# Title Page

| | | | |
|---|---|---|---|
| **Protocol Title:** | | A Randomized, Double-Blind, Placebo-Controlled Trial of CVN424 in Early Parkinson's Disease | |
| **Protocol Number:** | | CVN424-203 | |
| **Compound:** | | CVN424 | |
| **Indication:** | | Parkinson's Disease | |
| **Study Phase:** | | Phase 2b | |
| **Short Title:** | | Early Parkinson's Disease Monotherapy with CVN424 | |
| **Manufacturer:** | | Patheon, Milton Park, United Kingdom | |
| **Sponsor** | **Sponsor Name:** | Cerevance Beta, Inc. | |
| | **Legal Registered Address:** | One Marina Park Drive Suite 1410<br>Boston, MA 02210<br>United States | |
| **Regulatory Agency Identifier Number(s):** | | **Registry** | **Identifier Number** |
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| | | Amendment 2 (v3.0) | 10 July 2024 |

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# SPONSOR SIGNATORY

**Protocol Number:** CVN424-203

**Protocol Title:**
A Randomized, Double-Blind, Placebo-Controlled Trial of CVN424 in Early Parkinson's Disease

I, the undersigned, have approved of the clinical trial protocol with the date of 10 July 2024.

_____

[redacted], MD

**Medical Officer**

# INVESTIGATOR AGREEMENT

**Protocol Number:** CVN424-203

**Protocol Title:**
A Randomized, Double-Blind, Placebo-Controlled Trial of CVN424 in Early Parkinson's Disease

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in compliance with current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable national, state, and local laws and regulations, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Cerevance Beta, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about Cerevance Beta, Inc., understand this study, and are able to comply.

_____ _____

Principal Investigator Name (printed) Signature

_____

Date

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# List of Abbreviations

| | |
|---|---|
| ADL | Activities of Daily Living |
| AE(s) | adverse event(s) |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| $AUC_{(0-x)}$ | area under the plasma concentration-time curve from time 0 to x; where x = 6 hours or 96 hours |
| AV | atrioventricular |
| β-HCG | beta human chorionic gonadotropin |
| BDI | Beck Depression Inventory |
| CBD | cannabidiol |
| CFR | Code of Federal Regulations |
| CGI | Clinical Global Impression |
| CGI-S | Clinical Global Impression of Severity Scale |
| CIOMS | Council for International Organizations of Medical Sciences |
| CI | confidence interval |
| $C_{max}$ | maximum plasma drug concentration |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CMH | Cochran–Mantel–Haenszel |
| CNS | central nervous system |
| COMT | catechol-O-methyl transferase |
| COVID-19 | coronavirus disease 2019 |
| CS | Compound Symmetry |
| CSTC | cortico-striato thalamo-cortical |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CYP | Cytochrome P450 |
| DET | detection |
| DHTs | Digital Health Technologies |
| EAC | Enrollment Authorization Committee |
| ECG(s) | electrocardiogram(s) |
| eCRF(s) | electronic Case Report Form(s) |
| eGFR | estimated glomerular filtration rate |
| EEG | electroencephalogram |
| ESS | Epworth Sleepiness Scale |
| ET | early termination |
| FDA | (US) Food and Drug Administration |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |

| | |
|---|---|
| GPR6 | G protein-coupled receptor 6 |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDPE | high-density polyethylene |
| HIV | human immunodeficiency virus |
| HPLC-MS/MS | High-Performance Liquid Chromatography – Tandem Mass Spectrometry |
| HRT | hormonal replacement therapy |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IDN | identification |
| IDSSTS | International Digit Symbol Substitution Test – Symbols |
| IEC(s) | Independent Ethics Committee(s) |
| IND | investigational new drug |
| IRB(s) | Institutional Review Board(s) |
| IRT | interactive response technology |
| ISLT | International Shopping List Test |
| ISRL | International Shopping List Test – Delayed Recall |
| ITT | Intention-to-Treat |
| K2EDTA | dipotassium ethylene diamine tetraacetic acid |
| LS | least squares |
| MAOB | Monoamine Oxidase B |
| MAR | Missing at Random |
| MDS-UPDRS | Movement Disorder Society – Unified Parkinson's Disease Rating Scale |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intention-to-Treat |
| MMRM | Mixed Model for Repeated Measures |
| MMSE | Mini-Mental State Examination |
| MNAR | Missing Not at Random |
| MoCA | Montreal Cognitive Assessment |
| MSNs | medium spiny neurons |
| NMSS | Non-Motor Symptoms Scale |
| ONB | One Back |
| PD | Parkinson's Disease |
| PD-PROP™ | Parkinson's Disease Patient Report of Problems |
| PDSS | Parkinson's Disease Sleep Scale |
| PGI | Patient Global Impression |

| | |
|---|---|
| PGI-S | Patient Global Impression of Severity |
| PK | pharmacokinetic(s) |
| PWB-PROP™ | Personal Wellbeing Patient Report of Problems |
| QC | quality control |
| QTcB | QT interval corrected using Bazett's formula |
| QTcF | QT interval corrected using Fridericia's formula |
| RF | radiofrequency |
| SAE(s) | serious adverse event(s) |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SE | standard error |
| SoA | schedule of assessments |
| TEAE(s) | treatment emergent adverse event(s) |
| ULN | upper limit of normal |
| US(A) | United States (of America) |
| WOCBP | woman of childbearing potential |

# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:**
A Randomized, Double-Blind, Placebo-Controlled Trial of CVN424 in Early Parkinson's Disease

**Brief Title:**
Early Parkinson's Disease Monotherapy with CVN424

**Indication:**
Parkinson's Disease

**Rationale:**
This study will examine the potential of CVN424 to improve motor and non-motor functions in individuals with early untreated Parkinson's Disease (PD).

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary** | **Primary Efficacy Endpoint** |
| To determine the effect of CVN424 on motor features of early, untreated subjects with Parkinson's Disease (PD) | Change from Baseline to Week 12 on the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II + Part III (Motor Aspects of Experiences of Daily Living + Motor Examination) between CVN424 150 mg and placebo |
| **Secondary** | **Secondary Endpoints** |
| To further define the effects of CVN424 on motor and non-motor clinical features, function, and quality of life in PD | Change from Baseline to Week 12 in the following endpoints, arranged in hierarchical order:<br><br>• MDS-UPDRS Part III<br>• Clinical Global Impression of Severity Scale (CGI-S)<br>• Patient Global Impression of Severity Scale (PGI-S)<br>• MDS-UPDRS Part II<br>• MDS-UPDRS Part I<br>• Epworth Sleepiness Scale (ESS)<br>• Non-motor Symptoms Scale (NMSS)<br>• Sum of MDS-UPDRS of Parts I, II, and III |

| | |
|---|---|
| | • Parkinson's Disease Sleep Scale (PDSS-2) |
| To assess the safety and tolerability of CVN424 in the PD population | • Incidence and temporal profile of treatment emergent adverse events (TEAEs), evaluated by type/nature, severity/intensity, seriousness, and relatedness<br>• Incidence of related TEAEs of moderate or severe intensity<br>• Incidence of TEAEs leading to withdrawal of study drug<br>• Incidence of serious adverse events (SAEs)<br>• Changes in physical examination, vital signs (blood pressure and heart rate), electrocardiogram (ECG), laboratory values, and Columbia Suicide Severity Rating Scale (C-SSRS)<br>• Incidence and timing of abuse-related adverse events (AEs)<br>• Occurrence of withdrawal symptoms recorded at the follow-up visit<br>• Percentage of completers |
| **Exploratory** | **Exploratory Endpoints** |
| To describe the effects of CVN424 on motor performance, function, cognition, and sleep with other exploratory endpoints | Change from Baseline to Week 12 in the following endpoints:<br>• Modality Virtual Assessment<br>• CogState digital cognitive battery<br>• Schwab and England Activities of Daily Living (ADL)<br>• Starkstein Apathy Scale<br>• Electroencephalogram (EEG) derived sleep metrics<br>• PD-PROP™ and PWB-PROP™<br>• Pharmacokinetics (PK) |

**Overall Design:**
This is a Phase 2b multicenter, 12-week, randomized, parallel-group, double-blind, placebo-controlled clinical trial of CVN424 150 mg in early, untreated PD. It will evaluate CVN424 150 mg once a day against placebo.

There will be 7 in-person visits:

- Screening (Visit 1)
- Baseline/Randomization (Visit 2)
- Week 2 (Visit 3)
- Week 4 (Visit 4)
- Week 8 (Visit 5)
- Week 12/Early Termination Visit (Visit 6)
- Week 14/Safety Follow-up Visit (Visit 7)

After signing the informed consent form (ICF) and after all Screening procedures have been performed, subjects will be reviewed by an Enrollment Authorization Committee (EAC) for determination of eligibility and suitability for participation. Candidates may complete the screening visit in more than one day. Eligible subjects will be randomized in a 1:1 ratio to CVN424 150 mg or placebo at the Baseline Visit. Treatment will be initiated during the Baseline Visit. The study drug will be self-administered once daily at a consistent time in the morning and taken with food. The food taken with study drug may be a snack or typical morning meal and should include fat in its content (e.g., buttered toast, peanut butter on crackers, an egg, cream cheese on a bagel, full fat yogurt or milk)..

At Baseline (Visit 2), the primary endpoint (sum of Movement Disorder Society – Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part II + Part III), other secondary endpoints (Clinical Global Impression of Severity Scale [CGI-S], Patient Global Impression of Severity Scale [PGI-S], MDS-UPDRS Part I, Epworth Sleepiness Scale [ESS], Non-motor Symptom Scale [NMSS], Parkinson's Disease Sleep Scale [PDSS-2]), and exploratory endpoints (Parkinson's Disease Patient Report of Problems [PD-PROP™] and Personal Wellbeing Patient Report of Problems [PWB-PROP™]) will be assessed.

In-person clinic visits at Week 2, Week 4, Week 8, and Week 12 will assess both the primary and secondary endpoints, including exploratory endpoints, per the Schedule of Assessments (SoA).

Telephone visits will be conducted at Week 6 and Week 10 for safety and to check that Modality assessments have been completed.

Remote data collection between clinic visits will be conducted using the following technologies:

- Beacon Dreem overnight electroencephalogram (EEG): a wearable device that collects EEG signals to measure sleep metrics. This optional activity will be collected up to 3 consecutive nights before or after specified in-person clinic visits, per the SoA (see Section 8.2.8.4). Subjects who opt out of the Beacon Dreem EEG collection can continue their study participation in other study activities.
    - Modality Assessments: an audio-visual conversational technology to conduct customizable video interviews with subjects designed to test various aspects of their

speech, visuo-motor, prosodic (stress and intonation patterns), cognitive, and linguistic function. They include PD-PROP™, PWB-PROP™, and Schwab and England Activities of Daily Living (ADL) scale to enquire about specific problems and symptoms they are experiencing in daily and social activities. Subjects interact with a virtual agent using a web browser on any device of their choice. Subjects will be asked to complete the assessments at home (approximately 1-2 days prior to clinic visit). The assessments should take about 30 minutes to complete. Subjects who cannot complete all of the exploratory endpoint assessments, but who otherwise remain eligible for the study, can continue their participation (see Section 8.2.8.1). If a subject needs help to troubleshoot technical issues, their personal email ID will be shared with Modality. QC will be done by Modality staff who will review audio/video files throughout the conduct of the trial.

- Adverse events, concomitant medications, vital signs, safety laboratory parameters, and electrocardiogram (ECG) data will be collected and assessed throughout the study per the SoA.

**Brief Summary:**
The purpose of this study is to measure effect on motor features with CVN424 tablets compared to placebo in early, untreated PD and to evaluate the potential of CVN424 to improve motor and non-motor functions in subjects with early PD who are not taking dopaminergic or anti-PD therapies.

Study details include:

The study duration will be up to approximately 18 weeks.

The screening period duration will be up to 4 weeks.

The treatment duration will be up to 12 weeks, with a 2-week safety follow-up period.

The visit frequency will be every 2 weeks.

**Number of Subjects:**
Approximately 62 subjects will be enrolled and will be randomized in a 1:1 ratio to either CVN424 150 mg or placebo.

**Eligibility Criteria:**
**Inclusion Criteria:**

1. Diagnosis of PD consistent with United Kingdom Brain Bank and Movement Disorder Society Research Criteria for the Diagnosis of PD; must include bradykinesia with sequence effect, and motor asymmetry if no PD-type rest tremor.
2. Not receiving anti-parkinsonian therapy, and not expecting to require it for the duration of the study.
3. Men or women of all races who are at least 30 years at Screening.
4. Modified Hoehn and Yahr ≤ 2.5 at Screening.
5. Montreal Cognitive Assessment (MoCA) ≥ 26.

6. Freely ambulatory at time of Screening (with/without assistive device).
7. Female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to either remain abstinent or use adequate and reliable contraception throughout the study and at least 30 days after the last dose of study drug has been taken.
8. Able and willing to give written (signed and dated) informed consent approved by an institutional review board, and to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study.
9. Approved as an appropriate and suitable candidate by the EAC.

**Exclusion Criteria:**

1. Diagnosis of secondary or atypical parkinsonism.
2. Diagnosis of parkinsonian motor signs or symptoms ≥ 4 years before Screening Visit.
3. Previous surgical procedure for PD.
4. Prior treatment with a dopamine agonist, levodopa, monoamine oxidase B (MAOB) inhibitor, or adenosine A2A receptor antagonists for more than 28 total days prior to screening. Additional exclusionary parameters around PD treatment include:
    - Treatment with a dopamine agonist within 14 days of Screening.
    - Treatment with a MAOB inhibitor within 90 days of Screening.
5. Current use of any antipsychotic, metoclopramide, or reserpine. If previously used, this may not have been within 28 days of Screening or 5 elimination half-lives (whichever one is longer).
6. Current use of potent Cytochrome P450 (CYP) 3A4/5 inhibitors or inducers.
7. Clinically significant orthostatic hypotension.
8. Clinically significant hallucinations requiring antipsychotic use.
9. Known autoimmune, malignancy (except basal cell carcinoma), or hematologic disease (prior or current) likely to interfere with the safe participation of the subject or interfere with assessment of safety or efficacy based on the opinion of the investigator and the medical monitor.
10. Any clinically significant medical, surgical, or psychiatric abnormality that, in the judgment of the Investigator, is likely to interfere with study compliance, the safe participation of the subject, or the assessment of safety or efficacy.
11. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 2 times the upper limit of normal (ULN), and total bilirubin greater than 1.5 times ULN. Subjects with Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided that direct bilirubin is ≤ 1.5 times ULN.

12. Significant renal impairment as determined by eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation of ≤ 50 mL/min.
13. Subject has an ECG, prior documentation history, or clinical evidence of potentially unstable heart disease, including, but not limited to the following:
    a. QTcF > 470 msec for female subjects; > 450 msec for male subjects
    b. Complete right or left bundle branch block
    c. Myocardial infarction within 1 year prior to screening, unstable angina within 6 months, or a current concern for symptomatic ischemic heart disease in the opinion of the investigator
    d. Clinically significant atrial or ventricular dysrhythmia; the heart must be in predominantly normal sinus rhythm
    e. Second- or third-degree atrioventricular (AV) block
    f. NYHA Class II or higher congestive heart failure
    g. Clinically significant cardiomyopathy or cardiac structural abnormality, in the opinion of the investigator
    h. Any other cardiac condition that the Investigator feels may predispose the subject to ischemia or arrhythmia
14. Current (or within past 12 months) diagnosis or history of substance abuse (excluding nicotine or caffeine) by Diagnostic and Statistical Manual of Mental Disorders 5 criteria.
15. Positive urine drug screen for tetrahydrocannabinol or any drugs that may affect subject safety or interfere with efficacy assessments.
16. Medical or recreational use of marijuana within 2 months of the Screening Visit. Use of cannabidiol (CBD) is prohibited after the Screening Visit and throughout the study.
17. Currently active major depression as determined by Beck Depression Inventory-II (BDI-II) score of > 19.
18. Active suicidal ideation within 1 year prior to Screening Visit as determined by a positive response to Question 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS).
19. Currently lactating or pregnant, or planning to become pregnant during the study.
20. Current participation in another investigational clinical study and/or receipt of any investigational drug within 90 days prior to Screening.
21. Prior use of CVN424 investigational product.
22. Positive test for coronavirus disease 2019 (COVID-19). A subject who tests positive for COVID-19 will be eligible to be rescreened once result is negative.
23. Positive test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) consistent with current infection.

**Summary of Statistical Considerations:**
**Sample Size Determination:**

A sample size of approximately 62 subjects with a 1:1 randomization to CVN424 150 mg or placebo will provide 75% power to detect a difference of 5 or more points for the sum of MDS-UPDRS Parts II and III, assuming a standard deviation (SD) of 8, two-sided alpha of 0.10, and a 10% dropout rate.

The effect size of 5 points for Parts II + III is felt to reflect a meaningful threshold that, if achieved, would be comparable to other effective PD medications at 12 weeks (pramipexole, levodopa).

**Statistical Analysis Methods:**

The statistical analysis plan (SAP) will be finalized prior to database lock and unblinding of the study data and it will include a more technical and detailed description of the statistical analyses that will be performed.

All data analyses will be performed using at least one of the following analysis sets:

| | |
|---|---|
| Safety Analysis Set | Includes all subjects who have received at least 1 dose of study drug. All safety population analyses will be based on the treatment the subject received. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety analyses. |
| Modified Intention To Treat (mITT) | Includes all subjects who are randomized, and administered study drug, classified according to treatment received, and have at least one post-baseline evaluation of efficacy endpoints. |
| Intention-to-Treat (ITT) Set | Includes all randomized subjects. |
| Completer Set | Includes all subjects who completed all study treatment for 12 weeks. |
| Pharmacokinetic (PK) Analysis Set | Includes all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma concentration. |
| Per Protocol Set | Includes all subjects who completed the study and who received all study treatment and have no significant protocol deviations. All significant protocol deviations will be assessed, and a decision will be made on a case-by-case basis whether to exclude subjects from the Per Protocol analysis set prior to breaking the blind. All per protocol analyses will be based on the treatment the subject received. This set will be used as a sensitivity analysis for primary and secondary efficacy outcomes. |

**Efficacy Endpoint Analysis:**

Each efficacy endpoint (primary and secondary) will include a comparison of CVN424 versus placebo. The overall Type I error rate within the family of efficacy endpoints will be maintained by using Hochberg's step-up method to maintain alpha while comparing CVN424 to placebo. Efficacy endpoints will be evaluated in a hierarchical manner.

The primary estimand will be defined as follows:

| | |
|---|---|
| Population: | Subjects with PD as defined by inclusion/exclusion criteria and are in the mITT population |
| Variable: | The primary endpoint is the change from Baseline to Week 12 in the MDS-UPDRS Part II + Part III score (Motor Aspects of Experiences of Daily Living + Motor Examination) |
| Intercurrent Events and Proposed Strategy: | Treatment Discontinuation: Hypothetical Strategy<br>Initiation of Parkinsonian medication for treatment of motor features: Hypothetical Strategy |
| Population Level Summary: | Treatment difference of the least-squares mean change from Baseline to Week 12 in the MDS-UPDRS Part II + Part III score (Motor Aspects of Experiences of Daily Living + Motor Examination) between placebo and CVN424 groups |

Efficacy endpoints will be analyzed in the mITT population using a Mixed Model for Repeated Measures (MMRM) with no imputation. This will include response data from each post-baseline visit based on the mITT population. The baseline score will be included as a covariate as well as the treatment group (150 mg CVN424 or placebo), visits, interaction between treatment group and visit, as fixed factors in the MMRM. The difference between CVN424 versus placebo at the final visit will be estimated from the MMRM. An unstructured covariance matrix will be used initially, and if it fails to converge, a Compound Symmetry (CS) or an AR (1) matrix shall be employed, in that order.

Sensitivity analyses for efficacy endpoints will be conducted on the Intention-to-Treat (ITT) set with the multiple imputation method, both assuming that data are missing at random (MAR) and missing not at random (MNAR). Missing not at random analyses will include tipping point and jump-to-reference (placebo) assumptions. Further sensitivity analysis will be conducted on the completer and per-protocol set with MMRM.

Categorical secondary efficacy endpoints (proportion of subjects improving based on CGI-S or PGI-S) will be analyzed in the mITT population using the Cochran–Mantel–Haenszel (CMH) test. This test will include the frequency and percentage of proportions for each group, along with their respective 95% confidence interval (CI). Additionally, the difference in proportions between the treatment groups, along with its CI, will be calculated. As a sensitivity analysis, a GLIMMIX model that can incorporate all response data from each post-baseline visit into the analysis will be employed. The model will include the treatment group, visit, interaction between

treatment groups and visit. An unstructured covariance structure will be used for the repeated measures. The odds ratio for the treatment difference, 95% CI for the odds ratio, and p-value will be provided.

**Tolerability and Safety Analysis:**
Tolerability will be assessed by comparing percentages of premature drug and study discontinuations in the treatment groups (CVN424 versus placebo).

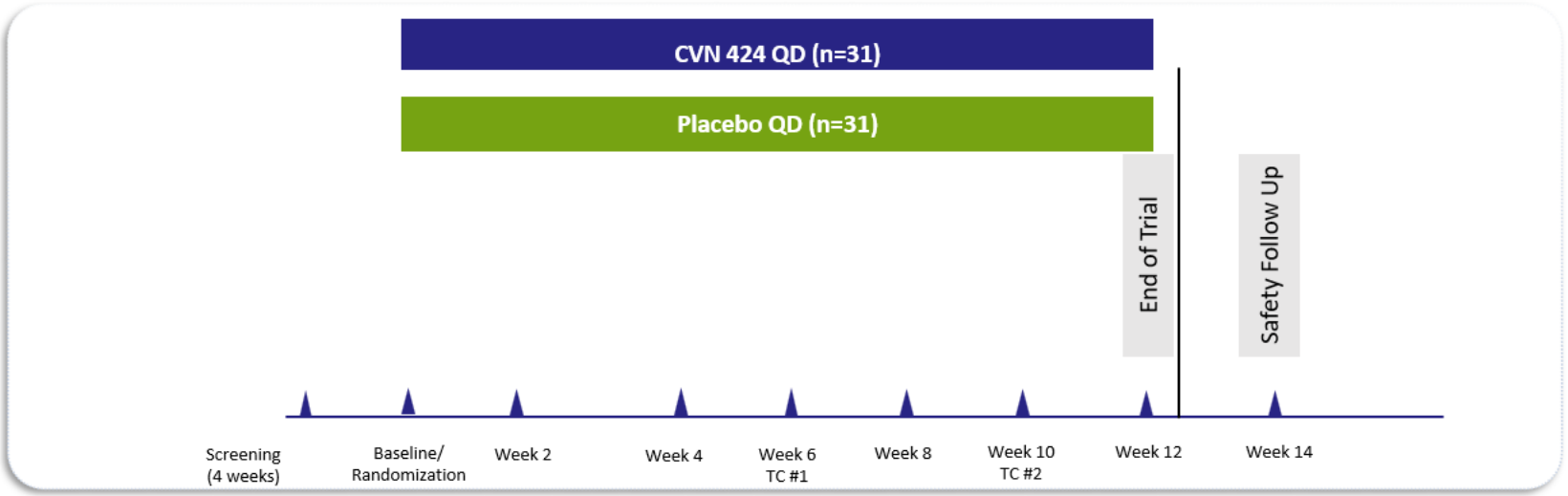
Treatment emergent adverse events (TEAEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group, organ class and preferred term, and duration. Further summaries will be done by seriousness, severity, relationship to study treatment and dose at the time of onset. Safety endpoints will be summarized with descriptive statistics.

**Data Monitoring Committee:**

No data monitoring committee will be appointed for this study.

## 1.2. Schema

**Figure 1. Study Schema**




Primary Endpoint

- Change from baseline to Week 12 on the MDS-UPRDS Parts II & III (Motor Aspects of Experiences of Daily Living + Motor Examination) between CVN424 150 mg and placebo

Safety Endpoints

- Incident of Treatment-emergent adverse events (TEAEs)
- Incidence of related TEAEs
- Incidence of TEAEs leading to withdrawal of study drug
- Incidence of serious adverse events (SAEs)
- Changes in physical examination, vital signs (blood pressure and heart rate), ECG, laboratory values, Columbia Suicide Severity Scale (C-SSRS)
- Incidence and timing of abuse-related AEs
- Occurrence of withdrawal symptoms recorded at follow-up visit
- Percentage of completers

MDS-UPRDS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale; TC = telephone call; QD = once a day.

## 1.3. Schedule of Assessments (SoA)

Table 1-1.Schedule of Assessments

| Study Period | SCR | Treatment Period | | | | | | | SFU[a] |
|---|---|---|---|---|---|---|---|---|---|
| Study Day/Week | (Day -28 to 0) | Baseline | Week 2 (± 1 day) | Week 4 (± 1 day) | Week 6 | Week 8 (± 1 day) | Week 10 | Week 12/ET[b] (± 1 day) | Week 14[c] |
| Visit Number | 1 | 2 | 3 | 4 | TC1 | 5 | TC2 | 6 | 7 |
| General and Safety Assessments | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Eligibility criteria | X | X | | | | | | | |
| Enrollment Authorization Committee Review | X | | | | | | | | |
| Randomization | | X | | | | | | | |
| Demography | X | | | | | | | | |
| Medical history | X | X | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X |
| Vital signs[d] | X | X | X | X | | X | | X | X |
| Height and weight[e] | X | | | | | | | X | X |
| AE/SAE collection | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | X | X | X | | X | | X | X[f] |
| Physical examination | X | | | | | | | X | X[f] |
| Neurological examination | X | | | | | | | X | X[f] |
| Laboratory Assessments (refer to Table 10-1) | | | | | | | | | |
| Clinical Laboratory Tests[g] | X | | | X | | X | | X | X[f] |
| Urine Drug Screen | X | X | | | | | | | |
| Pregnancy test[h] | X | X | | X | | X | | X | X |

| Study Period | SCR | Treatment Period | | | | | | | SFU[a] |
|---|---|---|---|---|---|---|---|---|---|
| Study Day/Week | (Day -28 to 0) | Baseline | Week 2 (± 1 day) | Week 4 (± 1 day) | Week 6 | Week 8 (± 1 day) | Week 10 | Week 12/ET[b] (± 1 day) | Week 14[c] |
| Visit Number | 1 | 2 | 3 | 4 | TC1 | 5 | TC2 | 6 | 7 |
| Plasma Pharmacokinetics; [redacted] | | [redacted] | | | | | | | |
| Study-specific Assessments | | | | | | | | | |
| MDS-UPDRS Part I | | X | X | X | | X | | X | X |
| MDS-UPDRS Part II | X | X | X | X | | X | | X | X |
| MDS-UPDRS Part III | X | X | X | X | | X | | X | X |
| CGI-S[j] | | X | X | X | | X | | X | |
| PGI-S[k] | | X | X | X | | X | | X | |
| ESS | | X | X | X | | X | | X | |
| NMSS | | X | | X | | X | | X | |
| PDSS-2 | | X | | X | | X | | X | |
| Starkstein Apathy Scale | | X | | X | | X | | X | |
| Modified Hoehn and Yahr Scale | X | | | | | | | | |
| MoCA | X | | | | | | | | |
| BDI-II | X | | | | | | | | |
| C-SSRS ("Lifetime") | X | | | | | | | | |
| C-SSRS ("Since Last Visit") | | X | X | X | | X | | X | X |
| Modality Assessments[l] | | X | X | X | X | X | X | X | X |

| Study Period | SCR | Treatment Period | | | | | | | SFU[a] |
|---|---|---|---|---|---|---|---|---|---|
| Study Day/Week | (Day -28 to 0) | Baseline | Week 2 (± 1 day) | Week 4 (± 1 day) | Week 6 | Week 8 (± 1 day) | Week 10 | Week 12/ET[b] (± 1 day) | Week 14[c] |
| Visit Number | 1 | 2 | 3 | 4 | TC1 | 5 | TC2 | 6 | 7 |
| Schwab and England ADL (by subject) | | X | | X | | X | | X | |
| PD-PROP™ and PWB-PROP™ | | X | | | | | | X | X |
| Cogstate Cognitive Computerized Battery Assessments[m] | X | X | | | | X | | X | X |
| Dreem Overnight EEG[n] | | X | | X | | | | X | X |
| Study Intervention | | | | | | | | | |
| In Clinic Study Drug Dosing | | X | | | | | | | |
| Study Drug Compliance and Accountability | | | X | X | | X | | X | |
| Study Drug Dispensation[o] | | X | X | X | | X | | | |

ADL = Activities of Daily Living; AE = adverse event; BDI-II = Beck Depression Inventory-II; CGI-S = Clinical Global Impression Scale—Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EEG = electroencephalogram; ESS = Epworth Sleepiness Scale; ET = early termination; MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NMSS = Non-motor Symptoms Scale; PD-PROP™ = Parkinson's Disease Patient Report of Problems; PDSS = Parkinson's Disease Sleep Scale; PGI-S = Patient Global Impression Scale—Severity; PWB-PROP™ = Personal Wellbeing Patient Report of Problems; RF = radiofrequency; SAE = serious adverse event; SCR = Screening; SFU = safety follow-up; TC = telephone call.

a Unscheduled visits may be conducted at any time for any reason.

b If a subject discontinues the study prematurely, the Week 12 procedures should be conducted.

c To occur approximately 14 days after Visit 6 (± 1 day).

d Vital signs include blood pressure and pulse rate (pre-dose and 1 hour after dosing), respiration, and body temperature. Refer to Section 8.3.2 for details. Blood pressure will be measured after at least 5 minutes supine and again within 1 to 3 minutes of standing. Study personnel will carefully monitor subjects for signs of orthostatic hypotension within 3 minutes of standing up from a supine position.

e Height at Screening only.

f To be collected only if there were abnormalities at Week 12 requiring follow-up.

g Refer to Table 10-1 for a list of all hematology, clinical chemistry, and urinalysis tests to be performed. Coagulation tests will be performed only at Screening.

h For women of childbearing potential, serum pregnancy test at Screening (central laboratory), and urine pregnancy tests at all other indicated visits (on site). Refer to Section 8.3.9 for details.

i Plasma pharmacokinetic samples to be collected pre-dose and at 4 hours post dose at Baseline/Visit 2 and at a single timepoint after the last administered dose (which may be the day before or on the day of visit) at Weeks 4, 8, and 12/Visits 4, 5, and 6. Time of administration of last administered dose must be recorded accurately to enable pharmacokinetic (PK) sample time assignment. At the same time that PK sample is collected, a blood sample for metabolite and [redacted]will also be collected.. Refer to Section 8.5 for details.

j CGI-S should be completed following the MDS-UPDRS by the same rater to assure that the CGI-S rater has spent some time with the subject just prior to that rating.

k PGI -S may benefit by occurring immediately following the MDS-UPDRS so that the subject has clearly in mind any symptoms they may experience that will be more evident after going through the MDS-UPDRS assessment.

l Modality assessments are to be conducted remotely, not during clinic visits (approximately 1-2 days prior to clinical visit). If a subject needs help to troubleshoot technical issues, their personal email ID will be shared with Modality. QC will be done by Modality staff who will review audio/video files throughout the conduct of the trial. Subjects who are unable to complete the Modality assessments can continue their study participation.

m Cogstate Computerized Battery testing will be conducted twice at screening for familiarization.

n Beacon Dreem Overnight electroencephalogram recording is optional and will occur up to 3 consecutive nights prior to randomization (Baseline) and Week 14 (Visit 7) visits, as well as immediately following Week 4 (Visit 4) and Week 12 (Visit 6) visits. Refer to Section 8.2.8.4 for details.

o Subject will be supplied with CVN424 for self-administered, at-home dosing.

# 2. Introduction

Parkinson's Disease (PD) is an adult-onset, progressive neurodegenerative disorder. While it has been traditionally regarded as a movement disorder, based on the hallmark features of tremor, bradykinesia and rigidity, it also includes a wide range of non-motor manifestations. Although currently available therapies can provide symptomatic relief mainly for motor symptoms, an effective treatment that could target both motor and non-motor symptoms across the disease stages remains a high unmet need (The American Parkinson Disease Association, 2023).

## 2.1. Study Rationale

Previous clinical studies, including a Phase 1 safety and pharmacokinetic (PK) study performed in 64 healthy volunteers (Study CVN424-101; NCT03657030), a relative bioavailability study conducted in 32 healthy volunteers (Study CVN424-102; NCT05635461), and a Phase 2a study as an adjunctive treatment in 136 PD subjects (Study CVN424-201; NCT04191577) support the use of the selected dose level of CVN424 in this study. The dose of 150 mg per day is expected to provide a potentially therapeutic level of G protein-coupled receptor 6 (GPR6) occupancy in brain tissue even at its steady state-nadir plasma concentration. Data from the completed Phase 1 and 2 studies show that CVN424 150 mg is safe and well tolerated in both healthy volunteers and individuals with PD taking anti-PD medications. No changes in vital signs or laboratory values of clinical significance were observed following CVN424 dosing.

In the Phase 2a study of CVN424 in subjects with PD and motor fluctuations (Study CVN424-201; NCT04191577), CVN424 150 mg demonstrated significant reduction in OFF time. Overall, the rates of treatment emergent adverse events (TEAEs) were low compared to other dopaminergic medications. Common dopaminergic TEAEs occurred at low rates, many in 1 or no subjects. There were no treatment-related severe adverse events (AEs) or serious adverse events (SAEs). The discontinuation rate due to TEAEs was low. These findings support continuing the development of CVN424 for the treatment of PD.

The present study will examine the potential of CVN424 to improve motor and non-motor functions in individuals with early PD not taking dopaminergic or anti-PD therapies. Thus, this study will provide evidence for further pursuing the development of CVN424 for the broader treatment of motor and non-motor symptoms of PD.

## 2.2. Background

### 2.2.1. Disease Background

Parkinson's disease is a progressive neurodegenerative disorder of the nervous system involving the gradual loss of dopaminergic neurons in the substantia nigra pars compacta that project to the striatum (Wichmann et al, 2011). There are estimated to be approximately 1 million individuals in the United States of America (USA) and > 10 million worldwide living with PD (The American Parkinson Disease Association, 2023). The clinical hallmark of the disease is the motor features of tremor, bradykinesia, rigidity, and postural instability. However, several non-motor symptoms, which could include hyposmia, apathy, depression, anxiety, pain, fatigue,

sleep disorders, autonomic dysfunction, and impairment in executive functions can be frequently identified in virtually all subjects even in the earlier stages (Pont-Sunyer et al, 2015; Zis et al, 2015). Clinically manifested PD is preceded by a potentially long prodromal period when non-motor symptoms of extra-nigral degeneration are present. Currently, establishment of prodromal symptoms has no clinical implications, although better understanding of the prodromal phase will probably have consequences when disease-modifying treatments become available. At present, no therapy can slow down or arrest the progression of PD but informed by new insights in genetic causes and mechanisms of neuronal death, several promising strategies are being tested for disease-modifying potential (Bloem et al, 2021).

Levodopa is the most effective medication therapy in the treatment of PD and is eventually needed by all patients as the disease progresses. With time, due to non-physiologic, fluctuating, striatal dopamine levels induced by intermittent oral dosing, the usually consistent benefit of levodopa gradually becomes variable (motor fluctuations) and abnormal movements can develop (dyskinesias) (Olanow et al, 2020). Most patients will eventually experience these motor complications as their disease progresses. Current treatments for motor fluctuations include levodopa dosage changes and addition of medications that supplement dopaminergic tone (dopamine agonists) or delay the breakdown of dopamine (catechol-O-methyl transferase [COMT] inhibitors or monoamine oxidase B [MAOB] inhibitors). Apomorphine rescue, levodopa gel delivered to the small intestine, and deep brain stimulation may also be employed. The efficacy and tolerability of these approaches varies considerably, underscoring the need for new treatments that promote consistent motor benefit (Gustavsson et al, 2011).

GPR6 is an orphan G-protein coupled receptor that is selectively expressed in the brain and is a non-dopaminergic target for the treatment of PD. In the brain, GPR6 is predominantly localized in the striatopallidal medium spiny neurons (MSNs) that also express dopamine D2 receptors (Brice et al, 2021; Lein et al, 2007; Margolin et al, 2022). GPR6 is a constitutively expressed and active G-coupled receptor that functionally opposes the Gi-coupled D2 receptors in indirect MSNs. Due to progressive loss of dopaminergic innervation, GPR6 is thought to drive the hyperactivity of the indirect pathway, likely responsible for several of the clinical features of PD. Inhibition of GPR6 using an inverse agonist is predicted to exert anti-parkinsonian effects by reducing the overactivity of striatopallidal output neurons in the indirect pathway without activating the dopamine D1-receptor-expressing MSNs of the direct (striatonigral) pathway.

For this reason, CVN424, a potent and selective inverse agonist of GPR6, has therapeutic promise to modify the function of pathways relevant in PD pathogenesis in a way that can benefit individuals with PD across stages of disease progression as either monotherapy or adjunctive therapy.

### 2.2.2. Investigational Product Background: CVN424

Human Studies with CVN424

Three studies have been completed with CVN424 in human subjects:

The first study was a Phase 1 single and multiple ascending dose study, with evaluation of food effect bioavailability of CVN424 (Study CVN424-101; NCT03657030). This first-in-human safety and tolerability study of CVN424 was conducted in 64 healthy male and female volunteers; the study findings are summarized in the Investigator's Brochure (IB). 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 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 resolved by the end of the study. Administration of the first dose of CVN424 was associated with an elevation in group mean and median body temperature. These changes were detectable at 1 hour post-dose (the earliest scheduled post-dose assessment), increased further by 6 hours post-dose, and spontaneously returned to baseline by 24 hours post-dose. The increases tended to be larger at higher doses but did not appear to be strictly dose proportional. A trend of increased heart rate while standing was also observed with a similar time course and relationship to dosage. These trends were not considered clinically significant, and no individual vital sign measurement was reported as an AE. In the multiple-dose cohorts, elevations in body temperature and heart rate were observed only after the first dose of CVN424; this was not observed 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 this 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-hours post-dose (median 1.5 hours). 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 hours. Accordingly, the PK profile of CVN424 in suspension formulation is considered appropriate for once daily oral dosing, with or without food.

The second healthy volunteer study (Study CVN424-102; NCT05635461) was performed to determine the relative bioavailability of 150 mg CVN424 administered in a single dose of suspension formulation compared to a 150 mg tablet, and to evaluate the food effect bioavailability of the 150 mg tablet. The study was conducted in 32 healthy male and female subjects. The results of the study showed that CVN424 in an oral tablet formulation administered in the fed state has similar exposure (area under the plasma concentration-time curve from time 0 to 96 hours [$AUC_{0\text{-}96h}$]) to CVN424 suspension administered in the fasted state. While maximum plasma drug concentration ($C_{max}$) in the tablet-fed conditions was 15% lower than that in the suspension-fasted conditions, for a drug administered for a chronic condition with efficacy believed to be driven by duration of exposure, the extent of exposure (AUC parameter) is the

most clinically relevant, and therefore the tablet-formulation administered under fed conditions is considered appropriate for clinical use.

No SAEs were reported in this study. Of the 88 reported TEAEs, 84 events were mild, and 4 events were moderate in severity; 65 events were considered by the Investigator to be related to study product. One subject (1%) was discontinued due to an unrelated TEAE (asymptomatic coronavirus disease 2019 [COVID-19]). One subject experienced a laboratory-described TEAE (asymptomatic bacteriuria) during study period 2 that was determined to be not related to study drug; the same subject was discontinued from study in study period 3 due to an out-of-reference-range laboratory result in a different parameter (low hemoglobin). All TEAEs had resolved without sequelae by the end of the study. There were a few abnormal findings across all treatment periods in the clinical laboratory, vital signs, orthostatic vital signs, 12-lead ECG, and physical examination assessments; however, these were generally minor and did not present any obvious trends. Mean vital sign and orthostatic response results, including body temperature and heart rate, remained within normal limits at all post-dose time points across all 3 treatment periods. No signal in increased suicidal ideation or behavior, as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS), was observed throughout the study.

In a 27-day, Phase 2a study of CVN424 in subjects diagnosed with PD with motor fluctuations (Study CVN424-201; NCT04191577), 136 subjects were enrolled and included in the primary efficacy analysis and safety analysis set. After the Screening visit, subjects were randomized in a 1:1:1 ratio into 1 of 3 study groups to receive once-daily low-dose (50 mg) CVN424, high-dose (150 mg) CVN424, or matching placebo on Day 0/Visit 1. Subjects not randomized to placebo, initiated treatment with 50 mg CVN424 on Day 1 (Visit 2) to allow for baseline assessments on Day 0. Thereafter, the low-dose group continued to receive 50 mg per day, while the high-dose cohort increased their dosage to 150 mg CVN424 per day, beginning on Day 8 ± 2 days (Visit 3) and continued this dose thereafter. The study drug was self-administered each morning on an outpatient basis as an oral suspension. Efficacy and safety evaluations were made throughout the study and follow-up safety and efficacy assessments occurred on Day 35/Visit 7, approximately 7 days after the final study drug dose. The primary endpoints for the study were safety and tolerability, and the primary efficacy endpoint was OFF time per day.

In this study, exposure to CVN424 increased with dose level from 50 to 150 mg. The increase in exposure with dose was slightly less than dose proportional. After CVN424 50 mg dosing, there was a trend for higher exposure in female subjects compared with male subjects. There were no apparent differences between female subjects and male subjects after CVN424 150 mg dosing, and PK parameters were comparable. After CVN424 50 mg dosing, $C_{max}$ and area under the plasma concentration-time curve from time 0 to 6 hours ($AUC_{0-6h}$) were slightly higher in the group of subjects with a weight of less than the median weight, compared with the group of subjects with a weight of greater than or equal to the median weight. Exposure parameters were generally comparable between weight groups after CVN424 150 mg dosing.

There was a higher incidence of TEAEs and treatment-related TEAEs among subjects treated with CVN424 (both dose groups) compared to placebo. Overall, there was a higher incidence of TEAEs in the CVN424 150 mg dose group than in the CVN424 50 mg group; however,

treatment-related TEAEs had a similar incidence in the 50 mg and 150 mg CVN424 dose groups. There were no treatment-related SAEs in this study. One SAE, an event of cardiac arrest in 1 (2.1%) subject in the CVN424 150 mg group, leading to study drug discontinuation and death, was reported as unrelated to study treatment.

Overall, the most common TEAEs (preferred terms) were headache (1 [2.3%] subject, 1 [2.2%] subject, and 4 [8.5%] subjects in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively) and nausea (1 [2.3%] subject, 2 [4.4%] subjects, and 3 [6.4%] subjects in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively). Overall, treatment-related TEAEs were more common in the CVN424 groups than in the placebo group (9.1%, 17.8%, and 19.1% of subjects in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively). Nausea was the most common treatment-related TEAE, with a total of 4 (2.9%) subjects experiencing 5 treatment-related events (0 [0%] subjects, 2 [4.4%] subjects, and 2 [4.3%] subjects in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively). Hallucinations, somnolence, confusion, orthostatic hypotension, and dyskinesia were each observed in fewer than 2 CVN424-treated subjects. Overall, approximately 67% of treatment-related TEAEs were mild in severity; the remainder were moderate in severity. There was no severe treatment-related TEAEs. There was a higher incidence of moderate treatment-related TEAEs in the CVN424 150 mg group (8.5%) than in the CVN424 50 mg (2.2%) and placebo groups (4.5%). Overall, 6 (4.4%) subjects discontinued study drug due to a TEAE: 2 (4.5%), 1 (2.2%), and 3 (6.4%) subjects in the placebo, CVN424 50 mg, and CVN424 150 mg groups, respectively. Of the 4 subjects who received CVN424, 2 subjects (1 each in the CVN424 50 mg and 150 mg groups) discontinued the study drug due to nausea.

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

Treatment with CVN424 was associated with a statistically significant and clinically meaningful improvement (relative to placebo) in OFF time with the 150 mg dose at Day 27 in the Primary Efficacy Analysis Set. On Day 27, the least squares (LS) mean (± standard error [SE]) for average daily hours of OFF time for the CVN424 150 mg vs placebo comparison was -1.30 (± 0.56) h; $p = 0.0418$ (Dunnett) and $p = 0.0225$ (Mixed Model for Repeated Measures [MMRM]). The CVN424 50 mg vs placebo comparison was not statistically significant at Day 27 ($p = 0.3302$ [Dunnett]; $p = 0.1985$ [MMRM]). At Day 27, the LS mean (± SE) for the combined CVN424 vs placebo comparison was -1.02 (± 0.50) h; $p = 0.0410$ (MMRM). Analysis of the Secondary Efficacy Analysis Set and a sensitivity analysis yielded results similar to the Primary Efficacy Analysis Set. Treatment with CVN424 50 mg and CVN424 150 mg was associated with a non-statistically significant numerical increase in ON time without troublesome dyskinesia on Day 15 and Day 27 vs placebo. ON time with troublesome dyskinesia was

generally constant throughout the course of the trial; changes from baseline to Day 27 were less than 12 minutes of worsening. In the CVN424 150 mg group, ON time with dyskinesia was generally constant throughout the study; the increase from baseline was less than 6 minutes on Day 27. Treatment with CVN424 50 mg and CVN424 150 mg was associated with an increase in ON time on Day 15 and Day 27; however, the differences between the CVN424 groups and placebo were not statistically significant.

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

Cerevance Beta Inc. conducted additional post-hoc analyses on the PD diary data, conforming to the Food and Drug Administration (FDA) standardized analysis for the PD diary. The PD diary was normalized to a 16-hour waking day, required 44/48 entries per day, required having both days of diaries, and only included subjects with at least one post-baseline data point. This post-hoc analysis was first conducted for the full analysis set and confirmed the result of the primary analysis, with greater numeric improvement compared to placebo on the reduction in OFF time (CVN424 150 mg had a 1.45-hour benefit compared to placebo; nominal p=0.01) and improvement in ON time without troublesome dyskinesia (CVN424 had a 0.96-hour benefit compared to placebo; p = 0.098). ON time with troublesome dyskinesia was comparable to the primary analysis. A second post-hoc analysis was conducted using FDA standards for the PD diary analysis, excluding subjects with a Baseline OFF time of 2-3 hours. Previous studies in PD subjects with motor fluctuations, with drugs proven effective, have demonstrated that subjects with 2-3 hours of OFF time are less likely to demonstrate change for clinical trials in PD subjects with motor fluctuations and will be the cutoff for the adequate and well-controlled trial of CVN424 in PD subjects with motor fluctuations. This analysis showed a more robust effect of CVN424 on reduction in OFF time (1.78-hour improvement vs placebo for the 150 mg dose; nominal p = 0.005) and improvement in ON time without troublesome dyskinesia (1.30-hour improvement vs placebo for the 150 mg dose; nominal p = 0.042). ON time with troublesome dyskinesia was similar to the primary analysis.

CVN424 is expected to be a pharmacological treatment for PD 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 prove useful for treatment of PD.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CVN424 is provided in the IB.

## 2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of CVN424 may be found in the IB.

### 2.3.1. Risk Assessment

Overall, CVN424 was safe and well-tolerated in Phase 1 and Phase 2 studies in both healthy volunteers and subjects with PD with motor complications. There were no treatment-related SAEs, and one severe AE was reported in the CVN424 150 mg group as well as the placebo groups. Overall, discontinuation due to AEs has occurred at low rates. There was a very low prevalence of known dopaminergic AEs with CVN424 (ie, nausea, vomiting, somnolence, dizziness, orthostatic hypotension, hallucinations). In the first-in-human Phase 1 study in healthy volunteers, mild and non-clinically significant increases in heart rate and temperature were seen with the first dose but did not persist with subsequent dosing. These changes were not observed in the Phase 2 study in PD subjects with motor fluctuations. One subject in the Phase 2 PD study experienced a cardiovascular SAE resulting in death on Day 2 of study treatment (50 mg dose), which was determined to be not related to study drug as the subject had a recent history of active coronary artery disease.

### 2.3.2. Benefit Assessment

Data from the Phase 2a study in subjects with PD with motor fluctuations demonstrated that CVN424 improved motor fluctuations compared to placebo. There were significant and clinically meaningful improvements in OFF time compared to placebo with numeric improvement in ON time without troublesome dyskinesia. Additional post-hoc analyses supported an even more robust effect on motor fluctuations. Additionally, CVN424 demonstrated signs of improvement in activities of daily living (ADL), overall function and statistically significant improvement in daytime alertness compared to placebo measured with the ESS. The latter finding is consistent with a direct effect of CVN424 rather than lack of off target dopaminergic effects since it was observed with the higher dose of CVN424. In addition, it is possible that the improvement of the ESS score may also reflect an improvement of cortico-striato-thalamo-cortical (CSTC) connectivity. Basal ganglia and CSTC pathways appear involved in the modulation of sleep (Hasegawa et al, 2020). Abnormal and impaired CSTC connectivity is involved in the pathophysiology of apathy, fatigue, and cognitive deficits and it has also been linked to excessive daytime sleepiness in PD (Gong et al, 2020; Zi et al. 2022). In support of this hypothesis are the findings that CVN424 improves behavior in an animal model of anhedonia, most likely decreasing the activity of the indirect pathway and thus improving ventral striatum-prefrontal cortex connectivity. Overall based on preclinical data as well as the previous study in PD subjects, there is reason to hypothesize that CVN424 can have anti-parkinsonian benefits in early PD patients.

### 2.3.3. Overall Benefit Risk Conclusion

Overall, based on data to date, the benefit/risk is favorable for CVN424 which has been generally safe and well-tolerated. The safety profile has the potential to be differentiated from other anti-PD drugs that affect the dopaminergic system but causing lower rates of well-established dopaminergic AEs. Additionally, rates of discontinuation due to AEs appear lower than with other dopaminergic treatments. Preliminary signs of efficacy are clinically meaningful, especially in the setting of lower rates of dopaminergic AEs. As this drug is still early in development, this study will have safety assessments of ECGs, clinical laboratory, C-SSRS, and collection of AEs over time to evaluate for any potential safety finding.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with CVN424 are justified by the anticipated benefits that may be afforded to patients with PD.

# 3. Objectives, Endpoints, and Estimands

**Table 3-1. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | **Primary Efficacy Endpoint** |
| To determine the effect of CVN424 on motor features of early, untreated subjects with Parkinson's Disease (PD) | Change from Baseline to Week 12 on the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II + Part III (Motor Aspects of Experiences of Daily Living + Motor Examination) between CVN424 150 mg and placebo |
| **Secondary** | **Secondary Endpoints** |
| To further define the effects of CVN424 on motor and non-motor clinical features, function, and quality of life in PD | Change from Baseline to Week 12 in the following endpoints, arranged in hierarchical order:<br><br>• MDS-UPDRS Part III<br>• Clinical Global Impression of Severity Scale (CGI-S)<br>• Patient Global Impression of Severity Scale (PGI-S)<br>• MDS-UPDRS Part II<br>• MDS-UPDRS Part I<br>• Epworth Sleepiness Scale (ESS)<br>• Non-motor Symptoms Scale (NMSS)<br>• Sum of MDS-UPDRS of Parts I, II, and III<br>• Parkinson's Disease Sleep Scale (PDSS-2) |
| To assess the safety and tolerability of CVN424 in the PD population | • Incidence and temporal profile of treatment emergent adverse events (TEAEs), evaluated by type/nature, severity/intensity, seriousness, and relatedness<br>• Incidence of related TEAEs of moderate or severe intensity<br>• Incidence of TEAEs leading to withdrawal of study drug<br>• Incidence of serious adverse events (SAEs) |

| | |
|---|---|
| | • Changes in physical examination, vital signs (blood pressure and heart rate), electrocardiogram (ECG), laboratory values, and Columbia Suicide Severity Rating Scale (C-SSRS)<br>• Incidence and timing of abuse-related adverse events (AEs)<br>• Occurrence of withdrawal symptoms recorded at the follow-up visit<br>• Percentage of completers |
| **Exploratory** | **Exploratory Endpoints** |
| To describe the effects of CVN424 on motor performance, function, cognition, and sleep with other exploratory endpoints | Change from Baseline to Week 12 in the following endpoints:<br><br>• Modality Virtual Assessment<br>• CogState digital cognitive battery<br>• Schwab and England Activities of Daily Living (ADL)<br>• Starkstein Apathy Scale<br>• Electroencephalogram (EEG) derived sleep metrics<br>• PD-PROP™ and PWB-PROP™<br>  • Pharmacokinetics (PK) |

# 4. Study Design

## 4.1. Overall Design

This is a Phase 2b multicenter, 12-week, randomized, parallel-group, double-blind, placebo-controlled clinical trial of CVN424 150 mg in early, untreated PD.

There will be 7 in-person visits and 2 telephone visits (see Schema in Section 1.2):

| | | |
|---|---|---|
| Screening (V1) | | Week 8 (V5) |
| Baseline/Randomization (V2) | | Week 10 (TC2) |
| Week 2 (V3) | | Week 12/Early Termination Visit (V6) |
| Week 4 (V4) | | Week 14/Safety Follow-up Visit (V7) |
| Week 6 (TC1) | | |

TC = telephone call; V = visit.

After signing the informed consent form (ICF) and after all Screening procedures have been performed, subjects will be reviewed by an Enrollment Authorization Committee (EAC) for determination of eligibility and suitability for participation. Candidates may complete the screening visit in more than one day. Eligible subjects will return for the Baseline Visit and assessments will be performed per the Schedule of Assessments (SoA) (see Section 1.3). Subjects will be randomized in a 1:1 ratio to CVN424 150 mg or placebo at the Baseline Visit. Treatment will be initiated during the Baseline Visit. The study drug will be self-administered once daily at a consistent time in the morning and taken with food. The food taken with study drug may be a snack or typical morning meal and should include fat in its content (e.g., buttered toast, peanut butter on crackers, an egg, cream cheese on a bagel, full fat yogurt or milk).

At Baseline (Visit 2), the primary endpoint (sum of MDS-UPDRS Part II + Part III), other secondary endpoints (Clinical Global Impression of Severity Scale [CGI-S], Patient Global Impression of Severity Scale [PGI-S], MDS-UPDRS Part I, ESS, NMSS, PDSS-2), and exploratory endpoints (PD-PROP™ and PWB-PROP™) will be assessed.

In-person clinic visits at Week 2, Week 4, Week 8, and Week 12 will assess the primary and secondary endpoints as well as exploratory endpoints per the SoA (see Section 1.3). Telephone visits will be conducted at Week 6 and Week 10 for safety, and to check that Modality assessments have been completed.

Remote data collection between clinic visits will be conducted using the following technologies:

- *Beacon Dreem overnight EEG*: a wearable device that collects EEG signals to measure sleep metrics. This optional activity will be collected up to 3 consecutive nights before or after specified in-person clinic visits, per the SoA (see Section 1.3). Subjects who opt out of the Beacon Dreem EEG collection can continue their study participation in other study activities.

- *Modality Assessments*: an audio-visual conversational technology to conduct customizable video interviews with subjects. Subjects will interact with a virtual agent using a web browser on the device of their choice to complete assessments designed to test various aspects of their speech, visuo-motor, prosodic (stress and intonation patterns), cognitive, and linguistic function. This will also include Parkinson's Disease Patient Report of Problems (PD-PROP™), Personal Wellbeing Patient Report of Problems (PWB-PROP™) and Schwab and England ADL to enquire about specific problems and symptoms they are experiencing in daily and social activities. Subjects will be asked to complete the assessments at home (approximately 1-2 days prior to clinic visit). The assessments should take about 30 minutes to complete. Subjects who cannot complete all of the exploratory assessments, but who otherwise remain eligible for the study, can continue their participation. If a subject needs help to troubleshoot technical issues, their personal email ID will be shared with Modality. QC will be done by Modality staff who will review audio/video files throughout the conduct of the trial.

- Adverse events (AEs), concomitant medications, vital signs, safety laboratory parameters, and ECG data will be collected and assessed throughout the study per the SoA (see Section 1.3).

- Subjects will return for a safety follow-up visit two weeks after Visit 6 (ie, last day of study drug dosing). Subjects will complete assessments per the SoA (see Section 1.3).

### 4.1.1. Study Duration for an Individual Subject

The study duration for an individual subject will be up to 18 weeks and will include an eligibility screening period of up to 4 weeks, treatment duration of up to 12 weeks, and 2 weeks of safety follow-up.

### 4.1.2. Number of Subjects

Approximately 62 subjects will be enrolled into the study with a 1:1 randomization to CVN424 or placebo.

#### 4.1.2.1. Replacement of Subjects

Subjects who withdraw or discontinue early from the study may be replaced at the Sponsor's discretion.

### 4.1.3. Number of Sites

Approximately 25 sites in the USA.

## 4.2. Scientific Rationale for Study Design

Previous clinical studies, including two Phase 1 studies in healthy volunteers and a Phase 2a study as an adjunctive treatment in subjects with PD and motor fluctuations, support the use of CVN424 in this study. Data from these studies showed that CVN424 150 mg was safe and well tolerated in both healthy volunteers and individuals with PD taking anti-PD medications. No changes in vital signs or laboratory values of clinical significance were observed following

CVN424 dosing. In the Phase 2a study, CVN424 150 mg demonstrated significant reduction in OFF time.

This study will examine the potential of CVN424 to improve motor and non-motor functions in individuals with early PD not taking dopaminergic or anti-PD therapies, to provide the evidence for further pursuing the development of CVN424 for the broader treatment of the motor and non-motor symptoms of PD.

For further details, see Background – Section 2.2.

## 4.3. Justification for Dose

The dose of CVN424 that will be administered in this study (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, which is predicted to achieve potentially therapeutic concentrations of drug exposure. CVN424 150 mg tablets will be administered orally, once a day, in the morning with a snack or typical morning meal, which should include fat in its content..

In the healthy volunteer study CVN424-102 (Study CVN424-102; NCT05635461), oral administration of 150 mg CVN424 tablets under fed conditions (approximately 30% fat content) resulted in an approximately 62% increase in overall exposure (AUCs) and a 204% increase in peak exposure ($C_{max}$) of plasma CVN424 compared to 150 mg CVN424 tablets given under fasted conditions. These results indicate that a high-fat, high-calorie meal increases both the extent and peak exposures of CVN424 tablets in plasma.

## 4.4. End of Study Definition

A subject is considered to have completed the study if he or she has completed all scheduled visits of the study, including the 2-week safety follow-up period (Week 14; refer to the SoA, Section 1.3).

## 4.5. End of Treatment Definition

A subject is considered to have completed treatment if he or she has completed 12 weeks of treatment with once daily dosing with CVN424 150 mg or placebo tablets.

# 5. Indication & Study Population

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 10.1.3). Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Diagnosis of PD consistent with United Kingdom Brain Bank and Movement Disorder Society Research Criteria for the Diagnosis of PD; must include bradykinesia with sequence effect, and motor asymmetry if no PD-type rest tremor.
2. Not receiving anti-parkinsonian therapy, and not expecting to require it for the duration of the study.
3. Men or women of all races who are at least 30 years at Screening.
4. Modified Hoehn and Yahr $\leq 2.5$ at Screening.
5. Montreal Cognitive Assessment (MoCA) $\geq 26$.
6. Freely ambulatory at time of Screening (with/without assistive device).
7. Female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to either remain abstinent or use adequate and reliable contraception throughout the study and at least 30 days after the last dose of study drug has been taken.
8. Able and willing to give written (signed and dated) informed consent approved by an institutional review board, and to comply with scheduled visits, treatment plan, laboratory tests, and other study-related procedures to complete the study.
9. Approved as an appropriate and suitable candidate by the EAC.

## 5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Diagnosis of secondary or atypical parkinsonism.
2. Diagnosis of parkinsonian motor signs or symptoms $\geq 4$ years before Screening Visit.
3. Previous surgical procedure for PD.
4. Prior treatment with a dopamine agonist, levodopa, MAOB inhibitor, or adenosine A2A receptor antagonists for more than 28 total days prior to screening. Additional exclusionary parameters around PD treatment include:
    - Treatment with a dopamine agonist within 14 days of Screening.
    - Treatment with a MAOB inhibitor within 90 days of Screening.

5. Current use of any antipsychotic, metoclopramide, or reserpine. If previously used, this may not have been within 28 days of Screening or 5 elimination half-lives (whichever one is longer).
6. Current use of potent Cytochrome P450 (CYP) 3A4/5 inhibitors or inducers.
7. Clinically significant orthostatic hypotension.
8. Clinically significant hallucinations requiring antipsychotic use.
9. Known autoimmune, malignancy (except basal cell carcinoma), or hematologic disease (prior or current) likely to interfere with the safe participation of the subject or interfere with assessment of safety or efficacy based on the opinion of the investigator and the medical monitor.
10. Any clinically significant medical, surgical, or psychiatric abnormality that, in the judgment of the Investigator, is likely to interfere with study compliance, the safe participation of the subject or the assessment of safety or efficacy.
11. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 2 times the upper limit of normal (ULN), and total bilirubin greater than 1.5 times ULN. Subjects with Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided that direct bilirubin is 1.5 times ULN.
12. Significant renal impairment as determined by eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation of ≤ 50 mL/min.
13. Subject has and ECG, prior documented history, or clinical evidence of potentially unstable heart disease, including, but not limited to the following:
    a. QTcF > 470 msec for female subjects; > 450 msec for male subjects
    b. Complete right or left bundle branch block
    c. Myocardial infarction within 1 year prior to screening, unstable angina within 6 months, or a current concern for symptomatic ischemic heart disease in the opinion of the investigator
    d. Clinically significant atrial or ventricular dysrhythmia; the heart must be in predominantly normal sinus rhythm
    e. Second- or third-degree atrioventricular (AV) block
    f. NYHA Class II or higher congestive heart failure
    g. Clinically significant cardiomyopathy or cardiac structural abnormality, in the opinion of the investigator
    h. Any other cardiac condition that the Investigator feels may predispose the subject to ischemia or arrhythmia
14. Current (or within past 12 months) diagnosis or history of substance abuse (excluding nicotine or caffeine) by Diagnostic and Statistical Manual of Mental Disorders 5 criteria.
15. Positive urine drug screen for tetrahydrocannabinol or any drugs that may affect subject safety or interfere with efficacy assessments.

16. Medical or recreational use of marijuana within 2 months of the Screening Visit. Use of cannabidiol (CBD) is prohibited after the Screening Visit and throughout the study.
17. Currently active major depression as determined by BDI-II score of > 19.
18. Active suicidal ideation within 1 year prior to Screening Visit as determined by a positive response to Question 4 or 5 on the C-SSRS.
19. Currently lactating or pregnant, or planning to become pregnant during the study.
20. Current participation in another investigational clinical study and/or receipt of any investigational drug within 90 days prior to Screening.
21. Prior use of CVN424 investigational product.
22. Positive test for COVID-19. A subject who tests positive for COVID-19 will be eligible to be rescreened once result is negative.
23. Positive test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) consistent with current infection.

## 5.3. Prohibited Medications and Lifestyle Considerations

Use of the agents in Table 5-1 (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

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 (eg, omeprazole, pantoprazole, lansoprazole)
- Histamine H2-receptor antagonists (eg, cimetidine, ranitidine, famotidine, nizatidine)
- Antacids taken within 4 hours of dosing

Use of CBD is prohibited after the Screening Visit and throughout the study.

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

**Table 5-1. Prohibited Medications and Dietary Products**

| Within 28 days prior to randomization or 5 elimination half-lives, whichever is longer |
|---|
| • Antipsychotics: Both typical and atypical antipsychotics, including, but not limited to: aripiprazole, fluphenazine, haloperidol, perphenazine, pimozide, thiothixene, trifluoperazine, loxapine, molindone, chlorpromazine, mesoridazine, thioridazine, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and pimavanserin.<br>• Other: metoclopramide, prochlorperazine, promethazine |

| |
|---|
| • Nutraceuticals (eg, St. John's wort, ginseng, kava, Ginkgo Biloba, Chinese herbs, and melatonin)<br>• Mucuna Pruriens |
| • Amphetamines<br>• Known strong inhibitors/inducers of cytochrome P-450 3A4/5, including rifampin, clarithromycin, ketoconazole, and itraconazole [CYTOCHROME P450 DRUG INTERACTION TABLE (iu.edu)]. |

### 5.3.1. Study Drug and Meals Considerations

Subjects will be dispensed study drug to be administered at home. The study drug should be taken once daily at a consistent time in the morning and taken with food. The food taken with study drug may be a snack or typical morning meal and should include fat in its content (e.g., buttered toast, peanut butter on crackers, an egg, cream cheese on a bagel, full fat yogurt or milk).

### 5.3.2. Study Drug Interruption or Suspension

Study drug may be temporarily suspended based on investigator judgement (eg, in response to a clinically significant adverse event suspected to be related to the study drug) and only after consultation with the Medical monitor.

A suspension may happen once during the study and should not exceed 10 days in duration.

If a participant cannot successfully resume investigational drug after suspension, they will discontinue study drug but may remain in the study for continued assessment.

### 5.3.3. Alcohol

Subjects must abstain from regular alcohol consumption exceeding 7 drinks/week for female subjects and 14 drinks/week for male subjects (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor).

### 5.3.4. Activity

Subjects must abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

## 5.4. Screen Failures

Screen failures are defined as subjects who consented to participate in the clinical trial but do not meet eligibility criteria and cannot be randomized in the study. Minimal information to be collected for screen failure documentation includes demography, reason for screen failure details, and eligibility criteria.

Subjects who do not meet the criteria for participation in this trial (screen failure) may be rescreened if the reason for screen failure has resolved. Rescreened subjects must be assigned a new subject identification number. A subject can be rescreened no more than 2 times.

# 6. Investigational Product and Concomitant Therapy

The CVN424 150 mg tablet drug product is a film-coated, immediate release tablet. The formulation is comprised of drug substance, CVN424, compendial excipients (mannitol, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate) and film-coating (Opadry®).

The matching placebo tablet components are microcrystalline cellulose, mannitol, magnesium stearate, and film-coating (Opadry®).

CVN424 150 mg tablets and matching placebo are packaged and labeled using the randomization code. Each bottle of study drug will be labeled in English and the language appropriate to the investigational site. Label text will be approved according to the Sponsor's procedures. Bottles will be labeled with pertinent study information and caution statements in accordance with regulatory requirements.

Refer to the Pharmacy Manual for more detailed information regarding the storage, preparation, destruction, and administration of each treatment.

## 6.1. Investigational Product Dispensation, Dosing and Regimen

The Investigator or Investigator's designee will instruct each subject (and their home caregiver, where applicable) on the dosing regimen. Study drug will be dispensed as 30 count tablets in properly labeled high-density polyethylene (HDPE) bottles.

The study drug will be self-administered once daily at a consistent time in the morning and taken with food. The food taken with study drug may be a snack or typical morning meal and should include fat in its content (e.g., buttered toast, peanut butter on crackers, an egg, cream cheese on a bagel, full fat yogurt or milk)..

The planned study arms and dose levels are provided in Table 6-1.

**Table 6-1. Study Arms**

| Arm Title | Study Drug | Placebo |
|---|---|---|
| **Arm Type** | CVN424 150 mg per day | Matching Placebo |
| **Arm Description** | 31 subjects receive 1 tablet (150 mg) per day | 31 subjects receive 1 tablet per day |
| **Associated Product Labels** | Each label will include the protocol number; unique bottle identification number; contents; route of administration; storage conditions; directions for use; FDA Caution Statement; Sponsor name, address and phone number; and a space for the sites to record the date dispensed, subject identification number and subject initials | |

FDA = US Food and Drug Administration.

No dosage adjustments are anticipated in this study.

In the event a subject misses taking a dose of study drug at the scheduled time, the subject should take that dose as soon as they remember, but no later than 6 hours beyond the scheduled time of administration. If it is greater than 6 hours beyond the scheduled dose, the subject should be instructed to skip that dose and resume dosing at the next regularly scheduled time.

## 6.2. Investigational Product Assignment, Storage, and Accountability

### 6.2.1. Investigational Product Storage

All study drug stored at the investigative site must be kept in an appropriate, limited-access, secure storage location until it is used or returned to the Sponsor or designee for destruction. All study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. Store the CVN424 150 mg tablets at controlled room temperature, 59°F to 77°F (15°C to 25°C).

### 6.2.2. Investigational Product Assignment Procedure

Randomization assignments will be generated using an online interactive response technology (IRT) system. All randomization information is accessible only by authorized study personnel. Study drug will be dispensed to subjects as tablets in properly labeled, capped bottles.

### 6.2.3. Investigational Product Accountability

Only subjects enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. The Investigator must maintain records of all study drug delivery to the site, site inventory used by each subject, and returned to the Sponsor or designee. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Drug supplies will be counted and reconciled at the site before being returned to the Sponsor or designee or before a site follows institutional policies for destruction.

Upon receipt of the study drug, the Investigator or designee must verify the contents of the shipments against the packing list and ensure the quantity is correct and received within the labeled storage conditions. The Investigator must maintain 100% accountability for all study drug received and dispensed during their full participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory; verifying that all bottles used are documented accurately on the log; and 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 drug 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 drug, retest/expiry date, and amount dispensed, including the initials of the person dispensing and receiving the study drug.

Subjects will return their bottles of study drug, whether empty or unused, at each in-person clinic study visit. The Investigator or designee must record the number of empty and unused bottles returned.

During the study, the assigned monitor will perform clinical study material accountability and reconciliation before clinical study materials are returned to the Sponsor or its designee for destruction. 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 drug during the study conduct.

Refer to the Pharmacy Manual for more detailed information regarding the storage, preparation, destruction, and administration of each treatment.

## 6.3. Randomization and Blinding

Subjects who continue to meet all the inclusion criteria and do not meet any of the exclusion criteria at the Baseline visit will be randomly assigned in a 1:1 ratio to CVN424 150 mg or placebo once daily using an online IRT system.

This is a double-blind study. All individuals involved in the conduct of the study, including subjects, Investigators, site staff, clinical research organization personnel, and Sponsor study personnel, will remain blinded to treatment assignments and dose throughout the study. The randomization schedule will not be released until all subjects have completed the study and the database has been locked.

At all times, study personnel will attempt to safeguard the integrity of the blind to minimize bias in the conduct of the study. If the Investigator or site study staff becomes aware of a subject's study treatment assignment, efforts should be made to not disclose assignments to other study staff, subjects, or their caregivers.

### 6.3.1. Breaking the Blind

Breaking the blind should not occur, except in the case of a medical emergency if specific emergency treatment or course of action would be determined by knowing the treatment

assignment of the subject. If possible, the Investigator should discuss the situation with the medical monitor before breaking the blind.

If an Investigator needs to know a subject's treatment assignment for a medical emergency, the Investigator may access this information via the IRT system.

If the blind is broken for an individual subject, the Sponsor should be informed as soon as possible. The date and reason for the unblinding must be documented in the subject's source documentation and eCRF. Any documentation indicating the subject's treatment assignment must be retained with the subject's source documents in a secure manner (ie, sealed envelope) so as not to unblind the treatment assignment to other site or Sponsor personnel.

If the blind is broken for a subject, the decisions to continue or discontinue study drug and whether the subject is asked to continue or discontinue the study will be based on the nature of the medical emergency as judged by the Investigator in consultation with the medical monitor, and not necessarily because the study blind was broken (although this may be a factor in the decisions).

When an AE is an unexpected, related SAE, the blind will be broken by the Sponsor only for that specific subject. The blind will be maintained for persons responsible for the ongoing conduct of the study and those responsible for data analysis and interpretation of results at the conclusion of the study. Unblinded information will only be accessible to those who need to be involved in the safety reporting to health authorities and an Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

## 6.4. Study Drug Compliance

Study drug will first be administered while subjects are at the clinical site (at the Baseline Visit). Subsequent doses will be self-administered at home. The date and time of each observed dose will be recorded in the source documents and in the eCRFs.

Treatment compliance will be assessed at each study visit as indicated in the SoA (see Section 1.3). Subjects will be instructed to bring all used/unused study drug bottles to each study visit. To assess subjects' compliance with study drug, manual tablet counts of study drug will be performed. At each visit, subjects will return all used/unused study drug bottles to the site, whether empty or full, for assessment of treatment compliance.

Overall, treatment noncompliance is defined as taking ≤ 80% or ≥ 120% of the planned study drug during a treatment period.

If a subject is found to be noncompliant with dosing, the Investigator will discuss the reasons for the noncompliance and then counsel the subject on the need to remain compliant.

Subjects who are significantly noncompliant may be discontinued from the study. A subject will be considered significantly noncompliant if the subject intentionally missed more than 20% of study drug during the study.

An inventory of the study drug dispensed will be performed by the site staff or pharmacist and recorded onto the Drug Accountability Log.

## 6.5. Treatment of Overdose

An overdose is defined as a known deliberate or accidental administration of investigational study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. For this study, any dose of CVN424 greater than 300 mg within a 24-hour time period will be considered an overdose.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s).

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Sections 8.4.4 and 10.3.4, Reporting of SAEs.

In the event of an overdose, supportive measures should be employed as needed, eg, administration of supportive therapy as dictated by the subject's clinical status, and initiation of additional clinical monitoring.

In the event of an overdose, the Investigator should evaluate the subject to determine, in consultation with the medical monitor, if possible, whether study drug should be interrupted, closely monitor the subject for any AE/SAE and laboratory abnormalities, obtain a plasma sample for PK analysis within 4 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis), and document the quantity of the excess dose as well as the duration of the overdose.

## 6.6. Prior and Concomitant Therapy

Concomitant medications are any drug given in addition to the study drug. These may be prescribed by a physician or over the counter.

At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from the signing of the 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.

Subjects must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) as specified in Table 5-1 within 28 days or 5 elimination half-lives (whichever is longer) before the start of study drug until completion of the follow-up visit. Proton pump inhibitors, histamine H2-receptor antagonists and antacids

(taken within 4 hours of dosing) are not prohibited prior to or during the study but should only be used if medically necessary because they may theoretically diminish CVN424 bioavailability. Subjects will be instructed not to take any new medications without first consulting with the Investigator or their delegate.

Paracetamol/Acetaminophen, at doses of ≤ 2 g/day, is permitted for use any time during the study, under the supervision of the Investigator. Other concomitant medications may be considered on a case-by-case basis by the Investigator, in consultation with the medical monitor, if required.

***Anti-parkinsonian medications***: Subjects can be enrolled in the study if they are not receiving anti-parkinsonian medications at the time of screening and if they are not expected to require symptomatic treatment for the entire length of the study. If medically necessary, subjects may need to begin medications to treat the motor symptoms of PD during the study. This is not actively encouraged, but is permitted in the judgment of the subject, Investigator, and in consultation with the medical monitor. Subjects who start PD medication will be taken off study drug, followed for safety, and complete study activities as best as possible.

### 6.6.1. Rescue Medicine

Not applicable.

# 7. Discontinuation of Study Drug and Subject Early Termination/Discontinuation or Withdrawal

## 7.1. Discontinuation of Study Drug

Subjects who discontinue from study drug will be followed up for safety. Remaining study assessments and procedures should be completed as indicated by the SoA (see Section 1.3).

## 7.2. Subject Early Termination/Discontinuation/Withdrawal From the Study

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

- Occurrence of AE(s): Clinical or laboratory events that, in the medical judgement of the Investigator, are grounds for discontinuation of the subject from the study.

- Protocol deviation: The subject failed to adhere to protocol requirements. Unless either the Investigator or medical monitor considers that continuation in the study may pose a safety risk to the subject, the subject may continue in the study. The protocol deviation will be documented in the subject's source documentation and eCRF.

- Withdrawal of consent: The subject provides a verbal or written request to withdraw from the study and withdraws consent to ensure that data collected up to the time of study withdrawal can be used for analysis.

- Physician decision.

- Lost to follow-up: A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site after multiple attempts (at least 3 times). Several attempts to contact the subject will be made by study staff and documented in the subject's source documentation. The date that the subject is considered lost to follow-up and the reason for the subject's subsequent discontinuation from the study will be documented in the subject's source documentation and eCRF.

- Voluntary withdrawal from the study: The subject verbalizes or states in writing their desire to withdraw from the study. Data already collected remains as part of 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 (eg, withdrawal due to an AE; withdrawal due to relocation).

- The Sponsor decides to terminate the study.

If a subject discontinues the study at any time after enrollment, but prior to the final scheduled study visit, the Investigator will promptly notify the Sponsor and make every effort to have the subject complete the safety follow-up assessment (ie, early termination (ET) assessments indicated in SoA [see Section 1.3]) as soon as feasible after discontinuation. Subjects who discontinue from the study early will be asked to return for an Early Termination Visit. The date of and reason for the subject's discontinuation from the study will be documented in the subject's source documentation and eCRF. All data collected up to the time of early termination will be used for final analyses, unless the subject withdraws consent to use the study data.

All subjects who discontinue the study with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or deemed medically stable by the Investigator in consultation with the medical monitor.

Subjects who are lost to follow-up or discontinue the study early may be replaced if deemed necessary by the Sponsor.

## 7.3. Lost to Follow-up

If a subject fails to return for clinic visits, every attempt must be made to make contact.

The site will attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and assess if the subject wishes to and/or should continue in the study.

Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.

If the investigative site is not able to reach or make contact with the subject or caregiver, he or she will be considered to have been lost to follow-up.

# 8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (see Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in the SoA (see Section 1.3), is essential and required for study conduct.

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

Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1. General Assessments

### 8.1.1. Medical History

The Investigator or designee will collect a complete medical history that started prior to screening through time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions. All findings will be recorded in the medical history eCRF. The current severity grade will be collected for each condition that has not resolved.

### 8.1.2. Prior Therapy

Prior therapies that were being taken/used from 28 days (90 days for MAOB inhibitors) prior to enrollment through the first dose of investigational product, will be collected.

For prior PD therapies, collect therapy name, dose, unit, frequency, start date, and stop date. For all other prior therapies, collect therapy name, start, and stop date.

### 8.1.3. Demographics

Demographic data will be collected at Screening, and will include sex, age, race, and ethnicity. The data will be collected to study their possible association with subject safety and treatment effectiveness.

## 8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (see Section 1.3).

#### 8.2.1. Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS (Goetz et al, 2008) is a comprehensive 50-question assessment of both motor and non-motor symptoms associated with PD. It features sections that require independent completion by people with PD and their caregivers, as well as sections to be completed by an approved rater. At each site, the same rater should perform all MDS-UPDRS assessments throughout the study, as best possible.

- Part I: Non-motor Aspects of Experiences of Daily Living. This has 13 items and is further grouped into two parts:
  - Part IA has items associated with behaviors that are assessed and completed by the rater based on information provided by the subject and caregiver.
  - Part IB is self-administered and completed by the subject with or without assistance or input from the caregiver, but independently of the rater.

Responses to both IA and IB can be reviewed by the rater to ensure information accuracy and/or provide additional information or clarification of the test items, if necessary.

  - Part II: Motor Aspects of Experiences of Daily Living. This part has 13 items. It is a self-administered questionnaire completed by the subject, which can be reviewed by the Investigator to ensure all responses are completed.
  - Part III: Motor Examination. This part of the MDS-UPDRS has 18 items evaluating the motor signs of PD (bradykinesia, tremor, rigidity, hand and leg movements, gait, balance, etc.).
- Part IV: Motor Complications. Part IV data will not be collected and used in the trial.

It is estimated that the MDS-UPDRS would take around 30 minutes to complete.

#### 8.2.2. Clinical Global Impression of Severity Scale (CGI-S)

The CGI-S (Padhi and Fineberg, 2010) is a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal/not at all ill) to 7 (amongst the most severely ill patients). This requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.

#### 8.2.3. Patient Global Impression of Severity Scale (PGI-S)

The PGI-S is a subject-completed assessment rating PD severity on a scale of 1 to 5 with 1 being none and 5 being very severe.

#### 8.2.4. Epworth Sleepiness Scale (ESS)

The ESS (Johns, 1992) is a subject self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0 to 3: would never doze, slight chance of dozing, moderate chance of dozing, and high chance of dozing), their usual chances of dozing off or falling asleep while engaged in eight different activities, such as sitting and reading, watching television, sitting inactive in a public place, etc. Most people engage in those activities at least

occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'. The questionnaire takes no more than 2 to 3 minutes to answer.

#### 8.2.5. Non-Motor Symptoms Scale (NMSS) for Parkinson's Disease

The NMSS for Parkinson's Disease (Chaudhuri et al, 2007) is a 30-item rater-based scale to assess the frequency and severity of NMSS in patients across all stages of PD. The NMSS measures the severity and frequency of non-motor symptoms across 9 dimensions (cardiovascular, including falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and miscellany). Responses are to quantify symptoms according to severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4). It is completed by a rater.

#### 8.2.6. Parkinson's Disease Sleep Scale (PDSS-2)

The PDSS-2 (Trenkwalder et al, 2011) is a 15-item subject-reported outcome measure to assess nocturnal disturbances in PD. It is a 5-point frequency scale (from "very often" [0] to "never" [4]), with a total score ranging from 0 to 60, where higher scores indicate greater impairment.

#### 8.2.7. Starkstein Apathy Scale (SAS)

The SAS is based on the construct of apathy proposed by Marin (Starkstein et al, 1992), characterized as the absence or lack of feeling, emotion, interest, or motivation. The Starkstein scale standardized Marin's construct into a set of criteria, based on the presence of diminished goal-directed behavior and diminished goal-directed cognition. The scale comprises 14 questions in which the respondent self-rates on a 4-point scale, ranging from "Not at all", "Slightly", "Some", and "A Lot". Ratings are a score from 3 to 0 for questions 1-8, and from 0 to 3 for questions 9-14, producing a total score out of 42. A score above 14 is usually considered the more severe level of apathy.

#### 8.2.8. Exploratory Efficacy Assessments

##### 8.2.8.1. The Modality System

The Modality System is an artificial intelligence interface that collects information about clinical performance. Subjects will communicate with a virtual agent via web browser on an electronic device. This virtual agent will interview them and give instructions for simple tasks to test various aspects of their speech, visuo-motor, prosodic (stress and intonation patterns), cognitive, and linguistic function. It includes the PD-PROP™ and PWB-PROP™ to enquire about specific problems and symptoms individuals are experiencing in daily and social activities. It is estimated these tasks will take about 30 minutes to complete.

Modality assessments will be conducted at home by the subject 1 to 2 days prior to the clinic visit. If a subject needs help to troubleshoot technical issues, their personal email ID will be shared with Modality. QC will be done by Modality staff, who will review audio/video files

throughout the conduct of the trial. Subjects who cannot complete all of the Modality assessments, but who otherwise remain eligible for the study, can continue their study participation.

8.2.8.1.1. ***The Parkinson's Disease Patient Report of Problems (PD-PROP™)***
The PD-PROP™ is a series of open-ended questions that asks individuals with PD to rank, in their own words, without restriction of content or length, up to 5 PD-related bothersome problems and their related effects on daily functioning.

8.2.8.1.2. ***Personal Wellbeing Patient Report of Problems (PWB-PROP™)***
The PWB-PROP™ is a series of open-ended questions that asks individuals with PD to rank, in their own words, without restriction of content or length, up to 5 PD-related bothersome problems related to their day-to-day life or personal wellbeing, such as personal, family, financial, social, or other aspects and their related effects on daily functioning.

### 8.2.8.2. Schwab and England Activities of Daily Living Scale (ADL)

The Schwab and England ADL scale (Schwab and England, 1968) estimates the abilities of individuals living with a disease relative to a completely independent situation. Scores range from 100%, which indicates a completely independent individual; 70% is not completely independent and may have more difficulty with activities which may take 3 to 4 times as long (eg, may take large part of day for chores); 40% is very dependent and can assist with all chores but can manage few alone; and zero percent which indicates an individual who is no longer functioning.

### 8.2.8.3. Cogstate Digital Cognitive Testing Battery

The Cogstate Computerized Testing Battery will be conducted twice at screening to familiarize the subject with the procedure.

Cogstate Digital Cognitive Testing Battery are computerized cognitive assessments of attention, executive function, verbal learning, and memory. Cogstate Digital Cognitive Testing Battery will occur at the timepoints specified in the SoA (see Section 1.3). The Cogstate Digital Cognitive Testing Battery implemented for this study includes the following tests:

8.2.8.3.1. ***Detection (DET; Psychomotor Function)***
The DET test is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The subject is asked to press the Yes key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response.

Duration of Test: 3 minutes.

***8.2.8.3.2. Identification (IDN; Attention)***
The IDN test is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The subject is asked whether the card displayed in the center of the screen is red. The

subject responds by pressing the Yes key when the joker card is red and the No key when it is black. The software measures the speed and accuracy of each response.

Duration of Test: 4 minutes.

#### *8.2.8.3.3. One Back (ONB; Working Memory)*

The ONB test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously.

The subject responds by pressing the Yes or No key. Since no card has been presented yet on the first trial, a correct first response is always No. The software measures the speed and accuracy of each response.

Duration of Test: 5 minutes.

#### *8.2.8.3.4. The International Shopping List Test (ISLT) and The International Shopping List Test – Delayed Recall (ISRL; Verbal Learning)*

The ISLT is a measure of verbal learning and uses a well-validated list-learning paradigm. High frequencies, high imagery, concrete nouns (items from a shopping list) are read to the subject by the test supervisor at the rate of one word every 2 seconds. Once all 12 words have been read, the subject is asked to recall as many of the words as he/she can as quickly as possible. The test supervisor records the words recalled by the subject on the testing device. When the subject can recall no more words, the same list is read a second time. The test supervisor records the words recalled by the subject on this trial. This is then repeated a third time.

Delayed recall and recognition conditions will also be used in this study. The delayed recall condition requires the subject to recall the words from the list 10-30 minutes later without having the list read again. During the recognition condition, the test supervisor reads a shopping list item that may or may not have been on the original list and the subject has to respond either affirmatively (if the item was on the original list) or negatively (if it was not). The software measures the number of correct responses as recorded by the test supervisor.

Duration of Test: 5 minutes for ISLT ± 1 minute for ISRL.

#### *8.2.8.3.5. International Digit Symbol Substitution Test – Symbols (IDSSTS; Processing Speed)*

The IDSSTS is a processing speed test that is based on the well-established digit symbol coding paradigm. In this test, subjects are presented with a legend that defines 9 symbols, with each symbol corresponding to a digit from 1 to 9. The subject is then presented with a conveyer belt in the middle of the screen that displays a series of empty boxes labelled with a number. The subject must select the symbol that corresponds to the number of a given highlighted box from symbol options presented at the bottom of the screen. The subject must try to place as many correct symbols in the boxes as possible over the duration of the test. Performance is measured by calculating the total number of correct responses.

Duration of Test: 3 minutes.

Total Estimated Time (with familiarization): approximately 19 minutes.

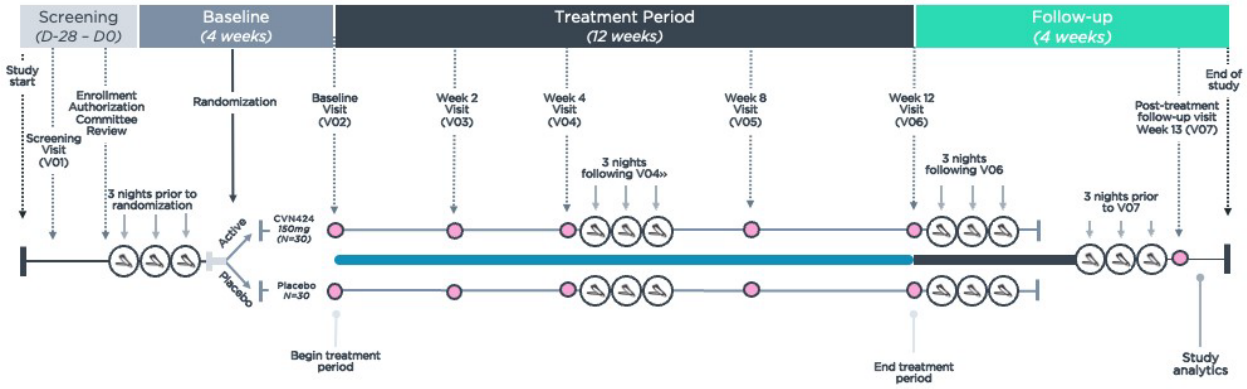
#### 8.2.8.4. Beacon Dreem EEG

The Beacon Dreem 3B device is a wearable EEG headband that collects EEG signals from dry EEG electrodes and head movement from an accelerometer to provide deep learning-powered sleep staging. If a subject opts into EEG, they or their authorized caregiver will receive initial training by the site staff at Screening before being shipped all Beacon Dreem System Components and provided device final configuration training from Beacon study staff. Training will include instructions for device setup, companion application and mobile phone use, device application, system maintenance, and troubleshooting recommendations. Subjects who opt out of the Beacon Dreem EEG collection can continue their study participation.

Overnight EEG recordings will occur up to 3 consecutive nights prior to Baseline (Visit 2) and Week 14 (Visit 7); as well as immediately following Week 4 (Visit 4) and Week 12 (Visit 6).

Change from baseline in EEG derived sleep metrics, including sleep macro-architectural features will be assessed between CVN424 150 mg and placebo at Week 4 (Visit 4) and Week 12 (Visit 6).

**Figure 2. Beacon Dreem EEG Schema**




## 8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

### 8.3.1. Physical and Neurological Examinations

A full physical examination will be performed by a trained physician as indicated in the SoA (Section 1.3). The physical examination will include:

- Body weight (kg)
- Height (cm) (at the Screening Visit only)

- General appearance
- Head, ears, eyes, nose, throat, and mouth
- Neck
- Heart
- Lungs
- Abdomen
- Musculoskeletal and neurological systems
- Extremities
- Skin

A standard neurological examination by a trained neurologist will be performed as indicated in the SoA (see Section 1.3). The same physician should perform all neurological examinations for a given subject, if possible.

### 8.3.2. Vital Signs

Vital signs will include temperature, respiration rate, heart rate, and blood pressure and will be collected at timepoints specified in the SoA (see Section 1.3). Blood pressure will be measured after at least 5 minutes supine and again within 1 to 3 minutes of standing. Study personnel will carefully monitor subjects for signs of orthostatic hypotension, defined as a systolic blood pressure decrease of ≥ 20 mm Hg and/or a diastolic blood pressure decrease of ≥ 10 mm Hg within 3 minutes of standing up from a supine position.

### 8.3.3. Electrocardiograms (ECGs)

Standard 12-lead ECGs will be recorded at time points specified in the SoA (see Section 1.3). ECG recordings will be obtained in a supine position following an approximately 10-minute period of rest. ECGs will be interpreted by qualified personnel at the central ECG lab. The Investigator or sub-Investigator will categorize the ECG findings using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. 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.

### 8.3.4. Modified Hoehn and Yahr Scale

The Modified Hoehn and Yahr scale (Hoehn and Yahr, 1967) captures typical patterns of progressive motor impairment, and is widely used for the staging of functional disability in PD. It includes stages 1 to 5, ranging from 0, absence of symptoms to 5, wheelchair-bound or

bedridden. The modified version of the Hoehn and Yahr scale includes midway stages to help describe the intermediate course of the disease.

### 8.3.5. Montreal Cognitive Assessment (MoCA)

The MoCA (Nasreddine et al, 2005) takes approximately 10 minutes to administer and was designed to detect mild cognitive impairment in elders scoring in the normal range on the Mini-Mental State Examination (MMSE). Thirty items assessing multiple cognitive domains are contained in the MoCA: short-term memory (5 points); visuospatial abilities via clock drawing (3 points), and a cube copy task (1 point); executive functioning via an adaptation of Trail Making Test Part B (1 point), phonemic fluency (1 point), and verbal abstraction (2 points); attention, concentration, and working memory via target detection (1 point), serial subtraction (3 points), digits forward (1 point), and digits backward (1 point); language via confrontation naming with low-familiarity animals (3 points), and repetition of complex sentences (2 points); and orientation to time and place (6 points). The MoCA is scored by obtaining an item total and the authors recommend a clinical cutoff score of 26.

### 8.3.6. The Beck Depression Inventory-II (BDI-II)

The BDI-II (Becket al, 1996) is a 21-item, self-rated scale that evaluates key symptoms of depression including mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, indecisiveness, body image change, work difficulty, insomnia, fatigability, loss of appetite, weight loss, somatic preoccupation, loss of libido, agitation, worthlessness, concentration difficulty, and loss of energy. The 21 symptoms and attitudes contained in the BDI reflect the intensity of the depression; items receive a rating of 0 to 3 to reflect their intensity and are summed linearly to create a score which ranges from 0 to 63. The BDI administration is straightforward, and it can be given as an interview by the clinician or as a self-report instrument (requiring a fifth or sixth grade reading level).

BDI-II scoring:

- 0-13 is considered none or minimal range depression
- 14-19 is considered mild depression
- 20-28 is considered moderate depression
- 29-63 is considered severe depression.

### 8.3.7. The Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al, 2011) is used to assess suicidal tendency. The Baseline/Screening version of the C-SSRS will be used at the Screening visit. This version assesses suicidality in a subject's lifetime and during the past 12 months. The "Since Last Visit" version of the C-SSRS will be used at all other visits. This version assesses suicidality since the subject's last visit. Efforts must be made to ensure that the same trained team member completes this questionnaire for each subject. A subject with any suicidal ideation that answers "Yes" to questions 4 or 5 in the C-SSRS questionnaire at Screening is excluded and should be referred to a mental health

professional. Sites must have institutional procedures in place that will be followed if a referral to a mental health professional is necessary.

### 8.3.8. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (see Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within two weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (see Section 1.3).

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

The tests detailed in Table 10-1 will be performed by the central laboratory. Unscheduled tests may be performed at any time during the clinical trial as determined necessary by the Investigator or required by local requirements.

### 8.3.9. Pregnancy Testing

Women who are pregnant or breastfeeding will not be included in this study (see Section 5).

Pregnancy testing will be performed at screening and after study start, as specified in the SoA (see Section 1.3), for all women of childbearing potential. Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator, or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study. The pregnancy test will be performed at the central laboratory using a beta-human chorionic gonadotropin (β-HCG) test for the screening visit. Urine pregnancy tests will be collected at subsequent visit as per the SoA (see Section 1.3).

## 8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug, or that caused the subject to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports, are provided in Section 10.3.

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

All SAEs will be collected from the signing of the ICF until 30 days following the last dose or early termination at the timepoints specified in the SoA (see Section 1.3).

All AEs will be collected from the signing of the ICF until 14 days following the last dose or early termination at the timepoints specified in the SoA (see Section 1.3).

Medical events that begin before the Screening Visit will be recorded as medical history/current medical conditions, not as AEs. However, if the study subject's condition worsens at any time during the study, it will be recorded as an AE.

All AEs will be captured in the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

All SAEs will be recorded and reported to the Sponsor or designee immediately within 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

If the Investigator has been made aware of any SAE, including a death, at any time after a subject has completed the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

### 8.4.2. Method of Detecting AEs and SAEs

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

### 8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.6) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Other supporting documentation of the event may be requested by Pharmacovigilance and/or study Sponsor and should be provided as soon as possible. Further information on follow-up procedures is provided in Section 10.3.

### 8.4.4. Regulatory Reporting Requirements for SAEs

The Investigator will immediately report to the Sponsor any SAE, whether or not considered study drug related, including those listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the study drug caused the event. Study endpoints that are SAEs (eg, all-cause mortality) must be reported in accordance with the protocol, unless there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested by Pharmacovigilance and/or study Sponsor and should be provided as soon as possible.

The Sponsor will be responsible for notifying the FDA or other applicable Regulatory Authority of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify FDA or other applicable Regulatory Authority and all participating Investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

### 8.4.5. 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, they 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 15 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 drug, eg, after Day 0 or within 12 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the medical monitor and Sponsor.

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 they became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

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

### 8.4.6. Adverse Events of Special Interest

**Abuse Potential Adverse Events**
The assessment of abuse potential is a regular part of the safety evaluation for any investigational compound that has central nervous system (CNS) activity. While preclinical or preliminary clinical data to date do not suggest a role of CVN424 for potential abuse or misuse, the Investigators will pay particular attention to any AE that emerges during the study treatment or after study drug discontinuation that may be suggestive of a signal of abuse potential.

The following categories of terms will be monitored per FDA recommendation:

- Euphoria-related terms
  - Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucinations; Inappropriate affect
- Terms indicative of impaired attention, cognition, and mood
  - Somnolence; Mood disorders and disturbances
- Dissociative/psychotic terms
  - Psychosis; Aggression; Confusion and disorientation
- Related terms not captured elsewhere
  - Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders

The study team will ensure adequate review, coding and follow-up of AEs recommended by the FDA for emerging patterns suggestive of misuse or abuse. For each abuse-related AE, the dedicated study team will write a detailed narrative based on a study-specific narrative template. Narratives will include time of onset and duration of the event, dose of drug taken, severity and outcome. When available, PK values will be provided for each subject who experiences abuse-related AEs.

To investigate the potential for abuse, misuse and diversion, an accurate check of study drug accountability will be performed at each study visit. Investigators must report any significant discrepancies that, in the opinion of the Investigator, raise the suspicion of abuse, misuse, or diversion:

- Failure to return unused study drug without explanation
- Running out of drug early
- Drug-seeking behaviors
- Returned drug is damaged or there is evidence of tampering.

Any signs that the subject may be misusing study drug should be reported as an AE accordingly.

## 8.5. Pharmacokinetics, Metabolite, and [redacted]

### 8.5.1. Pharmacokinetic, Metabolite, and [redacted] Sample Collection

Blood samples (one sample per scheduled time) for analysis of CVN424 plasma concentrations will be collected into chilled vacutainers containing dipotassium ethylenediaminetetraacetic acid (K2EDTA) according to the schedule in Table 8-1. Instructions for sample processing and shipment are provided in a separate laboratory manual.

**Table 8-1. Collection of Blood Samples for PK Analysis**

| Week/Visit | Time Post-dose (hours) |
|---|---|
| Baseline/Visit 2 | Pre-dose (0 h) and at 4 h post-dose (± 30 mins) |
| Week 4/Visit 4 | Post-dose (time not specified but actual time to be recorded based on time last dose was administered)[a] |
| Week 8/Visit 5 | Post-dose (time not specified but actual time to be recorded based on time last dose was administered)[a] |
| Week 12/Visit 6 | Post-dose (time not specified but actual time to be recorded based on time last dose was administered)[a] |

PK = pharmacokinetics.

a Time of last administered dose to be accurately recorded by subject. Time of last administered dose could be the day before visit or on the day of visit.

PK samples will be collected at the nominal timepoint within the allowable windows. The actual time of sample collection will be recorded.

Placebo samples will not be analyzed by the bioanalytical laboratory, except 2 samples per subject receiving placebo, one following the first dose (4 hours post-dose) and one at Week 8/Visit 5 to ensure from a safety perspective that no additional subjects could have been on active treatment.

An additional blood sample will be collected to analyze metabolite and [redacted] in a patient population that is PD drug naïve. The sample will be collected at each time PK is collected.

### 8.5.2. Bioanalytical Methods

Plasma concentrations of CVN424 will be measured using a validated high-performance liquid chromatography - tandem mass spectrometry (HPLC-MS/MS) method. Plasma samples will be archived to support potential post hoc laboratory testing.

### 8.5.3. Pharmacokinetic Parameters

Where possible, the PK parameters of CVN424 will be derived using the concentration-time data for all evaluable subjects and a population PK model. Actual sampling times will be used in all computations using sampling times.

# 9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock and unblinding of the study data and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary endpoints.

## 9.1. Sample Size Determination

A sample size of approximately 62 subjects with a 1:1 randomization to CVN424 150 mg or placebo will provide 75% power to detect a difference of 5 or more points for the sum of MDS-UPDRS Parts II and III, assuming a standard deviation (SD) of 8, two-sided alpha of 0.10, and a 10% dropout rate.

The effect size of 5 points for Part II + Part III is felt to reflect a meaningful threshold that, if achieved, would be comparable to other effective PD medications at 12 weeks (pramipexole, levodopa).

**Figure 3. Parameters for Sample Size and Power Calculations**

**Design: Continuous Endpoint: Two-Sample Test - Parallel Design - Difference of Means**

| Test Parameters | |
|---|---|
| Design ID | m=5,sd=8_d=0.1 |
| Design Type | Superiority |
| Number of Looks | 1 |
| Test Type | 2-Sided |
| Specified α | 0.1 |
| Power | 0.756 |
| **Model Parameters** | |
| Test Statistic | Z |
| Input Method | Individual Means |
| Mean Control ($\mu_c$) | 0 |
| Mean Treatment ($\mu_{t1}$) | 5 |
| $\delta = \mu_t - \mu_c$ | |
| Under H0 | 0 |
| Under H1 | 5 |
| Std. Deviation (σ) | 8 |
| Allocation Ratio ($n_t/n_c$) | 1 |
| **Accrual / Dropouts Parameters** | |
| Accrual Rate: | 15 |
| Response Lag: | 12 |
| Probability of Dropout: | 0.1 |

Sample sizes and completers have been rounded.

**Sample Size Information**

| | |
|---|---|
| Sample Size (n) | 62 |
| Treatment (n_t) | 31 |
| Control (n_c) | 31 |
| Completers (s) | 56 |
| Treatment (s_t) | 28 |
| Control (s_c) | 28 |
| Dropouts (d) | 6 |
| Treatment (d_t) | 3 |
| Control (d_c) | 3 |
| Information (I) | 0.219 |

**Accrual and Study Duration**

| | |
|---|---|
| Accrual Duration | 4.133 |
| Study Duration | 16.133 |

**Critical Points**

| | |
|---|---|
| Lower Critical Point | -1.645 |
| Upper Critical Point | 1.645 |

## 9.2. Populations For Analyses

All data analyses will be performed using at least one of the following analysis sets:

- Safety Analysis Set:
  Includes all subjects who have received at least 1 dose of study drug. All safety population

analyses will be based on the treatment the subject received. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety analyses.

- Modified Intention To Treat (mITT):
  Includes all subjects who are randomized, and administered study drug, classified according to the treatment received, and have at least one post-baseline evaluation of efficacy endpoints.
- Intention-to-Treat (ITT) Set:
  Includes all randomized subjects.
- Completer Set:
  Includes all subjects who completed all study treatment for 12 weeks.
- Pharmacokinetic Analysis Set:
  Includes all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma concentration.
- Per Protocol Analysis Set:
  Includes all subjects who completed the study and who received all study treatment and have no significant protocol deviations. All significant protocol deviations will be assessed, and a decision will be made on a case-by-case basis whether to exclude subjects from the Per Protocol analysis set prior to breaking the blind. All per protocol analyses will be based on the treatment the subject received. This set will be used as a sensitivity analysis for primary and secondary efficacy outcomes.

## 9.3. Statistical Analyses

### 9.3.1. Efficacy Endpoint Analysis

Hierarchy of Efficacy Endpoints:

Each efficacy endpoint (primary and secondary) includes a comparison of CVN424 versus placebo. The overall Type I error rate within the family of efficacy endpoints will be maintained by using Hochberg's step-up method to maintain alpha while comparing CVN424 to placebo. Efficacy endpoints will be evaluated in a hierarchical manner. Significance of successive endpoints cannot be claimed unless prior endpoints in the hierarchy are significant. Nominal p-values will be reported for descriptive purposes and interpreted in an exploratory manner.

**Analytic Methods**
*The primary estimand will be defined as follows:*

- *Population:* Subjects with PD as defined by inclusion/exclusion criteria and are in the mITT population
- *Variable:* The primary endpoint is the change from Baseline to Week 12 in the MDS-UPDRS Part II + Part III score (Motor Aspects of Experiences of Daily Living + Motor Examination)
- *Intercurrent Events and Proposed Strategy*: Treatment Discontinuation: Hypothetical Strategy. Initiation of Parkinsonian medication for treatment of motor features: Hypothetical Strategy

- *Population Level Summary*: Treatment difference of the least-squares mean change from Baseline to Week 12 in the MDS-UPDRS Part II + Part III score (Motor Aspects of Experiences of Daily Living + Motor Examination) between placebo and CVN424 groups.

Efficacy endpoints will be analyzed in the mITT population using a MMRM with no imputation. This will include response data from each post-baseline visit based on the mITT population (defined as subjects that are randomized, receive treatment, and have post-baseline data with respect to the primary endpoint). The baseline score will be included as a covariate as well as the treatment group (150 mg CVN424 or placebo), visits, interaction between treatment group and visit, as fixed factors in the MMRM. The difference between CVN424 versus placebo at the final visit will be estimated from the MMRM. An unstructured covariance matrix will be used initially, and if it fails to converge, a Compound Symmetry (CS) or an AR (1) matrix shall be employed, in that order.

Sensitivity analyses for efficacy endpoints will be conducted on the ITT set with the multiple imputation method, both assuming that data are missing at random (MAR) and missing not at random (MNAR). MNAR analyses will include tipping point and jump-to-reference (placebo) assumptions. Further sensitivity analysis will be conducted in the completer and per-protocol set with MMRM. Sensitivity analyses will also be conducted by including retrieved dropout data (data captured from subjects who are free of study treatment and may have started anti-parkinsonian medication).

Categorical secondary efficacy endpoints (proportion of subjects improving based on CGI-S or PGI-S) will be analyzed in the mITT population using the Cochran–Mantel–Haenszel (CMH) test. This test will include the frequency and percentage of proportions for each group, along with their respective 95% confidence interval (CI). Additionally, the difference in proportions between the treatment groups, along with its CI, will be calculated. As a sensitivity analysis, a GLIMMIX model that can incorporate all response data from each post-baseline visit into the analysis will be employed. The model will include the treatment group, visit, interaction between treatment groups and visit. An unstructured covariance structure will be used for the repeated measures. The odds ratio for the treatment difference, 95% CI for the odds ratio and p-value will be provided.

### 9.3.2. Tolerability and Safety Analysis

Tolerability will be assessed by comparing percentages of premature drug and study discontinuations in the treatment groups (CVN424 vs placebo).

The safety analysis, including suicidality, will be conducted on the Safety Analysis Set that includes all randomized subjects. TEAEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group, organ class and preferred term, and duration. Further summaries will be done by seriousness, severity, relationship to study treatment and dose at the time of onset. Safety endpoints will be summarized with descriptive statistics.

### 9.3.3. Data Monitoring Committee

No data monitoring committee will be appointed for this study.

# 10. Supporting Documentation and Operational Considerations

## 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of Title 21 of the Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

Informed consent forms describing in detail the study drug, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to the subject entering the study and before any protocol-related procedures are performed.

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the subject or their legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

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

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

A copy of the ICF(s) must be provided to the subject or their legally authorized representative.

Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

### 10.1.4. Data Protection

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

The subject must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to

the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### 10.1.5. Committees Structure

An EAC will review subject eligibility and suitability for participation prior to enrollment into the study. EAC approval will occur after laboratory and ECG results have been received and screening data has been entered into the electronic data capture system.

### 10.1.6. Dissemination of Clinical Study Data

The Sponsor will register and/or disclose the existence of and the results of clinical studies as required by local laws and regulations.

### 10.1.7. Data Quality Assurance

All subject data relating to the study will be recorded in eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in eCRF Completion Guidelines.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan. The monitors will verify that the clinical trial is conducted, data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, Good Laboratory Practices, Good Manufacturing Practices).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a time period that complies with local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 10.1.8. Source Documents

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

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the monitoring guidelines.

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

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

### 10.1.9. Study Termination

The Sponsor or designee reserves the right to terminate the study at any time for any reason at the sole discretion of the Sponsor.

Reasons for the early closure of the study by the Sponsor or Investigator may include but are not limited to:

Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

### 10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

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

### 10.1.11. Sample Storage and Destruction

Any blood PK sample collected according to the SoA (see Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Cerevance Beta, Inc. can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the therapeutic area, the dose response and/or prediction of response to CVN424, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 10 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the subject, the Investigator is to provide the Sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Cerevance Beta, Inc.

The Sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the Investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the Sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 10.1.4 for subject confidentiality.

## 10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 will be performed by the central laboratory.

- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

**Table 10-1. Protocol-required Laboratory Tests**

<table>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Coagulation</th></tr>
<tr><td rowspan="2">hematocrit<br>hemoglobin<br>platelet count<br>RBC count<br>RBC indices:<br>MCH<br>MCHC<br>MCV<br>%/nL reticulocytes<br>WBC count with differential:<br>neutrophils<br>lymphocytes<br>monocytes<br>eosinophils<br>basophils</td><td rowspan="2">albumin<br>alkaline phosphatase<br>ALT/SGPT<br>AST/SGOT<br>BUN<br>calcium<br>bicarbonate<br>chloride<br>creatinine<br>creatinine kinase<br>GGT<br>glucose [nonfasting]<br>LDH<br>potassium<br>sodium<br>total and direct bilirubin<br>total protein</td><td>INR<br>PT<br>PTT/aPTT</td></tr>
<tr><td>Urinalysis<br>specific gravity<br><br>pH, glucose, protein, blood, ketones, nitrite [by dipstick]<br><br>microscopic examination (if blood or protein is abnormal):<br>RBC/high power field<br>WBC/high power field<br>Epithelial cells, casts, etc.</td></tr>
<tr><th>Diagnostic Screening in Serum</th><th colspan="2">Diagnostic Screening in Urine/ Blood</th></tr>
<tr><td>Serum hCG[a]<br>FSH[b]<br>Hepatitis panel including:<br>• HBsAg<br>• Anti-HCV<br>HIV<br>COVID-19</td><td colspan="2">Drug screen including amphetamines, barbiturates, benzodiazepines, cocaine, opiates, methadone, methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), tetrahydrocannabinol (THC)<br><br>Urine Pregnancy Test[a]</td></tr>
</table>

ALT = alanine transaminase; anti-HCV = hepatitis C virus antibody; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; BUN = blood urea nitrogen; COVID-19 = coronavirus disease 2019; GGT = gamma-glutamyl transferase; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HIV = Human Immunodeficiency Virus; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell.

a Serum pregnancy test at screening and urine pregnancy test at all other indicated visits for women of child-bearing potential only.
b For women of child-bearing potential only.

## 10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1. Definition of AE

**AE Definition**

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

A TEAE is an AE that begins on or after administration of the first dose of trial medication or an increase in severity or frequency on or after administration of the first dose of trial medication.

**Events Meeting the AE Definition**

Any abnormal laboratory test results (hematology, clinical chemistry, coagulation, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the subject's condition).

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

**Events <u>not</u> Meeting the AE Definition**

Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

**a. Results in death**

**b. Is life threatening**

The term *life threatening* in the definition of *serious* 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, which hypothetically might have caused death, if it were more severe.

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

### 10.3.3. Recording and Follow-up of AE and/or SAE

**AE and SAE Recording**

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is not acceptable for the Investigator to send photocopies of the subject's medical records to Pharmacovigilance or the Sponsor in lieu of completion of the required form.

There may be instances when copies of medical records for certain cases are requested by Pharmacovigilance. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Pharmacovigilance.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of Intensity**

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

**Assessment of Causality**

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable *possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Pharmacovigilance. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Pharmacovigilance.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The relationship of each AE to study drug(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.

**Expectedness**

Pharmacovigilance and the medical monitor, in consultation with the Sponsor, will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

**Follow-up of AEs and SAEs**

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Pharmacovigilance or the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide Pharmacovigilance with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally submitted documents.

The Investigator will submit any updated SAE data to Pharmacovigilance within 24 hours of receipt of the information.

**Outcome**

The Investigator will be asked to record the outcome by choosing one of the following alternatives:

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

### 10.3.4. Reporting of SAEs

**SAE Reporting to Pharmacovigilance via an Electronic Data Collection Tool**

The primary mechanism for reporting an SAE to Pharmacovigilance will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.

Contacts for SAE reporting can be found in the safety reporting plan.

**SAE Reporting to Pharmacovigilance via Paper Data Collection Tool**

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor or the SAE coordinator.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

Contacts for SAE reporting can be found in the safety reporting plan.

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Definitions

**Woman of Childbearing Potential (WOCBP)**
Women in the following categories are considered WOCBP (fertile):

Following menarche

- From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

**Note:** Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

### 10.4.2. Contraception Guidance

| **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE**: |
|---|
| **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of < 1% per year when used consistently and correctly.* |
| • Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] |
| • Intrauterine device (IUD) |
| • Intrauterine hormone-releasing system (IUS)[c] |
| • Bilateral tubal occlusion |
| • Azoospermic partner (vasectomized or due to a medical cause)<br>*Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*<br>Note: documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview. |
| **Highly Effective Methods[b] That are User Dependent** *Failure rate of < 1% per year when used consistently and correctly.* |
| Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]<br>- oral<br>- intravaginal<br>- transdermal<br>- injectable |
| Progestogen-only hormone contraception associated with inhibition of ovulation[c]<br>- oral<br>- injectable |
| Sexual abstinence<br>*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.* |
| **Effective Methods[d] That are not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.* |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action |
| • Male or female condom with or without spermicide |
| • Cervical cap, diaphragm, or sponge with spermicide |

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|---|
| • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c] |
| a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.<br>b Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.<br>c Male condoms can be used in addition to hormonal contraception.<br>d Considered effective, but not highly effective - failure rate of ≥ 1% per year.<br>Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction). |

## 10.5. Appendix 5: Country-specific Requirements

Not applicable.

## 10.6. Appendix 6: Protocol Amendment History

## SUMMARY OF CHANGES

**Version 2.0 (17 January 2024) replaces Version 1.0 (22 June 2023)**

**Amendment 1: (17 January 2024)**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**Overall Rationale for the Amendment:** Clarification and consistency of sections listed below.

| Section # and Name | Description of Change |
|---|---|
| Title page | NCT number added |
| Overall | Spotlite Overnight has been replaced with Optional Beacon Dreem electroencephalogram recordings |
| Overall | Formatting and style |
| Synopsis, Section 3 Objectives, Endpoints, and Estimands | Endpoints were updated (primary, secondary and exploratory endpoints) |
| Synopsis, Section 4.1 Overall Design | Baseline assessments added.<br>Statements added to indicate subjects can continue participation even when unable to complete exploratory endpoint assessments.<br>Modality assessment duration and further instruction added. |
| Synopsis, Section 4.1.2, Section 6.1 Number of Subjects | Updated number of subjects to be enrolled. |
| Synopsis, Section 5.2 Exclusion Criteria | Exclusion criteria updated around cannabidiol use, autoimmune likelihood to interfere with subject safety or assessments, monoamine oxidase B (MAOB) treatment prior to Screening and duration of antipsychotic, metoclopramide or reserpine prior to Screening, PCR testing for COVID-19 removed. |
| Synopsis, Section 9.1 Sample Size Determination | Subject numbers updated and additional information provided. |
| Synopsis, Section 9.3.1 Efficacy Endpoint Analysis | Primary efficacy analysis language was updated.<br>Secondary efficacy language was updated. |
| Section 1.2 Schema | Schema was updated. |
| Section 1.3 Schedule of Assessments (SoA) | To facilitate enrollment and reduce study burden on participants/care givers; Emerald RF Continuous Monitoring is removed and change Beacon EEG procedure to be optional |

| | |
|---|---|
| | Footnotes updated to give better clarification on blood pressure measurements, modality assessments, coagulation test timing, and Cogstate cognitive computerized battery assessments. |
| Section 5.3 Prohibited Medications and Lifestyle Considerations | Use of cannabidiol use after Screening added.<br>Table 5-1 was updated with additional prohibited medications and dietary products. |
| Section 5.3.1 Study Drug and Meals Considerations | The amount of meal to eat before taking the study drug was updated. |
| 5.3.2 Study Drug Interruption or Suspension | New information about study drug interruption or suspension was added. |
| 5.3.3 Alcohol | Duration about when to stop consuming alcohol prior to screening was deleted. |
| 5.3.4 Activity | Type of activities recommended was cancelled. |
| 6.2.1 Investigational Product Storage | Storage temperature was updated. |
| Section 8.2.1 Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) | Additional information added to ensure same rater, where possible, performs assessments. |
| Section 8.2.3 Patient Global Impression of Severity Scale (PGI-S) | Severity scale grading updated |
| Section 8.2.4 Epworth Sleepiness Scale (ESS) | Scale criteria updated |
| Section 8.2.8.1 The Modality System | Additional instructions added and estimated time updated for assessment completion. |
| Section 8.2.8.4 Emerald RF Continuous Monitoring | Emerald deleted. |
| Section 8.2.8.5 EEG | Additional instructions added about training. Figure 2 updated. Change from baseline assessments updated including changing the EEG assessment to Optional |
| Section 8.3.7 The Columbia Suicide Severity Rating Scale (C-SSRS) | Assessment period updated to “during the past 12 months” |
| Section 8.5.1 Pharmacokinetic, Metabolite, and [redacted] Sample Collection | Addition of metabolite and [redacted] sample collection with PK sample collections |
| Appendix 2 Clinical Laboratory Tests | Drug screen tests were updated; COVID-19 was added as a diagnostic screening in serum. |

**Version 3.0 (10 July 2024) replaces Version 2.0 (17 January 2024)**

**Amendment 2: (10 July 2024)**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**Overall Rationale for the Amendment:** Clarification and consistency of sections listed below.

| Section # and Name | Description of Change |
|---|---|
| Synopsis, Section 4.1 Overall Design<br>4.1 Overall Design<br>4.3 Justification of Dose<br>5.3.1 Study Drug and Meals Considerations<br>6.1. Investigational Product Dispensation, Dosing and Regimen | Instructions for study drug administration were changed from, "Subjects will be dispensed study drug to be administered at home with the largest meal of the day at the same time every day, as best as possible", to "the study drug will be self-administered once daily at a consistent time in the morning and taken with food. The food taken with study drug may be a snack or typical morning meal and should include fat in its content (e.g., buttered toast, peanut butter on crackers, an egg, cream cheese on a bagel, full fat yogurt or milk)." |
| Synopsis, Section 4.1 Overall Design<br>5.2 Exclusion Criteria | Clarification of Exclusion Criteria #13 to include "ECG, prior documented history, or" clinical evidence of potentially unstable heart disease.<br>Clinical evidence of disease listed were revised to:<br>"c. Myocardial infarction within 1 year prior to screening, unstable angina within 6 months, or a current concern for symptomatic ischemic heart disease in the opinion of the investigator"<br>"f. NYHA Class II or higher congestive heart failure.". |
| Synopsis, Section 4.1 Overall Design<br>5.2 Exclusion Criteria | Clarification of Exclusion Criteria #22 to remove the statement, "Confirmatory test will be allowed at the discretion of the Investigator to rule out false positives." |

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