®) and included to match the appearance of the active drug suspension. CVN424 oral suspension is supplied to the clinical sites in bottles with contents and label individualized per randomization assignment.

8.1.2 Drug Storage

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

CVN424 oral suspension and matching placebo must be stored at 2°C-8°C (35.6°F-46.4°F); storage in subject's home refrigerator is permitted for their individual weekly drug supply. CVN424 oral suspension is stable for 2 weeks under refrigeration, and at room temperature for up to 24 h.

8.1.3 Dose and Regimen

Prior to treatment initiation, the investigator or investigator's designee will instruct each subject (and their home caregiver, where applicable) on dosing procedures, and observe the subject in a practice (i.e., unblinded placebo) self-administration to confirm the subject can properly self-administer the study drug at home.

The planned study arms and dose levels are provided in Table 3.

Table 3 Planned Study Arms and Dose Levels by Cohort

Study Arm	Planned Treatment*	No. of Subjects
Low-dose	CVN424 50 mg per day	40
High-dose	CVN424 150 mg per day	40
Placebo	Placebo	40

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

8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 9.5, PTEs and AEs.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 9.6.2, Collection and Reporting of SAEs.

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Study drug will be dispensed to subjects as a suspension in properly labeled, capped amber colored bottles. The suspension must be stored refrigerated (2-8°C) until use. If properly refrigerated, the suspension is stable for up to 14 days. At room temperature, the suspension is stable for up to 24 h.

Study drug may settle. Shake well before using to ensure complete resuspension.

8.3 Randomization Code Creation and Storage

Randomization assignments will be generated using an online interactive response system. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, prior to unblinding. After unblinding, no change should be made to any previously recorded assessment of the subject.

For unblinding a subject, requests can be initiated by contacting the Medical Monitor.

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

If an unblinded AE assessment raises concern for potential risks to this or other study subjects, the Sponsor in consultation with the Investigator and the Medical/Safety monitor will review available unblinded data and will decide whether it is appropriate for the subject to discontinue study treatment and/or withdraw from study, and whether changes to study design are necessary to protect the safety of other subjects.

The randomization schedule for all subjects will be released for analysis after the database is locked.

8.5 Accountability and Destruction of Sponsor-Supplied Drugs

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

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list, ensure the quantity is correct, and the medication is received within the labeled storage conditions. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment per instructions provided on the form. If there are discrepancies between the packing list versus 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 his or her 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 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 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. (For participating subjects receiving study medication, their ID number should substitute for initials.) The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Subjects will return their bottles of study medication, whether empty or unused, at weekly study visits. The investigator or designee must record the number of empty and unused bottles returned.

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

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

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

The requirements of the ICF are described in Section 14.2.

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

9.1.1.1 Pharmacogenomic Informed Consent Procedure

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

The pharmacogenomic sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

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

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

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

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes, including fundoscopy; (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 PTE/AE eCRF described in Section 9.6.

9.1.4 Weight, Height, and BMI

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

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

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

Results for BMI will be expressed with 1 decimal place and rounding is not allowed.

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

Vital signs will include oral temperature, respiration, heart rate, and blood pressure and be collected at timepoints specified in the Schedule of Study Procedures (Appendix A). Heart rate and blood pressure will be measured after at least 5 minutes supine and (when orthostatic vital signs are specified) again after 2 minutes standing.

Vital signs should be measured at the same time 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 subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of ICF through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at 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 Procedures for Clinical Laboratory Samples

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

Table 4 lists the tests that may be performed for each collected specimen.

Table 4 Clinical Laboratory Tests

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

Diagnostic Screening in Serum	Diagnostic Screening in Urine/ Blood
Serum hCG (a) FSH (b)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, alcohol, and cotinine (c) Urine hCG

FT4= free T4, FSH= follicle-stimulating hormone, GGT=γ-glutamyl transferase, hCG= human chorionic gonadotropin, RBC=red blood cells, TSH= thyrotropin, WBC=white blood cells.
(a) Serum hCG pregnancy test will be done at Screening in women subjects.
(b) FSH level will be obtained for female subjects at Screening if they are postmenopausal (i.e., last regular menstrual cycle >2 years) and not surgically sterile. The result must be >40 IU/L for the subject to be enrolled.

The central laboratory will perform all clinical laboratory tests per Appendix A. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Additional laboratory or diagnostic testing may be performed by accredited laboratories as needed to ensure subject safety, per Investigator discretion. 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 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.

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

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

(Please refer to Section 7.4 for discontinuation criteria, and Section 9.6.3 for the appropriate guidance on Reporting of Abnormal LFT in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN).

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 9.6.3 Reporting of Abnormal LFT for reporting requirements).

9.1.9 Contraception and Pregnancy Avoidance Procedure

From date of signing of ICF, throughout the duration of the study, and for 30 days after last dose of study medication, females of childbearing potential* must use acceptable method(s) of contraception; nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use acceptable method(s) of contraception throughout the duration of the study, and for 12 weeks after last dose of study medication. In addition, males must be advised not to donate sperm during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 2 years since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

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

Acceptable methods of contraception in this study include:

- Abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. If heterosexual intercourse does occur, an acceptable method of birth control is required.
- Surgical sterilization or postmenopausal
- Condom, diaphragm, or cervical cap with spermicide
- Hormonal contraception, including oral, injectable, transdermal, or implantable methods
- Intrauterine device (IUD)

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

9.1.10 Pregnancy

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

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 12 weeks after the last dose, should also be recorded following authorization from the subject's partner.

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

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

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

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

9.1.11 ECG Procedure

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

When an ECG is scheduled at the same time as blood draws or vital signs then the blood draws and vital signs will take priority and the ECG will be obtained before or after the scheduled blood draw/vital sign assessment.

ECG recordings will be obtained in a supine position following an approximate 10-minute period of rest. Should technical difficulties occur during 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 at the central ECG lab. 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.

9.1.12 Pharmacogenomic Sample Collection

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

One whole blood sample for DNA isolation and genotyping will be collected at time points specified in the Schedule of Study Procedures (Appendix A) and stored under frozen conditions. In addition, whole blood samples will be collected at time points specified in the Schedule of Study Procedures (Appendix A) for ribonucleic acid (RNA) pharmacogenomic analysis.

Specific purposes of this pharmacogenomic study include:

- Identifying genetic reasons why certain people respond differently to CVN424
- Finding out more information about how CVN424 works
- Generating information needed for research, development, and regulatory approval of tests to predict response to CVN424
- Identifying variations in genes related to the biological target of CVN424

This information may be used, for example, to develop a better understanding of the safety and efficacy of CVN424 and other study medications, and for improving the efficiency, design and study methods of future research studies.

The samples will be stored for no longer than 15 years after completion of the CVN424 study and/or until the drug development of CVN424 is no longer actively pursued by the sponsor or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from the sponsor. “Stored samples” in this context are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drug.

The sampling of whole blood for pharmacogenomic and genotyping analysis is mandatory; every subject must sign the ICF in order to participate in this study. Blood serum/plasma, DNA and/or RNA samples can be used to identify markers (e.g., potential metabolites, or drug metabolic enzyme and transporter polymorphisms) that may contribute to the variability in CVN424 PK, pharmacodynamics, or safety. Also, since pharmacogenomics is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

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

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

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with the subject identification number.

9.1.13 PK Sample Collection

9.1.13.1 Collection of Blood for PK Sampling

Blood samples (one sample per scheduled time) for analysis of CVN424 plasma concentrations will be collected into chilled Vacutainers containing K_2EDTA according to the schedules in Table 5 and Appendix A.

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

Serial blood samples for determination of CVN424 concentrations in plasma will be collected according to Table 5.

Table 5 Collection of Blood Plasma Samples for PK Analysis

Study Day	Time Post-dose (hours).
1, 8	Pre-dose and at 3 h post-dose
15, 27	Post-dose (time not specified)
22	Pre-dose and at 1, 1.5, 2, 4, and 6 h post-dose
35	Washout (time not specified)

The PK samples will be collected at the nominal time point within the allowable windows per Table 8. The actual time of sample collection will be recorded on the source document and eCRF.

Placebo samples will not be analyzed by the bioanalytical laboratory except 2 samples per subject receiving placebo, 1 following first-dose (i.e., 3 h post-dose) and 1 at the Day 27 visit to ensure from a safety perspective that no additional subjects could have been on active treatment.

9.1.13.2 Bioanalytical Methods

Plasma concentrations of CVN424 will be measured by high-performance liquid chromatography with tandem mass spectrometry or an alternative method of comparable sensitivity and specificity.

Plasma samples will be archived to support potential post hoc laboratory testing (e.g., biomarkers, potential characterization of unknown CVN424 metabolites).

9.1.14 PK Parameters

PK parameters of CVN424 will be derived using non-compartmental analysis methods from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters (Table 6) will be determined from concentrations of CVN424 in plasma:

Table 6 Pharmacokinetic Parameters

Symbol/Term	Definition
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty}=AUC_t+C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration.
AUC_6	Area under the plasma concentration-time curve from time 0 to 24 hours, calculated using the linear trapezoidal rule.
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration, calculated as Dose/AUC_{∞} after a single dose.
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.

Additional plasma PK parameters may be calculated, including analyses by gender (if possible).

9.1.15 Documentation of Screen Failure

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

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

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

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

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

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

9.1.16 Documentation of Randomization

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

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

9.2 Monitoring Subject Treatment Compliance

Study medication will first be administered (on Day 1) while subjects are under observation at the investigative site. Subsequent doses will be self-administered at home, or at the investigative site on selected Study Visit days. The date and time of each observed dose will be recorded in the source documents and on the eCRFs.

At each weekly visit, subjects will return to the site all study medication bottles, whether empty or full, for assessment of treatment compliance.

An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent.

9.3 Schedule of Observations and Procedures

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

9.3.1 Observations and Procedures

9.3.1.1 Screening

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

Subjects who have passed initial Screening procedures (Appendix A) will receive standardized instruction in how to complete the Patient Motor Diary (i.e., Hauser diary). After training, subjects and a skilled rater will complete Patient Motor Diary entries for at least 4 consecutive half-hour periods during a screening visit. The concordance testing session must include at least one ON and one OFF period; the test session will extend for up to 4 additional 30 min. periods until there is at least one in each state. Concordance must reach acceptance criterion (75%) for study eligibility.

Following a successful concordance test and prior to randomization, subjects must complete the Patient Motor Diary at home over 2 days and demonstrate (a) acceptable quality of the diary, with no more than 4 errors per day); and (b) average daily OFF time of at least 2 h and not one day below 1.0 h.

9.3.1.2 Study Visit, Baseline and Randomization (Day 0)

All eligible subjects who are being enrolled will present to their local site for a Baseline and Randomization visit. Baseline efficacy and safety assessments will be performed, including (but not limited to) UPDRS, CGI, PGI, Questionnaire for Impulsive-Compulsive Disorders (QUIP).

Following baseline assessments, subjects' treatment assignment will be randomized using the online interactive response system.

Arrangements will be made for the subject to attend their Day 1 visit.

9.3.1.3 Study Visit, Day 1

A urine hCG pregnancy test will be performed for female subjects of childbearing potential; pregnant women must not receive study drug.

The first dose of study drug (CVN424 or placebo) will be administered under direction of site personnel. Subjects not randomized to placebo will initiate treatment with 50 mg CVN424. Vital signs will be assessed hourly through at least 3 h post-dose. Orthostatic vital signs (non-triplicate) will be recorded pre-dose and at 3 h post-dose. Triplicate ECG will be obtained prior to dosing and approximately 3 h post-dose. Additional monitoring of vital signs and ECGs may continue beyond 3 h post-dose at the discretion of the Investigator.

Investigator or their delegate will manage incident AEs according to their medical judgment. The first dose of CVN424 may elicit an increase in body temperature and heart rate lasting several hours. These signs can be expected to spontaneously resolve within 24 h post-dose, and to lessen with repeated dosing. Antipyretic medication (e.g., Acetaminophen Extended Release Caplets, 650 mg) can be administered for symptomatic relief of fever.

A blood sample for PK analysis will be collected pre-dose and at 3 h post-dose, according to Table 5.

Subjects will be given a 10 day supply of study drug (as suspension in amber colored bottles) to be taken home and stored under refrigeration until use. Study drug will be self-administered each morning through Day 27 ±1 day.

9.3.1.4 Study Visit, Day 8 ±2 days

All subjects will present to their local site on Day 8 ±2 days, returning to the site all bottles of study medication, whether empty or unused.

Subjects will <u>not take study drug at home on the morning of the Day 8 Study Visit</u>. Administration of the daily dose of study drug will be deferred until <u>after</u> collection of a blood sample for determination of the study drug "trough" concentration.

Beginning on Visit Day 8, the high-dose cohort will increase their dosage to 150 mg CVN424 per day. This step-wise increase is intended to limit the changes that the first dose of 150 mg CVN424 may elicit in vital signs (notably, increased temperature and heart rate, which were dose-dependent and not clinically significant in a healthy volunteer study). The low-dose arm will continue to receive 50 mg per day.

Vital signs will be assessed hourly through at least 3 h post-dose. Orthostatic vital signs (non-triplicate) will be recorded pre-dose and at 3 h post-dose. Triplicate ECG will be obtained prior to dosing and approximately 3 h post-dose. Investigator or their delegate will manage incident AEs according to their medical judgment. Additional monitoring of vital signs and ECGs may continue beyond 3 h post-dose at the discretion of the Investigator.

A blood sample for PK analysis will be collected pre-dose and at 3 h post-dose, according to Table 5. During blood sampling, one additional tube of blood plasma will be collected for archiving (frozen storage) to support potential post hoc laboratory testing (e.g., biomarkers, potential characterization of unknown CVN424 metabolites).

After safety assessments, subjects will be given a 10 day supply of study drug to be taken home and stored under refrigeration until use.

9.3.1.5 Study Visit, Day 15 ±2 days

All subjects will present to their local site on Day 15 ±2 days, returning to the site all bottles of study medication, whether empty or unused.

Each subject will have completed a Patient Motor Diary recording their capabilities, limitations and motor symptoms over the prior 2 days (e.g., Days 13 and 14). Site will conduct assessments to complete the UPDRS, PGI, CGI, Epworth Sleepiness Scale, and Questionnaire for Impulsive-Compulsive Disorders. An untimed sample will be collected for PK analysis.

After safety assessments, subjects will be given a 10 day supply of study drug to be taken home and stored under refrigeration until use.

9.3.1.6 Study Visit, Day 22 ±2 days

All subjects will present to their local site on Day 22 ±2 days, returning to the site all bottles of study medication, whether empty or unused (time not specified).

Subjects will not take study drug at home on the morning of the Day 22 Study Visit. Administration of the daily dose of study drug will be deferred until after collection of a blood sample for determination of the study drug "trough" concentration. Following observed dosing, serial blood plasma samples will be collected for PK analysis according to the schedule in Table 5.

After safety assessments, subjects will be given a supply of study drug sufficient to last through dosing Day 27 ±1 day to be taken home and stored under refrigeration until use.

9.3.1.7 Study Visit, Day 27 ±1 day

All subjects will present to their local site on Day 27 ±1 day, returning to the site all bottles of study medication, whether empty or unused.

An untimed blood sample for PK analysis will be collected.

All subjects will have completed a Patient Motor Diary recording their capabilities, limitations and motor symptoms over the prior 2 days (e.g., Days 25 and 26). Site will conduct assessments to

complete the UPDRS. PGI, CGI, Epworth Sleepiness Scale, and Questionnaire for Impulsive-Compulsive Disorders.

9.3.1.8 Final Study Visit, Day 35 ±2 days

All subjects will present to their local site on Day 35 ±2 days. Site will conduct assessments to complete the UPDRS, PGI, CGI, and Epworth Sleepiness Scale, as well as safety assessments. An untimed sample will be collected for PK analysis. The investigator must complete the End of Study eCRF page.

Subjects who have abnormal, clinically significant (CS) findings at the Final Study Visit may be asked, per investigator's discretion, to return to the clinic subsequently to ensure appropriate safety follow-up.

9.3.2 Early Termination

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

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

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12, Pharmacogenomic Sample Collection. After extraction and purification, the genetic material will be preserved and retained at a biorepository selected by the sponsor for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is 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 personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

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

9.5 Definitions

9.5.1 PTE

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

9.5.2 AE

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

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

9.5.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be CS (i.e., if some action or intervention is required). 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 result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE

Pre-existing conditions:

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

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…")
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…")

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

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

9.5.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.

- The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe

3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization
- Includes any event or synonym described in the Medically Significant AE List (Table 7)

Table 7 Medically Significant AE List

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

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 9.6.2 and 9.7).

9.5.5 Severity of PTEs and AEs

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

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

9.5.6 Causality of AEs

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

Related:	An AE that follows a reasonable temporal sequence from 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 administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

9.5.7 Relationship to Study Procedures

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

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

9.5.8 Start Date

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

9.5.9 Stop Date

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

9.5.10 Frequency

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

9.5.11 Action Concerning Study Medication

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

9.5.12 Outcome

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

- Unknown – the course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study

9.6 Procedures

9.6.1 Collection and Reporting of AEs

9.6.1.1 PTE and AE Collection Period

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

Collection of AEs will commence from the time that the subject is first administered study medication Day 1. Collection of AEs will continue until 14 days following last dose. Ascertainment of AEs with onset or worsening after the Final Study Visit on Day 35 and within 14 days of last dose will rely on spontaneous reporting by the subject or caregiver.

9.6.1.2 PTE and AE Reporting

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

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

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

7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

9.6.2 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 h of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

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

The SAE form should be transmitted within 24 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.

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

9.6.3 Reporting of Abnormal LFT

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 9.6.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed.

9.7 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 h 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.

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as 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 where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

10.0 STUDY-SPECIFIC COMMITTEES

None.

(Review of incident and cumulative safety data and findings during study is the responsibility of the Medical Monitor and sponsor's Responsible Medical Officer.)

11.0 DATA HANDLING AND RECORDKEEPING

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

11.1 CRFs (Electronic)

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

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

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

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

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

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure 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 written permission of the sponsor.

11.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved,

until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

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

12.0 STATISTICAL METHODS

12.1 Statistical and Analytical Plans

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

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

12.1.1 Analysis Sets

Safety Set

The Safety Analysis Set will consist of all subjects who enrolled and received at least 1 dose of study drug, classified according to the treatment they actually received. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

Efficacy Set

The primary Efficacy Analysis set will consist of all subjects who were eligible, randomized, and received at least one dose of study drug, classified according to the treatment actually received. Secondary tests of efficacy will assess subjects who were eligible, randomized, and judged compliant with treatment and follow-up as classified prior to breaking the blind. The former is less stringent than a formal intent-to-treatment sample but estimates the efficacy one might expect among subjects who start using CVN424 at a specified dose, acknowledging that some will be intolerant or non-compliant. The latter estimates the maximal efficacy, the efficacy one might expect among subjects who are tolerant of and compliant with treatment. Subjects in this analysis set will be used for efficacy analyses.

PK Set

The PK set will consist of all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma concentration. Subjects in this analysis set will be used for analysis of pharmacodynamics.

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

12.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics (N, mean, SD [standard deviation], median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for placebo, each CVN424 dose level, CVN424 overall, and overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (gender, ethnicity, and race) will be tabulated for placebo, each CVN424

dose level, CVN424 overall, and overall. Individual subject demographic and baseline characteristics data will be listed.

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

12.1.3 PK Analysis

The concentration of CVN424 in plasma will be summarized by dose over each scheduled sampling time using descriptive statistics. Individual plasma concentration data versus time will be presented in a data listing.

PK parameters of CVN424 will be derived using non-compartmental analysis methods from the concentration-time data for all subjects in the PK set. 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
AUC_∞	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_\infty=AUC_t+C_{last}/\lambda_z$, where C_{last} is the last quantifiable concentration.
AUC_6	Area under the plasma concentration-time curve from time 0 to 6 hours, calculated using the linear trapezoidal rule.
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration, calculated as Dose/AUC_∞ after a single dose.
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.

Additional plasma PK parameters may be calculated, including analyses by gender (if possible). Descriptive statistics (arithmetic mean, SD, median, minimum and maximum) will be used to summarize most plasma (PK) parameters for CVN424. Geometric mean and coefficient of variation will be computed for right-skewed measures, e.g., C_{max} and AUCs. Plots of C_{max} and AUCs versus doses will be generated.

Pharmacodynamic analyses will investigate the possible relationship between CVN424 PK parameters and efficacy and safety outcomes. Population analysis of results may be considered. Details of planned PK analyses will be presented in the SAP.

12.1.4 Safety Analysis

12.1.4.1 AEs

All AEs will be coded by System Organ Class and Preferred Term 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 placebo, each CVN424 dose level and CVN424 overall by System Organ Class and Preferred Term. 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. Subgroup analyses will examine AEs among subjects categorized by selected demographic and disease characteristics. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs. All AEs will be listed.

12.1.4.2 Clinical Laboratory Evaluation

Individual results of laboratory tests from hematology, chemistry, urinalysis, and endocrine panels that are abnormal and CS will be summarized and listed. Observed values and change from baseline to post-dose laboratory data will be summarized for placebo, each CVN424 dose level and CVN424 overall. All clinical laboratory data will be listed.

12.1.4.3 Vital Signs

Individual results of vital signs that are abnormal and CS will be summarized and listed. Observed values and changes from Baseline in vital sign measurements will be summarized by placebo, each CVN424 dose level and CVN424 overall. All vital sign data will be provided in the data listings.

12.1.4.4 ECGs

Individual results of quantitative ECG parameters from the 12-lead safety ECGs that are abnormal and CS will be summarized and listed. Observed values and changes from baseline in quantitative ECG parameters will be summarized by placebo, 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 above groups. All ECG data will be provided in the data listings.

12.1.4.5 Other Variables

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

12.1.5 Efficacy Analysis

Serial assessments of average daily hours of OFF time as recorded in the Patient Motor Diary over the two days prior to each visit will be analyzed using mixed model for repeated measures (MMRM). The model will include fixed terms for treatment, visit, treatment x visit interaction and baseline measurement with subject-level unstructured covariance among repeated measurements. Other covariance structures may be used in case the model does not converge using unstructured

covariance structure. Additional covariates may be included based on review prior to breaking the blind. Two co-primary estimands of efficacy will estimate treatment-dependent difference in change from baseline to Day 27, one for each active dose vs. placebo, and will be tested using linear contrasts of least-square means. Each co-primary comparison will test for significance at one-tailed $p < 0.1$ to control the overall type 1 error rate at 20% based on Dunnett's method for comparing two treatments to the same control. Additional contrasts will be used to test for a dose-dependent effect of treatment and to estimate dosage-dependent differences in change from baseline at all other visits. Additional and exploratory efficacy endpoints will be analyzed in the same model and using the same estimands.

Responder analysis will ascertain the incidence of clinically significant improvement.

Subgroup analyses will ascertain the potential impact on efficacy of subgroup variables reflecting various demographic and disease-related characteristics.

12.2 Interim Analysis and Criteria for Early Termination

A futility analysis may be conducted once at least 50 patients have completed their Day 27 assessments. The focus of this unblinded analysis will be to assess the change from baseline in 2-day average OFF time at Day 27 as recorded in the Patient Motor Diary. Analysis of safety events and additional endpoints may be included. The analysis will be conducted by a biostatistician of the CRO who is not otherwise involved with the conduct of the study. Investigators, their study staff, patients, CRO team members, and the Sponsor will remain blinded. The outcomes of this analysis will include a recommendation to the Sponsor to:

1. Continue the study as planned; or
2. Discontinue randomization into one active treatment arm because of futility; or
3. Discontinue the study because of futility on both active treatment arms

The futility analysis will be described in the SAP.

12.3 Determination of Sample Size

The safety and tolerability of single- and repeated (7 daily) administration of CVN424, including doses higher than in the present study, were previously demonstrated in a study with 64 healthy volunteers. The target sample size of 45 subjects per treatment arm (total N=135) is considered to be sufficient for the preliminary evaluation of CVN424 safety, tolerability, and efficacy in a PD population. The study will have 90% power to detect at least one instance of any TEAE with an expected incidence of 0.10 per participant exposed at a given dosage of CVN424.

When the true effect of both dosages is zero, the study will have an 80% probability of declaring neither dosage of CVN424 significantly better than placebo at reducing OFF time based on the one-tailed $p < 0.1$ criterion, allowing 20% non-evaluable (e.g., loss to follow-up, incomplete data) and assuming a SD of 3 h for the change in OFF time from baseline to 27 days. When the true effect of a dosage is a reduction in average OFF time of at least 1.5 h, the study will have an 80% probability of declaring that dosage of CVN424 significant based on the one-tailed $p < 0.1$ criterion. By this construction, the study has 80% power to detect whether CVN424 does not reduce OFF time and

80% power to detect whether CVN424 at one or both of the two dosages tested reduces OFF time by at least 1.5 h.

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study-Site Monitoring Visits

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

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

13.2 Protocol Deviations

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

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

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 8 defines the windows allowed for sample collections.

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

Table 8 Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
Pre-dose	Pre-dose (0 h)
±5	immediately post-dose to ≤6 h
±15	>6 h to ≤12 h post-dose
±60	>12 h post-dose

13.3 Quality Assurance Audits and Regulatory Agency Inspections

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

14.0 ETHICAL ASPECTS OF THE STUDY

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

14.1 IRB and/or IEC Approval

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

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

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

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

14.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the 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 or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

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

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

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

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

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

14.3 Subject Confidentiality

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

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

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

14.4 Publication, Disclosure, and Clinical Trial Registration Policy

14.4.1 Publication and Disclosure

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

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

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

14.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, the sponsor will register this clinical trial on

ClinicalTrials.gov (and possibly on other publicly accessible websites) within 21 days after the first participant is consented.

Sponsor contact information, along with investigator's city, state (for North American investigators), country, and recruiting status will be registered and available for public viewing. For some registries, sponsor will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to callers requesting trial information. Once subjects receive investigator contact information, they may call the site and request enrollment into the trial. The investigative sites are encouraged to handle such trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to sponsor providing their contact information to callers must provide sponsor with a written notice requesting that their information not be listed on the registry site.

14.4.3 Clinical Trial Results Disclosure

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

14.5 Insurance and Compensation for Injury

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

15.0 REFERENCES

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Appendix A: Schedule of Study Procedures

Visit Number	**SCREENING**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Early Termination**
Study Day:	**Days -28 to -1**	**Days -2 & -1**	**Day 0**	**Day 1**	**Day 8 ±2 days**	**Day 15 ±2 days**	**Day 22 ±2 days**	**Day 27 ±1 day**	**Day 35 ±2 days**	
Informed consent	X (a)									
Inclusion/exclusion criteria	X									
Demographics	X (a)									
Medical history	X(a)									
Concurrent medical conditions	X (a)									
Medication history	X (a)									
Vital signs and weight (b)	X (a)		X	X	X	X	X	X	X	X
Physical examination	X (a)		X		X			X	X	X
Height and BMI	X (a)							X	X	X
Clinical laboratory tests (c)	X (a)		X	X	X			X	X	X
Screening laboratory tests (d)	X (a)									
Patient Motor Diary (Hauser diary) (e)	X	X				X		X		
Concomitant medications	X		X	X	X	X	X	X	X	X
ECG (f)	X (a)			X	X			X	X	X
Randomization			X							
Study drug dosing (g)				< -	-	-	-	- >		
DNA sample collection (h)			X							
RNA collection (i)				X						
PK blood collection (j)				X	X (k)	X	X	X	X	X
PTE assessment (l)	X		X	X						
AE assessment (m)			X	X	X	X	X	X	X	X
Study drug accountability					X	X	X	X	X	X
Unified Parkinson's Disease Rating Scale (UPDRS)			X			X		X	X	X
CGI			X			X		X	X	X
PGI			X			X		X	X	X

Visit Number	**SCREENING**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Early Term-ination**
Study Day:	**Days -28 to -1**	**Days -2 & -1**	**Day 0**	**Day 1**	**Day 8 ±2 days**	**Day 15 ±2 days**	**Day 22 ±2 days**	**Day 27 ±1 day**	**Day 35 ±2 days**	
Epworth Sleepiness Scale			X			X		X	X	X
Questionnaire for Impulsive-Compulsive Disorders (QUIP)			X			X		X		X
Beck Depression Inventory			X					X		X

(a) Initial Screening items, to be completed prior to other Screening assessments. Screening activities must occur within 28 days of randomization,but may be completed in fewer than 28 days. Screening days are nominally called Day -28 to Day -1,but will not necessarily correspond numerically to the calendar days prior to the Baseline Visit. By the same convention, the Patient Motor Diary will be recorded at home over 2 consecutive days during screening, but not necessarily on the 2 days immediately prior to the Baseline visit (Day 0).

(b) Vital signs (oral temperature, respiration, heart rate, and blood pressure) and weight will be recorded at Screening, Baseline, Day 1, and at subsequent Study Visits. On Day 1 and Day 8, the assessments will be conducted pre-dose [within 90 minutes prior to dosing], and at least hourly through 3 h post-dose. Triplicate orthostatic vital signs (blood pressure and heart rate) will be recorded 15 minutes apart at baseline. Orthostatic vital signs (non-triplicate) will be recorded pre-dose and at 3 h post-dose on Days 1 and 8. Orthostatic vital signs will be measured after at least 5 minutes supine and again at 2 minutes after standing at each scheduled orthostatic timepoint.

(c) Clinical laboratory tests (hematology, serum chemistry, urinalysis, and endocrine) will be collected at Screening, Baseline, Day 8, Day 27, Day 35, and Early Termination (if applicable) visits. Urine hCG pregnancy test will be performed on female subjects of childbearing potential on Day 1 prior to dosing.

(d) Screening laboratory testing will include all items included under 'Clinical Laboratory Tests" plus urine drug & cotinine screen, and for female subjects a serum pregnancy test (hCG). An FSH level will be obtained on post-menopausal women (defined as continuous amenorrhea of at least 2 years and not surgically sterile). One additional tube for plasma and one for serum will be collected for archiving (frozen storage) to support potential post hoc laboratory testing.

(e) Subjects will receive standardized instruction in how to complete the Patient Motor Diary (Hauser diary). After training, subjects who have passed initial Screening procedures will complete Patient Motor Diary entries for 4 consecutive 30-minute periods during a screening visit while observed and scored by a skilled rater. The concordance testing session must include at least one ON and one OFF period; the test session will extend for up to 4 additional 30 min. periods until there is at least one in each state. Concordance must be within 75% for subject eligibility.
Following a successful concordance test and prior to randomization, subjects must complete the Patient Motor Diary at home over 48 h and demonstrate both an acceptable quality of the diary, with no more than 4 errors per day, and average daily OFF time of at least 2 h and not one day below 1.0 h.
In advance of Study Visits on Day 15 and 27, subjects will complete Diary entries recording their capabilities, limitations and motor symptoms over the prior 2 days (e.g., Days 13 and 14, or Days 25 and 26).

(f) Triplicate standard 12-lead ECG will be recorded at Screening and on Days 1 and 8 pre-dose [within 1 h prior to dosing] and 3 h (+/- 15 minutes) post-dose. Triplicate standard 12-lead ECG will also be recorded at screening and on Day 27, Day 35 and Early Termination (if applicable).

(g) Upon randomization, the first dose of study drug will be administered under direction of site personnel. Near the conclusion of the Day 1 visit and subsequent weekly visits, subjects will be given a supply of study drug (as suspension in amber colored bottles) to be taken home and stored under refrigeration until use. Study drug will be self-administered each morning on days 2-28. However, for scheduled Study Visits on or around day 22, dosing must be deferred until after collection of a blood sample for determination of the study drug "trough" concentration.

(h) One blood sample will be collected for pharmacogenomic analysis at baseline; this will only be collected once per

subject.

(i) A whole blood sample will be collected pre-dose and 3 h post-dose on Day 1 for RNA pharmacogenomic analysis.
(j) Blood samples for PK analyses will be collected at timepoints indicated in Table 5.
(k) At Day 8 visit, one additional tube of blood plasma will be collected for archiving (frozen storage) to support potential post hoc laboratory testing (e.g., biomarkers, potential characterization of unknown CVN424 metabolites).
(l) PTEs will be collected from signing of informed consent up until dosing on Day 1.
(m) Any AE with onset or exacerbation after dosing on Day 1 will be captured as an AE.

Appendix B: Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on Investigators by the FDA are summarized in the "Statement of Investigator" (Form 1572) which must be completed and signed before the Investigator may participate in this study.

The Investigator agrees to assume the following responsibilities by signing a Form 1572.

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50 ICH and local regulations, are met.
8. Obtain valid ICF from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC.
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 to sponsor or destroy all unused sponsor-supplied drugs per sponsor instructions.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 h.

Appendix C: Investigator Consent to Use of Personal Information

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

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