Statistical Analysis Plan: CVN424-203

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Trial of CVN424 in Early Parkinson's Disease
Study Number:	CVN424-203
Study Phase:	CVN424
Sponsor:	Cerevance Beta, Inc.
NCT #:	NCT06006247
Version:	Final 2.0
Date:	17 January, 2025

Confidentiality Statement

Version History	
Version	**Description of Changes**
Final 1.0	Initial version.
Final 2.0	Updated parallel to Protocol amendment 2 and sponsor input. Following are major changes: • Hierarchy of endpoint is updated • Clarification that the study is powered for two-sided significance level of 0.05 and all statistical tests will be conducted on two-sided significance level of 0.05 • Some cosmetic and formatting updates • Adverse event (AE) leading to study drug interruption/suspension details added • Efficacy plots added • Section 8 updated considering updated in latest protocol amendment • Assumption on plasma concentration below limit of quantification • adjustments made, and some formatting and style instructions added • Baseline parameters re-arranged • Added details of time to Parkinson's Disease (PD) diagnosis at study drug initiation • Time matched placebo adjusted QT corrected intervals tabulation added • Visit windowing for efficacy tabulation added for Week 12/Early termination visit • Addition of appendices for imputation of partial dates, PCI criteria, and planned lab assays, with example tables added

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2 SIGNATURE PAGE

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

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR	Assessment/collection/result
ADL	Activities of Daily Living
AE(s)	Adverse event(s)
AESI	Adverse event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C virus antibodies
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BDI-II	Beck Depression Inventory-II
BLQ	Below the lower limit of quantification
BMI	Body mass index
CFB	Change from baseline
CGI-S	Clinical Global Impression of Severity Scale
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CPP	Cepstral Peak Prominence
COVID	Coronavirus Disease
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Canonical Timing Alignment
DBP	Diastolic blood pressure
DBL	Database lock
DDK	Diadochokinetic
EAC	Enrollment Authorization Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EEG	Electroencephalogram
ESS	Epworth Sleepiness Scale
FSH	Follicle-stimulating hormone

Abbreviation	Definition
GLIMMIX	Generalized linear mixed model
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HNR	Harmonics to Noise Ratio
HR	Heart rate
ICF	Informed consent form
ITT	Intention-to-Treat
LSM	Least-squares mean
MAR	Missing at random
MDMA	Methylenedioxymethamphetamine
MDS – UPDRS	Movement Disorder Society – Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
M-EDL	Motor Aspects of Experiences of Daily Living
MHDECOD	Medical History with Medical Decoded Values
MI	Multiple Imputation
mITT	Modified Intent-to-treat
MMRM	Mixed model repeated measure
MNAR	Missing not at random
MoCA	Montreal Cognitive Assessment
nM-EDL	Non-motor Aspects of Experiences of Daily Living
NMSS	Non-motor Symptoms Scale
PD	Parkinson's disease
PD-PROP™	Parkinson's Disease Patient Report of Problems
PDSS-2	Parkinson's Disease Sleep Scale-2
PGI-S	Patient Global Impression of Severity Scale
PK	Pharmacokinetics
PKS	Pharmacokinetic Analysis Set
PPS	Per Protocol Analysis Set
PR	Pulse rate
PROP	Patient Report of Problems

Abbreviation	Definition
PT	Preferred term
PWB-PROP™	Personal Wellbeing Patient Report of Problems
QC	Quality check
QTcB	QT interval, corrected using Bazett's formula
QTcF	QT interval, corrected using Fridericia's formula
S&E	Schwab and England
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Starkstein Apathy Scale
SAS®	Statistical Analysis Software®
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard Error
SFAS	Safety Analysis Set
SoA	Schedule of Assessments
SOC	System organ class
TEAE(s)	Treatment emergent adverse event(s)
UN	Unstructured

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the framework for the reporting, summarization and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on Protocol CVN424-203 Amendment 2 (v3.0), dated 10 July, 2024.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective

The primary objective and associated endpoint are specified in Table 1.

Table 1. Primary Objectives and Endpoints

Objectives	Endpoints
To determine the effect of CVN424 on motor features of early, untreated subjects with Parkinson's Disease (PD)	Change from Baseline (CFB) 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

5.2 Secondary Objectives

The secondary objectives and associated endpoints are specified in Table 2.

Table 2. Secondary Objectives and Endpoints

Objectives	Endpoints
To further define the effects of CVN424 on motor and non-motor clinical features, function, and quality of life in Parkinson's Disease (PD)	• Change from Baseline (CFB) to Week 12 on the following endpoints between CVN424 150 mg and placebo, arranged in hierarchical order: o Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS – UPDRS) Part III o MDS – UPDRS Part II o Epworth Sleepiness Scale (ESS) o MDS – UPDRS Part I o Non-motor Symptoms Scale (NMSS) o Sum of MDS – UPDRS of Parts I, II, and III o Parkinson's Disease Sleep Scale-2 (PDSS-2) o Clinical Global Impression of Severity Scale (CGI-S) o Patient Global Impression of Severity Scale (PGI-S)
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 • Incidence of related TEAEs of moderate or severe intensity • 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), electrocardiogram (ECG), laboratory values, and Columbia Suicide Severity Rating Scale (C-SSRS)

Objectives	Endpoints
	• Incidence and timing of abuse-related adverse events (AEs) • Occurrence of withdrawal symptoms recorded at the follow--up visit • Percentage of completers

5.3 Exploratory Objectives

The exploratory objectives and associated endpoints are specified in Table 3.

Table 3. Exploratory Objectives and Endpoints

Objectives	Endpoints
To describe the effects of CVN424 on motor performance, function, cognition, and sleep with other exploratory endpoints	• Change from Baseline (CFB) to Week 12 in the following endpoints: o Modality Virtual Assessment o CogState digital cognitive battery o Schwab and England (S&E) Activities of Daily Living (ADL) o Starkstein Apathy Scale (SAS) o Electroencephalogram (EEG) derived sleep metrics o Parkinson's Disease Patient Report of Problems (PD-PROP™) and Personal Wellbeing Patient Report of Problems (PWB-PROP™) o Pharmacokinetics (PK)

6 STUDY DESIGN CONSIDERATIONS

6.1 Study 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 Parkinson's Disease (PD). It will evaluate CVN424 150 mg once a day against placebo.

There will be seven in-person visits and 2 telephone visits:

- Screening (Visit 1)
- Baseline/Randomization (Visit 2)
- Week 2 (Visit 3)
- Week 4 (Visit 4)
- Week 6 (Telephone Call 1)
- Week 8 (Visit 5)
- Week 10 (Telephone Call 2)
- 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. 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.

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-2 (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, Appendix 1).

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 will be collected up to 3 consecutive nights before or after specified in-person clinic visits, per the SoA (Appendix 1). Subjects who opt out of the Beacon Dreem EEG collection can continue their study participation in other study activities.

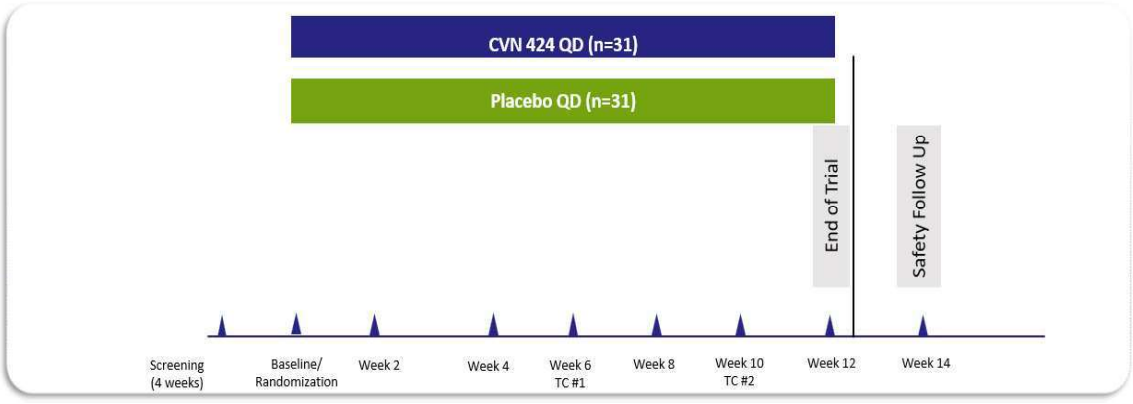
- Modality Assessments: an audio-visual conversational technology to conduct customizable video interviews with subjects designed to test various aspects of their speech, visuo-motor, prosodic (stress and intonation patterns), cognitive, and linguistic function. It also includes PD-PROP™, PWB-PROP™, and Schwab and England (S&E) 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 at instructed study times. The assessments should take about thirty minutes to complete. Subjects who cannot complete all the exploratory endpoint 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. Quality control (QC) will be done by Modality staff who will review audio/video files throughout the conduct of the trial. Modality data are collected remotely between clinic visits as well.

- Adverse events (AEs), concomitant medications, vital signs, safety laboratory parameters, and electrocardiogram (ECG) data will be collected and assessed throughout the study per the SoA (Appendix 1).

- 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 (Appendix 1).

The complete study design is illustrated in Figure 1.

Figure 1. Study Schema



TC = telephone call; QD = once a day.

6.1.1 Safety Review Committee/Data Monitoring Committee

Not applicable.

6.1.2 Justification of Sample Size

A sample size of approximately 62 subjects with a 1:1 randomization to CVN424 150 mg or placebo will provide 80% 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 7 (McGarry et al, 2024), two-sided alpha of 0.05, and a 10% dropout rate.

The effect size of 5 points for MDS – UPDRS 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).

6.2 Efficacy Measures

6.2.1 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. Its questions are divided into four parts:

- Part I: Non-motor Aspects of Experiences of Daily Living (nM-EDL)
- Part II: Motor Aspects of Experiences of Daily Living (M-EDL)
- Part III: Motor Examination
- Part IV: Motor Complications

The summary of questions in each part is described in Section 8.2.1 of the Protocol. Part IV is not in scope of this study and will not be collected.

MDS – UPDRS Part I

Part I of MDS – UPDRS, also known as nM-EDL, is one of the secondary measures for this study. MDS – UPDRS Part I contains 13 items grouped into 2 further parts:

- Part IA (consisting of 6 items) is associated with behaviors that are assessed and completed by the rater based on information provided by the subject and caregiver.
- Part IB (consisting of 7 items) is self-administered and completed by the subject with or without assistance or input from the caregiver, but independently of the rater.

Each item of this questionnaire is briefly summarized in Table 4. The MDS – UPDRS Part I will be performed as outlined in the SoA (Appendix 1).

Table 4. Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS – UPDRS) Part I

S. No.	Questions	Normal (0)	Slight (1)	Mild (2)	Moderate (3)	Severe (4)
	Part IA: Complex behaviours: [completed by rater]					
1.A	Source of information	Patient ☐	Caregiver ☐		Patient + Caregiver ☐	
1.1	Cognitive impairment	0	1	2	3	4
1.2	Hallucinations and psychosis	0	1	2	3	4
1.3	Depressed mood	0	1	2	3	4
1.4	Anxious mood	0	1	2	3	4
1.5	Apathy	0	1	2	3	4
1.6	Features of Dopamine dysregulation syndrome (DDS)	0	1	2	3	4
	Part IB: Patient Questionnaire (maybe reviewed by rater)					
1.6a	Who is filling out questionnaire	Patient ☐	Caregiver ☐		Patient + Caregiver ☐	
1.7	Sleep problems	0	1	2	3	4
1.8	Daytime sleepiness	0	1	2	3	4
1.9	Pain and other sensations	0	1	2	3	4
1.1	Urinary problems	0	1	2	3	4
1.11	Constipation problems	0	1	2	3	4
1.12	Light headedness on standing	0	1	2	3	4
1.13	Fatigue	0	1	2	3	4

The sum of all responses of items in MDS – UPDRS Part I questionnaire is MDS – UPDRS Part I sum score. The MDS – UPDRS Part I sum score ranges from 0 to 52. This is a measure for one of the secondary endpoints for the study.

In case of missing individual items, if the number of missing MDS – UPDRS Part I individual items is 1, the MDS – UPDRS Part I sum score will be calculated as:

$$= \left(\frac{\text{Sum of available item scores}}{\text{Number of items with non} - \text{missing scores}}\right) \times 13$$

In case the number of missing Part I individual items is more than 1, the MDS – UPDRS Part I sum score will be set as missing (Goetz et al, 2015).

MDS – UPDRS Part II

Part II of MDS – UPDRS, also known as M-EDL, is one of the secondary (and part of primary) endpoints for this study. Each item of this questionnaire is briefly summarized in Table 5. The MDS – UPDRS Part II assessment will be performed as outlined in the SoA (Appendix 1).

Table 5. MDS – UPDRS Part II

S. No.	Questions	Normal (0)	Slight (1)	Mild (2)	Moderate (3)	Severe (4)
2.1	Speech	0	1	2	3	4
2.2	Saliva and drooling	0	1	2	3	4
2.3	Chewing and swallowing	0	1	2	3	4
2.4	Eating tasks	0	1	2	3	4

S. No.	Questions	Normal (0)	Slight (1)	Mild (2)	Moderate (3)	Severe (4)
2.5	Dressing	0	1	2	3	4
2.6	Hygiene	0	1	2	3	4
2.7	Handwriting	0	1	2	3	4
2.8	Doing hobbies and other activities	0	1	2	3	4
2.9	Turning in bed	0	1	2	3	4
2.10	Tremor	0	1	2	3	4
2.11	Getting out of bed, a car, or a deep chair	0	1	2	3	4
2.12	Walking and balance	0	1	2	3	4
2.13	Freezing	0	1	2	3	4

The sum of all responses of items in MDS – UPDRS Part II questionnaire is MDS – UPDRS Part II sum score. The MDS – UPDRS Part II sum score ranges from 0 to 52. This is a measure for one of the secondary endpoints for the study.

In case of missing individual items, if the number of missing MDS – UPDRS Part II individual items is 2 or less, the MDS – UPDRS Part II sum score will be calculated as:

$$= \left(\frac{\text{Sum of available item scores}}{\text{Number of items with non} - \text{missing scores}}\right) \times 13$$

In case the number of missing Part II individual items is more than 2, the MDS – UPDRS Part II sum score will be set as missing (Goetz et al, 2015).

MDS – UPDRS Part III

Part III of this questionnaire (ie, MDS – UPDRS Part III; motor examination) is a measure of the assessment for the primary and secondary endpoint of this study and each item is briefly summarized in Table **6**. The MDS – UPDRS Part III assessment will be performed as outlined in the SoA (Appendix 1).

Table 6. MDS – UPDRS Part III

S. No.	Questions	Normal (0)	Slight (1)	Mild (2)	Moderate (3)	Severe (4)
3a	Is the patient on medication?	No	Yes			
3b	Patient's clinical state	Off	On			
3c	Is the patient on levodopa?	No	Yes			
3.1	Speech	0	1	2	3	4
3.2	Facial expression	0	1	2	3	4
3.3a	Rigidity – Neck	0	1	2	3	4
3.3b	Rigidity – Right upper extremity	0	1	2	3	4
3.3c	Rigidity – Left upper extremity	0	1	2	3	4
3.3d	Rigidity – Right lower extremity	0	1	2	3	4
3.3e	Rigidity – Left lower extremity	0	1	2	3	4
3.4a	Finger tapping – Right hand	0	1	2	3	4
3.4b	Finger tapping – Left hand	0	1	2	3	4
3.5a	Hand movements – Right hand	0	1	2	3	4
3.5b	Hand movements – Left hand	0	1	2	3	4

S. No.	Questions	Normal (0)	Slight (1)	Mild (2)	Moderate (3)	Severe (4)
3.6a	Pronation- supination movements – Right hand	0	1	2	3	4
3.6b	Pronation- supination movements – Left hand	0	1	2	3	4
3.7a	Toe tapping – Right foot	0	1	2	3	4
3.7b	Toe tapping – Left foot	0	1	2	3	4
3.8a	Leg agility – Right leg	0	1	2	3	4
3.8b	Leg agility – Left leg	0	1	2	3	4
3.9	Arising from chair	0	1	2	3	4
3.10	Gait	0	1	2	3	4
3.11	Freezing of gait	0	1	2	3	4
3.12	Postural stability	0	1	2	3	4
3.13	Posture	0	1	2	3	4
3.14	Global spontaneity of movement	0	1	2	3	4
3.15a	Postural tremor – Right hand	0	1	2	3	4
3.15b	Postural tremor – Left hand	0	1	2	3	4
3.16a	Kinetic tremor – Right hand	0	1	2	3	4
3.16b	Kinetic tremor – Left hand	0	1	2	3	4
3.17a	Rest tremor amplitude – Right upper extremity	0	1	2	3	4
3.17b	Rest tremor amplitude – Left upper extremity	0	1	2	3	4
3.17c	Rest tremor amplitude – Right lower extremity	0	1	2	3	4
3.17d	Rest tremor amplitude – Left lower extremity	0	1	2	3	4
3.17e	Rest tremor amplitude – Lip/jaw	0	1	2	3	4
3.18	Constancy of rest tremor	0	1	2	3	4

The sum of all responses of items in the MDS – UPDRS Part III questionnaire is MDS – UPDRS Part III sum score. The MDS – UPDRS Part III sum score ranges from 0 to 132. This is a measure for one of the secondary endpoints for the study.

In case of missing individual items, if the number of missing MDS – UPDRS Part III individual items is 7 or less, the MDS – UPDRS Part III sum score will be calculated as:

$$= \left(\frac{\text{Sum of available item scores}}{\text{Number of items with non} - \text{missing scores}}\right) \times 33$$

In case the number of missing Part III individual items is more than 7, the MDS – UPDRS Part III sum score will be set as missing (Goetz et al, 2015).

The information for these questionnaires is obtained from electronic Case Report Form (eCRF) page: MDS – UPDRS.

Apart from the domain specific sum, there are two additional measures derived from MDS – UPDRS and used as endpoint for the study.

Total MDS – UPDRS Score

The total MDS – UPDRS score is the sum of all three (Part I, Part II, and Part III) domain specific sum scores, ie, sum of MDS – UPDRS Part I, II, and III sum scores. Hence, the total MDS – UPDRS score ranges from 0 to 236. This is a measure for one of the secondary endpoints for the study.

If any of the three sum scores is missing (as calculated and imputed above), the total MDS – UPDRS score will be set as missing.

MDS – UPDRS Part II + Part III Score

The MDS – UPDRS Part II + Part III sum score is the sum of two (Part II and Part III) domain specific total scores, ie, sum of MDS – UPDRS Part II and III sum scores. Hence, the total MDS – UPDRS Part II + Part III score ranges from 0 to 184. This is the measure for the primary endpoint for the study.

If any of the two sum scores is missing (as calculated and imputed above), the MDS – UPDRS Part II + Part III sum score will be set as missing.

6.2.2 Clinical Global Impression of Severity Scale (CGI-S)

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). The description of each point on the scale is presented in Table 7. The CGI-S assessment will be performed as outlined in the SoA (Appendix 1).

Table 7. Clinical Global Impression of Severity (CGI-S) Scale

Score	Description
1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

Clinical Global Impression of Severity (CGI-S) Score Responder

A subject who shows at least a 1-point improvement (ie, CGIS score at Week 12 < baseline value) will be classified as a CGI-S responder at Week 12. Hence, the subjects for whom CGI-S score at Week 12 ≥ baseline value will be classified as a non-responder. The subjects with missing responses at Week 12 will be considered as non-responders.

The proportion of improvement from baseline to Week 12 is a categorical secondary measure, ie, the proportion of subjects improving based on a CGI-S score at Week 12 is a measure for this secondary endpoint.

The information for CGI-S will be obtained from the eCRF page: Clinician Global Impression of Severity Scale.

6.2.3 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; 1 being none and 5 being very severe. The description of each point on scale is presented in Table 8. The PGI-S assessment will be performed as outlined in the SoA (Appendix 1).

Table 8. Patient Global Impression of Severity (PGI-S) Scale

Score	Description
1	None
2	Mild
3	Moderate
4	Severe
5	Very severe

A subject that shows at least a 1-point improvement (ie, PGI-S Score at Week 12 < baseline value) will be classified as a PGI-S responder at Week 12. Hence, subjects for whom PGI-S Score at Week 12 ≥ baseline value will be classified as non-responders. The subjects with missing responses at Week 12 will be considered as non-responders.

The proportion of improvement from baseline to Week 12, ie, the proportion of subjects improving based on a PGI-S score at Week 12 is a measure for this secondary endpoint.

The information for PGI-S will be obtained from the eCRF page: Patient Global Impression Severity Scale.

6.2.4 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, their usual chances of dozing in 8 different activities. The different activities which are part of this scale are listed in Table 9. The ESS will be performed as outlined in the SoA (Appendix 1).

Table 9. Epworth Sleepiness Scale (ESS)

S. No.	Activities	No	Slight	Moderate	High
1	Sitting and reading	0	1	2	3
2	Watching Television	0	1	2	3
3	Sitting inactive in a public place, (ie, meeting or theatre)	0	1	2	3

S. No.	Activities	No	Slight	Moderate	High
4	As a passenger in a car for an hour without a break	0	1	2	3
5	Lying down to rest in the afternoon when circumstances permit	0	1	2	3
6	Sitting and talking to someone	0	1	2	3
7	Sitting quietly after a lunch without alcohol	0	1	2	3
8	In a car or bus, while stopped for a few minutes in traffic	0	1	2	3

The ESS total score is derived as the sum of the 8 item scores and ranges from 0 to 24. The higher the ESS total score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'.

If one or more item scores are missing, then the ESS total score will be set as missing, as it is not feasible to interpolate missing item scores.

The information for these presentations will be obtained from the eCRF page: Epworth Sleepiness Scale.

6.2.5 Non-motor Symptoms Scale (NMSS)

The NMSS for PD (Chaudhuri et al, 2007) is a 30-item (across 9 dimensions) rater-based scale to assess the frequency and severity of NMSS in subjects across all stages of PD. The description of each item on the scale and the associated domains are presented in Table **10**. The NMSS will be performed as outlined in the SoA (Appendix 1).

Table 10. Non-motor Symptoms Scale (NMSS)

S. No.	Item
A	Cardiovascular including falls
1	Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?
2	Does the patient fall because of fainting or blacking out?
B	Sleep/fatigue
3	Does the patient doze off or fall asleep unintentionally during daytime activities (for example, during conversation, during mealtimes, or while watching television or reading)?
4	Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?
5	Does the patient have difficulties falling or staying asleep?
6	Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?
C	Mood /Cognition
7	Has the patient lost interest in his/her surroundings?
8	Has the patient lost interest in doing things or lack motivation to start new activities?
9	Does the patient feel nervous, worried, or frightened for no apparent reason?
10	Does the patient seem sad or depressed or has he/she reported such feelings?
11	Does the patient have flat moods without the normal "highs" and "lows"?
12	Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?
D	Perceptual problems/hallucinations
13	Does the patient indicate that he/she sees things that are not there?

S. No.	Item
14	Does the patient have beliefs that you know are not true (for example, about being harmed, being robbed or being unfaithful)?
15	Does the patient experience double vision (2 separate real objects and not blurred vision)?
E	Attention/ Memory
16	Does the patient have problems sustaining concentration during activities (for example, reading or having a conversation)?
17	Does the patient forget things that he/she has been told a short time ago or events that happened in the last few days?
18	Does the patient forget to do things (for example, take tablets or turn off domestic appliances)?
F	Gastrointestinal tract
19	Does the patient dribble saliva during the day?
20	Does the patient have difficulty swallowing?
21	Does the patient suffer from constipation (Bowel action less than three times weekly)?
G	Urinary
22	Does the patient have difficulty holding urine (urgency)?
23	Does the patient have to void within 2 hours of last voiding (frequency)?
24	Does the patient have to get up regularly at night to pass urine (nocturia)?
H	Sexual function
25	Does the patient have altered interest in sex (Very much increased or decreased, please underline)?
26	Does the patient have problems having sex?
I	Miscellaneous
27	Does the patient suffer from pain not explained by other known conditions (Is it related to intake of drugs and is it relieved by anti-Parkinson drugs)?
28	Does the patient report a change in ability to taste or smell?
29	Does the patient report a recent change in weight (not related to dieting)?
30	Does the patient experience excessive sweating (not related to hot weather)?

Responses are to quantify symptoms according to severity (using a scale of 0 to 3) and frequency (using a scale of 0 to 4).

The frequency will be rated on 5-point scale as: 0 = Never; 1 = Rarely (< 1/wk); 2 = Often (1/wk); 3 = Frequent (several times per week); and 4 = Very Frequent (daily or all the time). The severity will be rated on 4-point scale as: 0 = None, 1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient. The final score for each item will be calculated as the product of the severity and frequency scores. Thus, the range for each item will be from 0 to 12. The total NMSS total score will be derived as the sum of the final scores for each item and ranges from 0 to 360.

The score for each domain for the NMSS scale will also be calculated as NMSS sub-domain scores.

If one or more item scores are missing for specific domains, then the NMSS sub-domain score will be set as missing. The NMSS total score will also be set as missing for such cases.

The information for these presentations will be obtained from the eCRF page: Non-Motor Symptoms Scale.

6.2.6 Parkinson's Disease Sleep Scale-2 (PDSS-2)

The PDSS-2 (Trenkwalder et al, 2011) assessment is a 15-item subject-reported outcome measure to assess nocturnal disturbances in PD. It is a 5-point frequency scale (ranging from "very often" [0] to "never" [4]). The PDSS-2 total score will be derived as the sum of all these 15 items, and ranges from 0 to 60, where higher scores indicate greater impairment. The description of each item on the scale is presented in Table 11. The PDSS-2 will be performed as outlined in the SoA (Appendix 1).

Table 11. Parkinson's Disease Sleep Scale-2 (PDSS-2)

S. No.	Activities	Very often	Often	Sometimes	Occasionally	Never
1	Overall, did you sleep well during the last week?	0	1	2	3	4
2	Did you have difficulty falling asleep each night?	0	1	2	3	4
3	Did you have difficulty staying asleep?	0	1	2	3	4
4	Did you have restlessness of legs or arms at nights causing disruption of sleep?	0	1	2	3	4
5	Was your sleep disturbed due to an urge to move your legs or arms?	0	1	2	3	4
6	Did you suffer from distressing dreams at night?	0	1	2	3	4
7	Did you suffer from distressing hallucinations at night (seeing or hearing things that do not exist)?	0	1	2	3	4
8	Did you get up at night to urinate?	0	1	2	3	4
9	Did you feel uncomfortable at night because you were unable to turn over in bed or move due to immobility?	0	1	2	3	4
10	Did you feel pain in your arms or legs which woke you up while you were sleeping during the night?	0	1	2	3	4
11	Did you have muscle cramps in your arms or legs which woke you up while you were sleeping during the night?	0	1	2	3	4
12	Did you wake up earlier than usual with painful posturing of arms and legs?	0	1	2	3	4
13	On waking in the morning or during the night, did you experience tremor?	0	1	2	3	4
14	Did you feel tired and sleepy after waking up in the morning?	0	1	2	3	4
15	Did you wake up at night due to snoring or difficulties with breathing?	0	1	2	3	4

If one or more item scores are missing, then the PDSS-2 total score will be set as missing, as it is not feasible to interpolate missing item scores.

The information for these presentations will be obtained from the eCRF page: Parkinson's Disease Sleep Scale.

6.3 Exploratory Measures

6.3.1 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 Patient Report of Problems (PROP) verbatims of participant's Modality assessments, ie, 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 30 minutes to complete. Modality assessments are to be conducted remotely, at home by the subject 1-2 days prior to the clinic visit. Subjects who are unable to complete the Modality data collection can continue their study participation.

The detail of each question is outlined in Modality Data Dictionary for Cerevance.

The information for these presentations will be obtained from the eCRF page: Modality Assessments and external data: PROP verbatims of participant's Modality assessments.

Refer Table 12 below for an outline of the Modality assessments and the metrics that will be used in the analysis at the end of the study. Refer to the data dictionary attached to the Cerevance data transfer agreement for a comprehensive list of data variables and metrics.

6.3.1.1 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.

6.3.1.2 Personal Wellbeing Patient Report of Problems (PWB-PROP™)

The PWB-PROP™ is a series of open-ended questions that asks individuals, 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. This is a live file and will be finalized before database lock (DBL).

Table 12. Modality Assessments and Metrics

Task	Metrics	Clinical Meaningfulness of Features
Parkinson's Disease Patient Report of Problems (PD-PROP)	• PD-PROP symptoms and domains	Clinically meaningful classification of patient responses into domains and symptoms relevant to Parkinson's disease (PD).

Task	Metrics	Clinical Meaningfulness of Features
Personal Wellbeing Patient Report of Problems (PWB-PROP)	• PWB-PROP symptoms and domains	Clinically meaningful classification of patient responses relevant to personal well-being.
Vowels – Vowel Space Area (VSA)	• Formants and VSA • Cepstral Peak Prominence (CPP) • Harmonics to Noise Ratio (HNR)	First 3 formants for each vowel. F1 is inversely related to vowel height. F2 is related to the degree of backness (tongue position) and is important for intelligibility. F3 is important for the roundedness of vowels (/i/ vs /j/). CPP is a robust overall measure of dysphonic voice characteristics. HNR is the ratio of periodic (clear) voicing and aperiodic (perceived as noise) and is important in acoustic analysis to diagnose pathologic voices. Low HNR is an indicator of the existence of dysarthria and is common in PD.
Counting	• Speaking duration • Lip/jaw velocity, acceleration and jerk	PD inhibits movement of the respiratory system, decreasing speaking duration. Lip/jaw velocity can be notably decreased (slow speech) or increased (stuttering).
Pitch Glide	• Fundamental frequency (F0) min and max	F0 (pitch) range is reduced in PD.
Diadochokinetic (DDK) Task	• Number of syllables produced • Total duration • Repetition rate (syllables/second) • Jaw speed, acceleration, and jerk • Lip aperture, speed, acceleration, and jerk • Mouth surface area	DDK tasks allow us to measure the alternating motion of articulators when making sounds in the front, middle, and back of the mouth. We compute well-studied measures of speech deterioration, such as the rate, duration, and number of syllables produced.
Sentence Intelligibility Test (SIT)	• Canonical Timing Alignment (CTA) • Articulation rate and duration • Speaking rate and duration • Percent pause time	CTA in connected speech correlates with intelligibility. Articulation rate is the pace at which speech segments are produced and does not take into account speaker-specific ways of conveying information (hesitations, pausing, emotional expressions). CTA, speaking and articulation rates are commonly decreased in PD. Pause time refers to the accumulation of pause duration over the course of a given speech sample.
Reading Passage	• CTA • Articulation rate and duration • Speaking rate and duration • Percent pause time • Lip aperture, speed, acceleration, and jerk	CTA in connected speech correlates with intelligibility. Articulation rate is the pace at which speech segments are produced and does not take into account speaker-specific ways of conveying information (hesitations, pausing, emotional expressions). CTA, speaking and articulation rates are commonly decreased in PD. Pause time refers to the accumulation of pause duration over the course of a given speech sample. People with PD frequently present with hypomimia, which is a symptom of PD that limits the accurate

Task	Metrics	Clinical Meaningfulness of Features
	• Jaw speed, acceleration, and jerk	expression of emotion in the face due to a decrease in the speed and coordination with which the facial musculature is activated.
Picture Description	• Speaking duration • Percent pause time • Lip opening and speed • Mouth surface area	Self-generated speech is a closer measure of a person's natural speech than reading. The established literature on within-speaker variability in PD recommends the use of multiple methods and tasks when assessing intelligibility
Spontaneous Speech	• Eye opening • Eyebrow height • Lip opening and speed • Speaking duration	Self-generated speech is a closer measure of a person's natural speech than reading. The established literature on within-speaker variability in PD recommends the use of multiple methods and tasks when assessing intelligibility
Finger Tapping	• Finger tapping speed • Finger tapping maximum distance	Bradykinesia (slowness of movement) is considered the fundamental motor feature of PD

6.3.2 Cogstate Digital Cognitive Testing Battery

Cogstate Digital Cognitive Testing Battery are computerized cognitive assessments of attention, executive function, verbal learning, and memory. The tests implemented in Cogstate Digital Cognitive Testing Battery assessments are outlined in Table 13. The Cogstate Digital Cognitive Testing Battery assessment will be performed as outlined in the SoA (Appendix 1).

Table 13. Cogstate Digital Cognitive Testing Battery Outcomes

S. No.	Test	Domain	Primary Outcome and it's Nature
1	Detection Test (DET)*	Psychomotor Function	• Speed of performance
2	Identification Test (IDN)*	Attention	• Speed of performance
3	International Daily Symbol Substitution Test – Symbols (IDSSTS)	Processing Speed	• Number of correct responses made throughout the test
4	International Shopping List Test (ISLT)	Verbal Learning	• Number of correct responses remembering the word list on three consecutive trials
5	International Shopping List Test – Delayed Recall (ISRL-DR)	Memory	• Number of correct responses remembering the list after a delay
6	One Back Test (ONB)	Working Memory	• Speed of performance • Accuracy of performance • Arcsine square root proportion correct (Additional outcome)

* Mean of the $\log_{10}$ transformed reaction times for correct responses.

The information for these presentations will be obtained from the eCRF page: Cogstate Digital Assessments and associated external data files.

6.3.3 Schwab and England Activities of Daily Living (S&E ADL)

The S&E 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% to 0% with a margin of 10% for each point on the scale. The score and description of the score is outlined in Table 14. The S&E ADL will be performed as outlined in the SoA (Appendix 1).

Table 14. Schwab and England Activities of Daily Living (S&E ADL)

S. No.	Activities
100%	Completely independent. Able to do all chores without slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
90%	Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. Might take twice as long. Beginning to be aware of difficulty.
80%	Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
70%	Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
60%	Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
50%	More dependent. Help with half, slower, etc. Difficulty with everything.
40%	Very dependent. Can assist with all chores, but few alone.
30%	With effort, now and then does a few chores alone or begins alone. Much help needed.
20%	Nothing alone. Can be a slight help with some chores. Severe invalid.
10%	Totally dependent, helpless. Complete invalid.
0%	Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden

The information for these presentations will be obtained from the eCRF page: Modality Assessments and associated external datasets.

6.3.4 Starkstein Apathy Scale (SAS)

The SAS (Starkstein et al, 1992) is a 14-question subject-reported outcome measure to assess construct of apathy. The response for each question is rated on a 4-point scale, ranging from “Not at all”, “Slightly”, “Some”, and “A Lot”. The description of each item on the scale is presented in Table 15. The PDSS-2 will be performed as outlined in the SoA (Appendix 1).

Table 15. Starkstein Apathy Scale (SAS)

S. No.	Activities	Not at All	Slightly	Some	A lot
1	Are you interested in learning new things?	3	2	1	0
2	Does anything interest you?	3	2	1	0
3	Are you concerned about your condition?	3	2	1	0
4	Do you put much effort into things?	3	2	1	0
5	Are you always looking for something to do?	3	2	1	0
6	Do you have plans and goals for the future?	3	2	1	0
7	Do you have motivation?	3	2	1	0
8	Do you have the energy for daily activities?	3	2	1	0
9	Does someone have to tell you what to do each day?	0	1	2	3
10	Are you indifferent to things?	0	1	2	3
11	Are you unconcerned with many things?	0	1	2	3
12	Do you need a push to get started on things?	0	1	2	3
13	Are you neither happy nor sad, just in between?	0	1	2	3
14	Would you consider yourself apathetic?	0	1	2	3

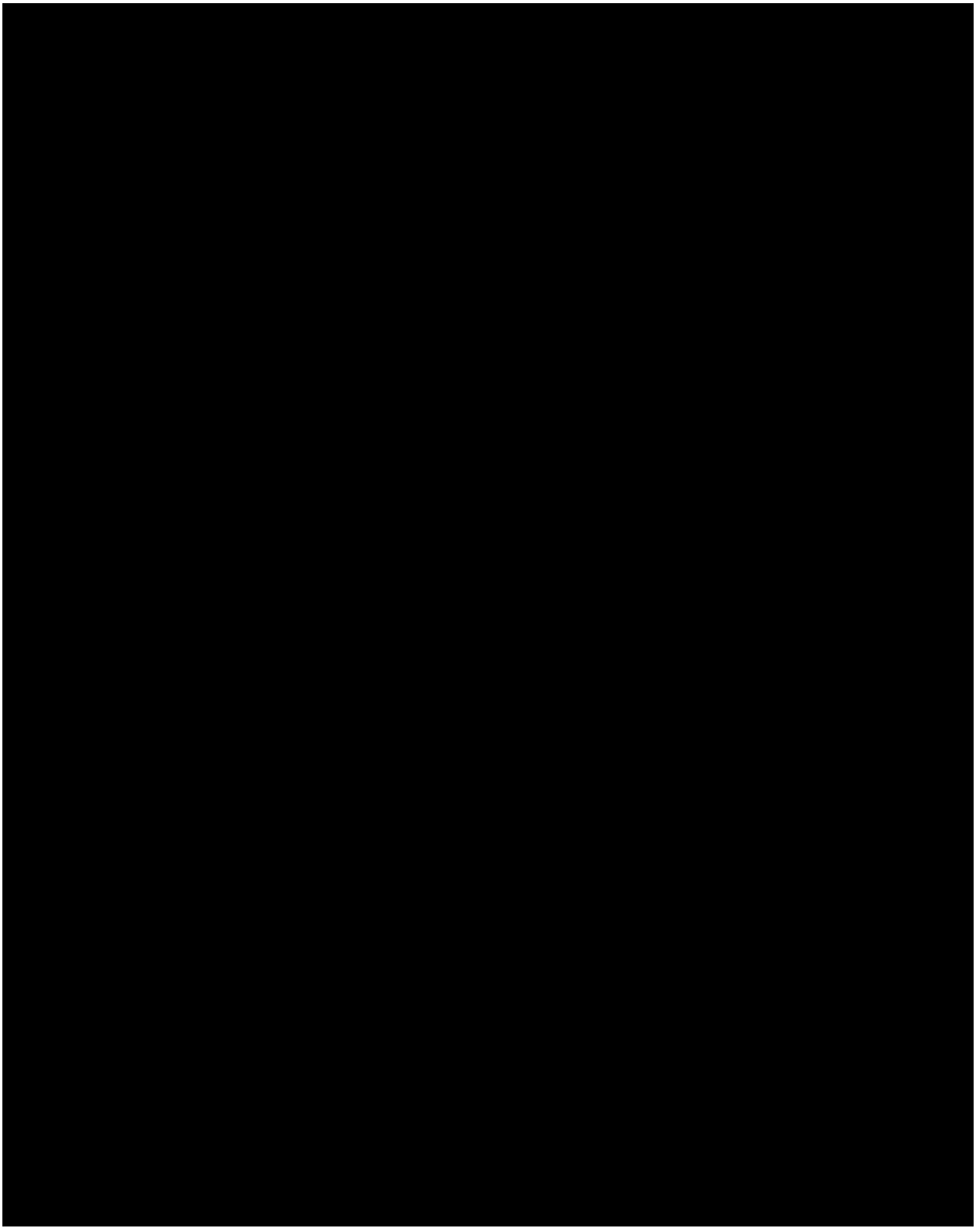
Scores range from 3 to 0 for questions 1-8, and from 0 to 3 for questions 9-14, producing a total score out of 42. The sum of all 14 questions is the SAS total score. A SAS total score above 14 is usually considered the more severe level of apathy.

The information for these presentations will be obtained from the eCRF page: Starkstein Apathy Scale (SAS).

6.3.5 Beacon Dreem Overnight electroencephalogram (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. Study subjects (or authorized caregiver) will receive an initial training by the site staff at Screening, before being shipped all 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 are unable to complete the 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). The descriptions of Beacon sleep parameters captured, and their definitions are outlined in Table 16. The various Sleep Stage Transitions Definitions are outlined in Table 17.



[redacted]

Table 17. Sleep Stage Transitions and Derivations

S. No.	Stage Transitions (decimal)	Definition
1.	Transition from N1 to N2	(Number of transitions from N1 to N2)/(Total number of transitions from N1)
2.	Transition from N1 to N3	(Number of transitions from N1 to N3)/(Total number of transitions from N1)
3.	Transition from N1 to REM	(Number of transitions from N1 to REM)/(Total number of transitions from N1)
4.	Transition from N1 to Wake	(Number of transitions from N1 to Wake)/(Total number of transitions from N1)
5.	Transition from N2 to N1	(Number of transitions from N2 to N1)/(Total number of transitions from N2)
6.	Transition from N2 to N3	(Number of transitions from N2 to N3)/(Total number of transitions from N2)
7.	Transition from N2 to REM	(Number of transitions from N2 to REM)/(Total number of transitions from N2)
8.	Transition from N2 to Wake	(Number of transitions from N2 to Wake)/(Total number of transitions from N2)
9.	Transition from N3 to N1	(Number of transitions from N3 to N1)/(Total number of transitions from N3)
10.	Transition from N3 to N2	(Number of transitions from N3 to N2)/(Total number of transitions from N3)
11.	Transition from N3 to REM	(Number of transitions from N3 to REM)/(Total number of transitions from N3)
12.	Transition from N3 to Wake	(Number of transitions from N3 to Wake)/(Total number of transitions from N3)
13.	Transition from REM to N1	(Number of transitions from REM to N1)/(Total number of transitions from REM)
14.	Transition from REM to N2	(Number of transitions from REM to N2)/(Total number of transitions from REM)
15.	Transition from REM to N3	(Number of transitions from REM to N3)/(Total number of transitions from REM)
16.	Transition from REM to Wake	(Number of transitions from REM to Wake)/(Total number of transitions from REM)
17.	Transition from Wake to N1	(Number of transitions from Wake to N1)/(Total number of transitions from Wake)
18.	Transition from Wake to N2	(Number of transitions from Wake to N2)/(Total number of transitions from Wake)
19.	Transition from Wake to N3	(Number of transitions from Wake to N3)/(Total number of transitions from Wake)
20.	Transition from Wake to REM	(Number of transitions from Wake to REM)/(Total number of transitions from Wake)

The information for these presentations will be obtained from the eCRF page: Dreem Overnight EEG and associated external data.

6.3.6 Pharmacokinetics (PK)

PK is one of the exploratory objectives for the study and blood samples will be collected pre-dose and 4 hours post dose on Day 1, and post dose at the following site visits: Week 4, Week 8, and Week 12. More details on the sample collections are described in Section 8.5.1 of the Protocol.

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

The data for these presentations will be obtained from external data provided by the PK external vendor and from the PK laboratory and Pharmacokinetics Sample Collection eCRF page.

6.4 Safety Measures

6.4.1 Adverse Events

The following AE definitions are applicable to this study:

- AE reporting period: AEs will be collected from the signing of the ICF until 14 days (30 days for Serious adverse event (SAE)) following the last dose or early termination.
- AE: Any untoward medical occurrence in a clinical study/subject, temporally associated with the use of study intervention, whether considered related to the study intervention or not.
- TEAE: A TEAE is an AE that begins on or after administration of the first dose of study drug or an increase in severity or frequency on or after first dose of study drug. The treatment emergent status for an AE will be derived using the AE start dates as per definition. For partial dates, see Appendix 2.
- SAE: Defined as any AE that is indicated as serious on the AEs Details eCRF, as per investigator's assessment.
- AE of special Interest (AESI): All AEs marked as AESI in eCRF.
- Drug Related AE: Defined as any AE that is indicated as "Related" to study drug on the AEs Details eCRF, as per investigator's assessment. Missing relatedness will be counted as related AEs.
- Duration of Hospitalization: Duration per hospital stay is calculated in hours as:
    - Hospitalization Duration (day) = [(Discharge Date – Admission Date) + 1]

- AE leading to study drug interruption/suspension: This is not directly collected in eCRF and is derived programmatically as per sponsor instruction outlined in Note to file dated 15 October 2024. This is derived by considering “Action taken with study treatment” from "Drug withdrawn" to “Drug Interrupted” for AEs which resulted in study drug interruption for few days and restarted medication again.

- AE leading to treatment discontinuation: Defined as any AE that has an “action taken” indicated as “Drug Withdrawn” on the AEs Details eCRF.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0, Mar 2022 or later. For partial dates, please refer Appendix 2.

The data for these presentations will be obtained from the Adverse Events Details eCRF.

6.4.2 Laboratory Assessments

Clinical laboratory assessments to be performed are detailed in Appendix 4 and will be conducted at timepoints indicated in the SoA (Appendix 1).

The data for these presentations will be obtained from the following eCRF pages (and associated laboratory analysis results):

- Laboratory Sample Collection

- Urine Drug Screen

- Pregnancy Test

6.4.3 Vital Signs

Vital sign assessments, listed in Table 18 below, will be performed as detailed in Section 8.3.2 of the Protocol, and will be conducted at every drug administration visit as indicated in the SoA (Appendix 1).

Table 18. Vital Sign Tests Performed

S. No.	Test
1.	Body temperature (°C)
2.	Heart rate/Pulse (bpm)
3.	Respiratory rate (breaths/min)
4.	Supine/Standing Diastolic blood pressure (DBP) (mmHg)
5.	Supine/Standing Systolic blood pressure (SBP) (mmHg)
6.	Weight (kg)
7.	Height (cm)

Diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart/pulse rate is planned to measure pre-dose and 1 hour post dose assessment. Blood pressure will be measured after at least 5 minutes supine and again within 1 to 3 minutes of standing.

The data for these presentations will be obtained from the Vital Sign eCRF pages.

6.4.4 Electrocardiograms (ECG)

Standard 12-lead ECGs will be recorded at timepoints specified in the SoA (Appendix 1) using an automatic ECG machine. Single measurements are acceptable at all timepoints recorded and will be recorded after an approximately 10-minute period of rest in a supine position.

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 applicable measurements are listed in Table 19, below.

Table 19. ECG Measurements

Test
Numeric parameters • Electrocardiograms (ECG) mean heart rate (bpm) • Respiratory rate interval (msec), Aggregate • Pulse rate interval (msec), Aggregate • QRS interval (msec), Aggregate • QT interval (msec), Aggregate • QT interval, corrected using Bazett's formula (QTcB, msec), Aggregate • QT interval, corrected using Fridericia's formula (QTcF, msec), Aggregate
Categorical parameters • Interpretation • Atrioventricular Conduction • Axis and Voltage • Chamber Hypertrophy or Enlargement • Intraventricular-Intraatrial Conduction • Myocardial Infarction • Pacemaker • Sinus Node Rhythms and Arrhythmias • Supraventricular Arrhythmias • Supraventricular Tachyarrhythmias • ST Segment, T wave, and U wave • Technical Quality • Ventricular Arrhythmias • Ventricular Tachyarrhythmias

The data for these presentations will be obtained from the 12-lead ECG eCRF pages and ECG external data.

6.4.5 Physical and Neurological Examination

Physical and neurological examination will be conducted at planned visits as outlined in the SoA (Appendix 1). The planned physical examination measurements are listed in Table 20.

Table 20. Physical Examination Measurements

Measurement
Body weight (kg)
Height (cm)
Cardiovascular
General Appearance
Head, ears, eyes, nose, throat, and mouth
Neck
Heart
Lungs
Abdomen
Musculoskeletal and neurological systems
Extremities
Skin

Also, a list of parameters and parameter classifications planned for neurological examination measurements is provided in Table 21

Table 21. Neurological Examination Measurements

Neurological Examination Part	Parameter classification	Parameters	
Part I	Cranial nerves	• Cranial nerves I • Cranial nerves II • Cranial nerves III, IV, VI • Cranial nerves V	• Cranial nerves VII Cranial nerves VIII • Cranial nerves IX, X • Cranial nerves XI • Cranial nerves XII
Part II	Motor system / Muscle strength	• Right arm • Left arm	• Right leg • Left leg
Part III	Coordination	Finger-to-nose • Right hand • Left hand	Heel-to-shin • Right leg • Left leg
Part IV	Sensory/Sensation (Pain, Light Touch, Position, Vibration)	• Right arm • Left arm	• Right leg • Left leg
Part V	Reflexes (muscle stretch)	• Right arm biceps and triceps • Left arm biceps and triceps • Right leg patellar and achilles • Left leg patellar and achilles	
	Plantar response	Right foot Left foot	Right leg Left leg
Not applicable	Romberg Test		

The information for the listing will be obtained from the following eCRF pages:

- Physical Examination
- Neurological Examination

6.4.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Posner et al, 2011) is used to assess suicidal tendency and is a prospective semi-structured interview comprised of the following areas of assessment: Ideation, Intensity of Ideation, Behavior, and Lethality.

The Columbia Suicide Severity Rating Scale – Screening/Baseline Version will be measured at Baseline. Any positive answer to its behavior subcomponents identifies a subject as with "Suicidal Behavior at Baseline". Similarly, any positive answer to its ideation subcomponents identifies a subject as with "Suicidal Ideation at Baseline". A subject identified with either "Suicidal Behavior at Baseline" or with "Suicidal Ideation at Baseline" will also be classified as with "Suicidal Behavior or Ideation at Baseline".

The Columbia Suicide Severity Rating Scale – Since Last Visit Version will be assessed at the post-baseline visits. Any positive answer to its behavior subcomponents at any of the post-baseline visits identifies a subject as with "Suicidal Behavior During Study". Similarly, any positive answer to its ideation subcomponents at any of the post-baseline visits identifies a subject as with "Suicidal Ideation During Study". A subject identified with either "Suicidal Behavior During Study" or with "Suicidal Ideation During Study" will also be classified as with "Suicidal Behavior or Ideation During Study". The C-SSRS will be performed as outlined in the SoA (Appendix 1).

The information for these presentations will be obtained from the following eCRF pages:

- C-SSRS ("Lifetime")
- C-SSRS ("Since Last Visit")

7 STUDY POPULATIONS

7.1 Analysis Populations

The following analysis sets are planned for analysis and are defined in Table 22:

Table 22. Participant Analysis Sets and Descriptions

Participant Analysis Set	Description
Screened Subjects	• All subjects who signed informed consent form (ICF) and registered for the study.
Enrolled Subjects	• All screened subjects who are eligible for randomization after Enrollment Authorization Committee (EAC) review for determination of eligibility.
Intention-to-Treat (ITT)	• Includes all randomized subjects.
Safety Analysis Set (SFAS)	• Includes all subjects who have received at least one dose of study drug.
Modified Intention-to-Treat (mITT)	• Includes all subjects who are randomized, and administered study drug, classified according to the treatment they are randomized to, and have at least one postbaseline evaluation of efficacy endpoints.
Completer Set	• Includes all subjects who completed study treatment for 12 weeks and have the corresponding Week 12 efficacy assessment.
Pharmacokinetic Analysis Set (PKS)	• Includes all subjects who received at least one dose of study drug and have at least 1 measurable plasma concentration.
Per Protocol Analysis Set (PPS)	• 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.

Safety analysis set (SFAS) will be used for demographic, baseline characteristics, and safety analyses. Pharmacokinetic analysis set (PKS) will be used for PK analyses. Per protocol analysis set (PPS) and Completer Set will be used for supplementary analysis for primary outcome.

mITT will be used for the primary analyses of all efficacy (both primary and secondary) outcomes. ITT will be used for sensitivity analyses of primary outcome analysis. All efficacy analyses (for mITT, ITT, PPS and Completer sets) will be conducted by classifying the subjects according to the randomized treatment.

7.2 Subgroups

Subgroup analyses will be performed for the primary endpoint for the following baseline classifications:

- Age group 1 (< median age at baseline and ≥ median age at baseline)
- Age group 2 (< 60 years age at baseline and ≥ 60 years age at baseline)
- Sex (Male and Female)

- MDS – UPDRS Part II + Part III sum score group (< median MDS – UPDRS Part II + Part III sum score at baseline and ≥ median MDS – UPDRS Part II + Part III sum score at baseline)

- MDS – UPDRS Part II sum score group (< median MDS – UPDRS Part II sum score at baseline and ≥ median MDS – UPDRS Part II sum score at baseline)

- MDS – UPDRS Part III sum score group (< median MDS – UPDRS Part III sum score at baseline and ≥ median MDS – UPDRS Part III sum score at baseline)

- Weight group (< median weight at baseline and ≥ median weight at baseline)

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The endpoints, proportion of improvement from baseline to Week 12 in CGI-S and PGI-S, are planned to be analyzed using Cochran–Mantel–Haenszel (CMH) in protocol, but as the study do not consider any stratification factors, the CMH will reduce to chi-square test for association. Thus, the analysis for these endpoints is performed using chi-square test of association. Detailed of the same is outlined in Section 10.6.3 and Section 10.6.4.

The hierarchical order of the primary and secondary endpoints was planned to be performed according to the order described in Section 3 of Protocol V3. As per sponsor request, the hierarchical order of secondary endpoints is updated in Section 5.2. The revised order of secondary endpoints reflects the intention to prioritize the evaluation of the individual components of the primary endpoint. Also, the hierarchy of CGI-S and PGI-S was lowered considering low proportion of responders in blinded data.

Recently published data (McGarry et al, 2024) suggests that the SD of change in MDS-UPDRS Parts II +Part III sum score at Weeks 12 in patients with early PD is about 7 points, instead of 8 points. Based on this, the assumption for SD and alpha were considered as 8 (instead of 7) and 0.05 (instead of 0.10). The detailed sample size calculation is discussed in Section 6.1.2.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 General Conventions

Summary statistics will be presented for categorical data as number and percentage [n (%)], where the percentage is displayed to one decimal point (eg, 98.1).

Descriptive statistics will be presented for continuous data with applicable decimal precision as follows in relation to the source data (indicated as N), with a maximum of three decimals to be displayed:

- Number, (n)
- Mean, (N + 1)
- SD, (N + 2)
- Median, (N + 1)
- Minimum, (N + 0)
- Maximum, (N + 0)

Study day is calculated relative to the first dose of study drug administration under this protocol and will thus in most cases coincide with the visit naming (eg, Week 2 will be on study day = 14, Week 4 will be on study day = 28, etc.)

- If the current assessment/collection/result (ACR) date is on or after first dose of study drug administration:

  Study Day = (Current ACR Date – First dose of Study Drug administration Date) + 1

- If the current ACR date is before first dose of study drug administration:

  Study Day = (Current ACR Date – First dose of Study Drug administration Date)

Study day will not be calculated if either the current ACR or the first dose of study drug administration is incomplete or missing.

All tables will be displayed by treatment group: CVN424 150 mg or placebo.

9.2 Baseline Definition

Values from the most recent ACR (including ACRs from planned or unscheduled visits) prior to the first dose of study drug (ie, on Day 1) will be considered for the Baseline value. If the potential Baseline ACR is on Day 1 (and time is not recorded), it is assumed that the ACR occurred before the start of first dose of study drug administration.

9.3 Change from Baseline Definition

CFB is calculated as the difference between post-baseline observation and associated baseline observation, ie, CFB is calculated as:

CFB = Observed value – Baseline Value

9.4 Handling of Missing Information

9.4.1 Handling of Partial Dates

Handling of partial dates is explained in Appendix 2.

9.4.2 Missing Efficacy data

Missing efficacy data will not be imputed for any analysis except the multiple imputation (MI) sensitivity analysis for primary and secondary efficacy endpoints. However, missing items of questionnaires will be imputed, as defined in various sub-sections of Section 6.2 for the respective efficacy measures. The details for imputation rules for the MI sensitivity analysis are described in Section 9.4.2.1 and Section 10.6.1.2.

9.4.2.1 Multiple Imputation (MI) for Missing Data

MI allows you to analyze incomplete data with regular data analysis tools. Impute means to "fill in". With singular imputation methods, the mean, median, or some other statistic is used to impute the missing values and carries with it a level of uncertainty about which values to impute. MI narrows uncertainty about missing values by calculating several different options ("imputations"). Several versions of the same data set are created, which are then combined to make the "best" values.

MI is not simply a one-step procedure, but a series of steps and its inference involves three distinct phases:

1. The missing data are filled in m times to generate m complete data sets.
    a. Fit your data to an appropriate model. Model fitting takes data from samples and attempts to find the best fit model.
    b. Estimate a missing data point using the selected model.
2. The m complete data sets are analyzed by using standard Statistical Analysis Software® (SAS®) procedures.
3. The results from the m complete data sets are combined using Rubens rules for the inference.

9.4.3 Handling of Plasma Concentration Below Lower Limit of Quantification

Plasma PK concentration values that are below the lower limit of quantification (BLQ) will be considered zero for pre-dose samples, half of lower limit of quantification for post dose samples. For individual PK figures, BLQ values will be considered as missing after the last none BLQ value for calculation of summary statistics.

In listing presentations, these values will be marked/footnoted as being BLQ.

9.5 Statistical Hypotheses

Considering μ(CFB,CVN424) as mean CFB for CVN424 arm and μ(CFB,Placebo) as mean CFB for Placebo arm, the null hypothesis to test required difference of mean will be:

$$H_0: \mu(CFB,CVN424) - \mu(CFB,Placebo) = 0$$

And the alternate hypothesis will be:

$$H_1: \mu(CFB,CVN424) - \mu(CFB,Placebo) \neq 0$$

9.6 Multiplicity Adjustment

Efficacy endpoints (primary and secondary) will be evaluated in a fixed hierarchical manner as outlined in Section 8, ie, significance of successive endpoints cannot be claimed unless prior endpoints in the hierarchy are significant. However, in case the formal hierarchical statistical testing is terminated, nominal p-values will be provided for all planned comparisons.

9.7 Interim Analysis

No interim analysis is planned for this study.

9.8 Pooling Strategy for Study Sites

Data from all subjects will be pooled across all sites and subjects will be summarized per treatment arms only (CVN424 150 mg and placebo).

9.9 Visit Windows/Unscheduled Visits

In general, no mapping/renaming of visits (unscheduled or otherwise) will be done for this study. That is, scheduled visit data will be used for summarization in tables as collected on the eCRF. The renaming would be done, for example Week 2 (Visit 2) would become Week 2 for display representation. However, all collected data (scheduled and unscheduled visits) will be listed.

For efficacy analyses, the early termination visit will be mapped to the nearest visit to occurrence of early termination visit, rather than Week 12 as outlined in SoA (Appendix 1).

Unscheduled visits will be considered eligible for identification of Baseline values. Results from unscheduled visits will also be considered eligible for testing of abnormalities (eg, laboratory, ECG, and vital signs) at any post-baseline assessment, but will not be considered for per visit assessment.

10 STATISTICAL ANALYSIS METHODS

10.1 Subject Disposition

Criteria for study inclusion, exclusion, screen failure and discontinuation of study drug or participant withdrawal from the study are described in detail in Sections 5.1, 5.2, 5.4 and Sections 7.1 and 7.2 of the Protocol. The following disposition listings are planned, using the analysis set indicated in brackets:

- Screen failures and Inclusion/exclusion violations (Screened)
- Subject Randomization (Randomized)
- Disposition: includes subject completion/discontinuation information from study/treatment (ITT)
- Inclusion/exclusion from analysis sets (ITT)

The following disposition related items are planned to be tabulated using summary and descriptive statistics (as applicable), using the analysis set indicated in brackets:

- Subjects disposition (Screened): Number of subjects screened, enrolled.
- Subjects disposition (ITT): Randomized, treated; and the number of subjects completed and discontinued with breakdown by reason for subject's discontinuation (from both study drug administration and study)
- Inclusion/exclusion violations (ITT): Includes reason for exclusion from each analysis set, if applicable

The data for these presentations will be obtained from the following eCRF pages:

- Subject Enrollment
- Screen Failure
- Inclusion & Exclusion Criteria
- End of Study
- End of Treatment

10.1.1 Protocol Deviations

All subjects' data will be reviewed for the occurrence of protocol deviations (as defined in Section 7.2 of the Protocol). Protocol deviations will be listed for the ITT analysis set.

Summaries will be presented for all protocol deviations showing the number and percentage of subjects within each deviation severity and deviation category using the ITT analysis set.

Deviation severities are as follows:

- Major
- Minor

Deviation categories are as follows:

- Informed Consent
- Eligibility and Entry Criteria
- Concomitant Medication Criteria
- Laboratory Assessment Criteria
- Study Procedures Criteria
- Serious Adverse Event Criteria
- Randomization Criteria
- Visit Schedule Criteria
- Administrative Criteria
- IP Compliance
- Source Document Criteria
- Efficacy Criteria
- PK Assessments
- Other Criteria

The data for these presentations will be obtained from the Protocol Deviation eCRF page.

To identify significant protocol deviations, the study team, along with a sponsor representative, will discuss each major and critical protocol deviation and finalize the protocol deviations which are significant prior to DBL.

10.2 Demographics and Baseline Characteristics

Demographics and baseline characteristic information will be obtained as specified in Section 8.1.3 of the Protocol. The following demographic and baseline characteristics are planned to be listed, using the SFAS:

- Subject demographics:

- Age (years)
- Age Group Classification 1
  - Baseline Age < Median Age at Baseline
  - Baseline Age ≥ Median Age at Baseline
- Age Group Classification 2
  - Baseline Age < 60 (years) at Baseline
  - Baseline Age ≥ 60 (years) at Baseline
- Sex
- Race
- Ethnicity

- Baseline vital characteristics:
  - Weight (kg)
    - Weight group subgroup classification
      - < median weight at baseline
      - ≥ median weight at baseline
  - Height (cm)
  - Body mass index (BMI) (kg/m^2)
- Childbearing potential
- Time since PD diagnosis
- MDS – UPDRS Subgroup classifications:
  - MDS – UPDRS Part II + Part III sum score group
    - < median MDS – UPDRS Part II + Part III sum score at baseline and
    - ≥ median MDS – UPDRS Part II + Part III sum score at baseline
  - MDS – UPDRS Part II sum score group

        - < median MDS – UPDRS Part II sum score at baseline
        - ≥ median MDS – UPDRS Part II sum score at baseline
    - MDS – UPDRS Part III sum score group
        - < median MDS – UPDRS Part III sum score at baseline
        - ≥ median MDS – UPDRS Part III sum score at baseline
- Baseline laboratory assessment
    - Serum human chorionic gonadotropin (hCG) - for women of childbearing potential only.
    - Follicle-stimulating hormone (FSH) - for women of childbearing potential only.
    - Hepatitis panel including:
        - Hepatitis B surface antigen (HBsAg)
        - Hepatitis C virus antibodies (Anti-HCV)
        - Human Immunodeficiency Virus (HIV)

The median age, weight and various MDS – UPDRS sum scores are calculated for all randomized subjects.

The BMI at Baseline will be derived using the following formula:

$$Baseline\ BMI = Baseline\ weight\ (kg) \div [Baseline\ height\ (m)]^2$$

PD diagnosis information will be pulled from medical history with medical decoded values (ie, MHDECOD) as “Parkinson's disease” coded using MedDRA version 25.0, Mar 2022 or later. Time since PD diagnosis at Baseline will be derived using the following formula:

$$Time\ since\ PD\ diagnosis\ (days) = Date\ of\ first\ dose - Date\ of\ start\ of\ earliest\ PD + 1$$

For imputation of partial dates of the start of PD, refer to Appendix 2.

The above demographic and baseline characteristics items are planned to be tabulated using summary and descriptive statistics (as applicable) for SFAS.

The data for these presentations will be obtained from the following eCRF pages:

- Demography
- Vital signs

- Laboratory Sample Collection and associated external data
- Medical History (for time since PD diagnosis)
- MDS – UPDRS

10.2.1 Other Baseline Characteristics

10.2.1.1 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 Hoehn and Yahr scale assessment will be conducted at visits as indicated in the SoA (Appendix 1). Each stage of this scale is described in Table 23.

Table 23. Modified Hoehn and Yahr Scale Stage

Stage	Stage Score Description
Stage 0	No signs of disease
Stage 1	Unilateral involvement only
Stage 1.5	Unilateral and axial involvement
Stage 2	Bilateral involvement without impairment of balance
Stage 2.5	Mild bilateral disease, with recovery on pull test
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severe disability; still able to walk or stand unassisted
Stage 5	Wheelchair bound or bedridden unless aided

Modified Hoehn and Yahr scores will be tabulated using counts and percentages by treatment for the SFAS at Screening.

The Modified Hoehn and Yahr scale assessments results will be listed for the SFAS.

The data for these presentations will be obtained from the Modified Hoehn and Yahr Scale eCRF pages.

10.2.1.2 Montreal Cognitive Assessment (MoCA)

The MoCA (Nasreddine et al, 2005) was designed to detect mild cognitive impairment in elders scoring in the normal range on the Mini-Mental State Examination. It assesses 30 different items into various cognitive domains. The total possible score is 30 points (maximum) and is obtained by adding all scores of all cognitive domains scores. For MoCA, the authors recommend a clinical cutoff score of 26 for normal cognition. The classification of MoCA total score is outlined in Table 24.

Table 24. Montreal Cognitive Assessment (MoCA) Total Score Classification

MoCA Total Score Classification	Score Range
Normal cognition	26-30 points
Not normal cognitive impairment	≤ 25 points

The following MoCA parameters at Screening will be tabulated for the SFAS:

- Summary statistics for the domain and total MoCA scores
- Incidence of MoCA total score interpretation classification

Each item in the MoCA, its domain scores and the total score will be listed for the SFAS.

The data for these presentations will be obtained from the Montreal Cognitive Assessment eCRF pages.

10.2.1.3 Beck Depression Inventory-II (BDI-II)

The BDI-II (Beck et al, 1996) assessment is a 21-item (or symptoms), self-rated scale that evaluates key symptoms of depression. Its item response reflects 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 BID-II score will be classified into the following scoring ranges:

- 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.

The following BID-II assessments at Screening will be tabulated for the SFAS:

- Summary statistics for the total BID-II score
- Incidence of BID-II score classifications

Each item from the BID-II assessment, and the BID-II total score will be listed for the SFAS.

The data for these presentations will be obtained from The Beck Depression Inventory-II eCRF pages.

10.3 Medical History

All displays (tables, and listings) for medical history will be presented for SFAS.

The medical history terms will be coded using MedDRA version 25.0, Mar 2022 or later. Sample collection for viral serology and Coronavirus Disease (COVID-19) screening will be conducted as specified in Section 10.2 and Section 8.1.1 of the Protocol, at the timepoints indicated in the SoA (Appendix 1). Viral serology analysis and COVID-19 screening will be done by an external vendor and, therefore, will not form part of this SAP.

The medical history for medical conditions or events reported will be listed. The column for medical history related to PD and medical history ongoing at screening will be added.

Medical history will be tabulated by system organ class (SOC), and preferred term (PT). The SOCs, and PTs will be sorted by number of decreasing frequencies in the total arm. Multiple medical history events for the same subject will be counted only once for reporting classifications: SOC/PT. The number of medical history incidents will also be reported along with number of subjects. A separate table for medical history ongoing at screening will also be presented.

The data for these presentations will be obtained from the following eCRF pages:

- Medical History
- Medical History Details

10.4 Prior and Concomitant Medications and Procedures

All displays (tables, and listings) for prior and concomitant medications/procedures will be presented for SFAS.

A prior medication or procedure is defined as having started and ended prior to the first dose of study drug administration. Conversely, a concomitant medication or procedure is defined as either having started prior to first dose of study drug administration and ended on/after first dose of study drug administration, is ongoing at Baseline or, having started on/after first dose of study drug administration. Medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Global Mar 2022 format or later.

Details for recording prior and concomitant medications and procedures are described in Section 6.6 of the Protocol.

Listings of prior and concomitant medications AND prior procedures will be presented separately.

All prior and concomitant medications will be summarized by WHO-DD Anatomical Therapeutic Chemical (ATC) level 3 and PT.

Medications related with PD will be identified using ATC level 3 code N04. All prior and concomitant medications related with PD will also be summarized by WHO-DD ATC level 4 and PT.

The ATC levels, and PTs will be sorted by number of decreasing frequencies in the total arm. Multiple medications for the same subject will be counted only once for reporting classifications: ATC class/PT. The number of medications will also be reported along with number of subjects.

Non-pharmacologic treatments/procedure taken during the trial will also be summarized by primary reason for treatment/procedure.

The data for these presentations will be obtained from the following eCRF pages:

- Prior and Concomitant Medications
- Prior and Concomitant Medications Details
- Non-Pharmacologic Treatments/Procedure Details

The prior/concomitant status will be derived using the medication/procedure start and stop dates as per definition provided at the start of this section. For partial dates, see Appendix 2.

10.5 Treatment Compliance and Exposure

All displays (tables, and listings) for treatment exposure will be presented for SFAS.

A listing of subject exposure (days) to all the study drug administration of CVN424 or placebo will be presented. Study drug dispensing and return information and treatment compliance (%) will also be listed over time. Overall treatment compliance will be listed in a separate listing.

Summary statistics of the duration of study drug exposure and study drug interruptions/ suspension (days), study drug administration (days), and treatment compliance (%) over visit interval and overall will be presented. Frequency counts and percentages for the number of subjects with at least one drug dispensing/drug return missing and the number of subjects with $\leq$ 80% and > 80% compliance over visit interval and overall will also be presented.

Study drug exposure duration (days) will be calculated as: Date of last study drug administration– Date of first study drug administration + 1 – duration of study drug interruptions/suspension.

Study drug consumed (mg) will be calculated as: 150 times the sum of all study drug consumed during the study, ie, 150 mg times the sum of (Study drug dispensed at previous visit - Study drug returned at current visit), for all planned study drug dispensed/return visits: Baseline, Week 2, Week 4, Week 8, and Week 12.

Treatment compliance (%) will be calculated as: study drug consumed divided by 150 times study drug exposure duration. The number of days for which study drug administration is interrupted will be excluded from calculation of duration of study drug administration. The number of subjects with at least 80% compliance will also be summarized.

The data for these presentations will be obtained from the following eCRF pages:

- Study Drug Dispensation
- Study Drug Administration and Reporting
- Study Drug Accountability and Compliance

10.6 Efficacy

Each primary and secondary analysis will be performed using the mITT analysis set.

10.6.1 Primary Estimand

The population: modified Intent-to-Treat (mITT) analysis set

Subject-level outcome variable: CFB at Week 12 in the MDS – UPDRS Part II+ Part III score

Treatments: the treatments to be compared are CVN424 150 mg and placebo. The treatments will be compared according to the randomized groups, regardless of the treatment that was actually received.

Population-level summary measures: Treatment difference (CVN424 150 mg vs placebo) of the least-square mean (LSM) CFB at Week 12 in the MDS – UPDRS Part II + Part III score

Intercurrent events:

- Premature discontinuation of study treatment
- Initiation of PD medication for treatment of motor features during the study

For the data that are missing due to premature discontinuation of study treatment, an assumption of Missing at Random (MAR) will be made. No specific imputation will be done for these missing data, because the likelihood-based analysis approach can manage patients with incomplete data under the assumption of MAR. If possible, the collection of data will be continued after the discontinuation of the study treatment and all data collected after study treatment discontinuation will be used according to the treatment policy strategy.

For patients who start using PD medication for treatment of motor features during the study, the data collected after start of such treatment will be set as missing and an assumption of MAR will be made, similarly as for premature discontinuations.

10.6.1.1 Primary Analysis

The CFB of the total MDS – UPDRS Part II + Part III score at Week 12, comparing treatments, is the primary endpoint for the study, ie, the difference in the CFB to Week 12 in the MDS – UPDRS Part II + Part III total scores between CVN424 150 mg and placebo.

This primary efficacy endpoint will be analyzed in the mITT analysis set using mixed model repeated measures (MMRM). The model will include treatment group (CVN424 150 mg vs

placebo), visit (each post-baseline visit up to Week 12) and treatment group by post-baseline visit as fixed effects and associated baseline assessment as covariate. The model will use post-baseline visit as a repeated component in the model and will include response data from each post-baseline visit up to and including Week 12.

An unstructured (UN) covariance matrix will be used initially, and if it fails to converge, a Compound Symmetry (CS) or an Autoregressive (AR(1)) matrix shall be employed, in that order. The subject will be used as random effect and Kenward-Roger (KR) approximation will be used to estimate denominator degrees of freedom.

The LSM along with associated standard error (SE) and associated 95% confidence interval (CI) will be reported for each treatment group and the treatment difference (CVN424 150 mg or placebo) at Week 12 will be reported. Also, the estimates for each post-baseline visit up to Week 12 will also be displayed.

The data after the first occurrence of concomitant medication for PD motor features, will be set as missing considering hypothetical scenario. The rest of all available data will be used, even after subject discontinuation of study treatment, as per treatment policy. The primary analysis will be conducted using MMRM model without any imputation. The following SAS® code will be used as reference for above analysis:

10.6.1.2 Sensitivity Analyses

The primary efficacy analysis will be repeated (considering model assumptions as specified in Section 10.6.1.1) using the ITT analysis set with the MI method (described in Section 9.4.2.1), both assuming that data are MAR and missing not at random (MNAR) as sensitivity analyses. MNAR imputation will include both tipping point and copy-reference (placebo) assumptions.

The following sub-sections define the handling of intercurrent events, assumptions, and imputation of missing observed values for various sensitivity analysis.

10.6.1.2.1 Sensitivity Analyses 1 – Missing at Random (MAR) – Hypothetical Scenario for Medication for PD Motor Features

The data after the first occurrence of concomitant medication for PD motor features, will be set as missing for observed values as hypothetical scenario. The rest of all the available data will be used, even after subject discontinuation of study treatment, as per treatment policy.

An assumption of MAR for missing observed values will be considered for implementing MI over MMRM analysis.

10.6.1.2.2 Sensitivity Analyses 2 – Missing not at Random (MNAR) (Copy-Reference) – Hypothetical Scenario for Medication for PD Motor Features

The data after the first occurrence of concomitant medication for PD motor features, will be set as missing for observed values as hypothetical scenario. The rest of all the available data will be used, even after subject discontinuation of study treatment, as per treatment policy.

An assumption of MNAR for missing observed values will be considered for implementing MI over MMRM analysis. MNAR imputation will include copy-reference (placebo) assumptions.

10.6.1.2.3 Sensitivity Analyses 3 – MAR – Treatment Policy for Medication for PD Motor Features

All available data will be used, even after subject discontinuation of study treatment or after first occurrence of concomitant medication for PD motor features, as per treatment policy.

An assumption of MAR for missing observed values will be considered for implementing MI over MMRM analysis.

10.6.1.2.4 Sensitivity Analyses 4 – MNAR (Copy-Reference) – Treatment Policy for Medication for PD Motor Features

All available data will be used, even after subject discontinuation of study treatment or after first occurrence of concomitant medication for PD motor features, as per treatment policy.

An assumption of MNAR for missing observed values will be considered for implementing MI over MMRM analysis. MNAR imputation will include copy-reference (placebo) assumptions.

10.6.1.2.5 Sensitivity Analyses 5 – MNAR (Tipping Point) – Hypothetical Scenario for Medication for PD Motor Features

The data after first occurrence of concomitant medication for PD motor features, will be set as missing for observed values as hypothetical scenario. Rest of all available data will be used, even after subject discontinuation of study treatment, as per treatment policy.

An assumption of MNAR for missing observed values will be considered for implementing MI over MMRM analysis. MNAR imputation will include tipping point assumptions.

10.6.1.3 Supplementary Analyses

The primary analysis will be repeated (considering model assumptions as specified in Section 10.6.1.1) for the Completer set and PPS using the same MMRM model as the supplementary analyses.

Summary statistics for the observed and CFB values over time will be performed on the primary endpoint measure (ie, MDS – UPDRS Part II + Part III sum score) based on the mITT analysis set.

The analysis will be repeated for the ITT analysis set as a supplementary analysis considering intercurrent events. For this analysis, the data after first occurrence of concomitant medication for PD motor features, will be set as missing for observed values as hypothetical scenario. Rest of all available data will be used, even after subject discontinuation of study treatment, as per treatment policy.

The following figures for the primary endpoint are planned to illustrate the change and variation of MDS – UPDRS Part II + Part III sum score by treatment over time using the mITT analysis set:

- Mean observed values score over time (with SD as error bars)
- Mean change from baseline values score over time (with SD as error bars)
- LSM for change from baseline score over time (with SE as error bars)

The LSM estimates being plotted here will derive using same MMRM model estimation as described for primary endpoint in Section 10.6.1.1.

10.6.1.4 Subgroup Analyses

The primary analysis will be repeated for the following subgroups using the mITT analysis set considering all assumptions as specified in Section 10.6.1:

- Age group 1 (< median age at baseline and ≥ median age at baseline)
- Age group 2 (< 60 years age at baseline and ≥ 60 years age at baseline)
- Sex (Male and Female)
- MDS – UPDRS Part II + Part III sum score group (< median MDS – UPDRS Part II + Part III sum score at baseline and ≥ median MDS – UPDRS Part II + Part III sum score at baseline)
- MDS – UPDRS Part II sum score group (< median MDS – UPDRS Part II sum score at baseline and ≥ median MDS – UPDRS Part II sum score at baseline)
- MDS – UPDRS Part III sum score group (< median MDS – UPDRS Part III sum score at baseline and ≥ median MDS – UPDRS Part III sum score at baseline)

10.6.2 Secondary Analysis - MDS – UPDRS Derived Endpoints

The following measures for secondary endpoints are derived from MDS – UPDRS:

- Total MDS – UPDRS Part III score: Sum of responses of all MDS – UPDRS Part III questions

- Total MDS – UPDRS Part II score: Sum of responses of all MDS – UPDRS Part II questions
- Total MDS – UPDRS Part I score: Sum of responses of all MDS – UPDRS Part I questions
- Total MDS – UPDRS score: Sum of total MDS – UPDRS Part I, Part II and Part III scores

The CFB of these measures at each post-baseline visit up to Week 12, comparing treatments, are the respective secondary endpoints for study. Hence, associated secondary endpoints are the difference in the CFB to Week 12 in these measures between CVN424 150 mg and placebo.

These secondary efficacy endpoints will be analyzed considering MMRM models based on the mITT analysis set as secondary analysis. All assumptions regarding dependent variable, covariate, fixed effects, repeated measure, interaction effects, covariance matrix and estimates remain the same as specified in Section 10.6.1.1. For baseline value, the associated baseline will be considered as covariate. Also, the estimates for each post-baseline visit up to Week 12 will be reported in parallel.

10.6.2.1 Supplementary Analyses

Summary statistics for the observed and CFB values over time will be performed on each of the secondary endpoints listed in Section 10.6.2 for the mITT analysis set.

The individual response of each item in MDS – UPDRS questionnaire will be listed for the ITT analysis set. Also, the domain specific sum score, total MDS – UPDRS score, and Part II + Part III sum score will be listed for the mITT analysis set. Flags for mITT, PPS, and completer set analysis set will be added.

The mean (SD) observed total score, mean (SD) change from baseline score and LSM (SE) for MDS – UPDRS Part II sum score and MDS – UPDRS Part III sum score by treatment over time using mITT analysis set at outlined in Section 10.6.1.3

10.6.3 Secondary Analysis - CGI-S Responder

The CGI-S responder status is a categorical secondary efficacy endpoint derived from CFB to Week 12 in CGI-S total score. Thus, the proportion of subjects improving based on CGI-S total score at Week 12 is the required secondary endpoint and will be analyzed using a chi-square test based on the mITT analysis set. The summary will include the proportion and percentage of subjects for each treatment group along with the respective 95% CIs. Additionally, the difference in proportions between the treatment groups, along with its CI and p-value, will be calculated. The missing responses at any visit will be derived as described in Section 6.2.2. Also, the estimates for each post-baseline visit up to Week 12 will be reported in parallel.

The following SAS® code will be used as reference for the above analysis:

[redacted]

10.6.3.1 Supplementary Analyses

This categorical secondary efficacy endpoint will be analyzed using a generalized linear mixed model (GLIMMIX) that can incorporate all response data from each post-baseline visit into the analysis, using the mITT analysis set. This analysis is supplementary to the analysis described in Section 10.6.3. For this analysis, no imputation will be done for missing responses.

The model will include the treatment group (CVN424 150 mg vs placebo), and visit (each post-baseline visit) as fixed effects and interaction between treatment groups and visit as random effect. An unstructured (UN) 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. The number of responders and non-responders at Week 12 will also be presented.

Also, the estimates for each post-baseline visit up to Week 12 will be reported in parallel.

The following SAS® code will be used as reference for the above analysis:

[redacted]

Summary statistics for the observed and CFB values over time will be performed on this endpoint for the mITT analysis set.

The incidence of CGI-S responders and non-responders over time will be summarized using count and percentage for the mITT analysis set.

The CGI-S responses and responder status over time will be listed for the ITT analysis set. A flag for mITT analysis set will be added to the listing.

10.6.4 Secondary Analysis - PGI-S Responder

The PGI-S responder status is a categorical secondary efficacy endpoint derived from CFB to each post-baseline visit up to Week 12 in the PGI-S total score. Thus, the proportion of subjects improving based on PGI-S total score at Week 12 is the required secondary endpoint and will be analyzed using the chi-square test based on the mITT analysis set as described in Section 10.6.3.

10.6.4.1 Supplementary Analyses

This categorical secondary efficacy endpoint will be analyzed using the GLIMMIX procedure for the mITT analysis set as supplementary analysis. The assumptions for the analysis remain the same as described in Section 10.6.3.1.

The following analyses will also be performed on this secondary endpoint measure for the mITT analysis set:

- Summary statistics for the observed and CFB values over time
- Incidence of PGI-S responders and non-responders over time

The PGI-S responses and responder status over time will be listed for the ITT analysis set. Flags for mITT analysis set will be added.

10.6.5 Secondary Analysis - ESS Total Score

The CFB of ESS total score at each post-baseline visit up to Week 12, comparing treatments, is one of the secondary endpoints for the study. This secondary efficacy endpoint will be analyzed considering MMRM models based on the mITT analysis set as secondary analysis. All assumptions regarding dependent variable, covariate, fixed effects, repeated measure, interaction effects, covariance matrix and estimates remain the same as specified in Section 10.6.1.1. For baseline, the associated baseline will be considered as covariate.

10.6.5.1 Supplementary Analyses

Summary statistics for the observed and CFB values over time will be performed on this endpoint for mITT as supplementary analyses.

The ESS responses over time will be listed for the ITT analysis set with a flag for the mITT analysis set.

The mean (SD) observed total score, mean (SD) change from baseline score and LS means (SE) for ESS total score by treatment over time using mITT analysis set at outlined in Section 10.6.1.3.

10.6.6 Secondary Analysis – NMSS Total Score

The CFB of NMSS total score at each post-baseline visit up to Week 12, comparing treatments, is one of the secondary endpoints for the study. This secondary efficacy endpoint will be analyzed considering MMRM models based on the mITT analysis set as secondary analysis. All assumptions regarding dependent variable, covariate, fixed effects, repeated measure, interaction effects, covariance matrix and estimates remain the same as specified in Section 10.6.1.1. For baseline, the associated baseline will be considered as covariate.

10.6.6.1 Supplementary Analyses

Summary statistics for the observed and CFB values over time will be performed on this endpoint for mITT as supplementary analyses.

The NMSS responses over time will be listed for the ITT analysis set with a flag for the mITT analysis set.

10.6.7 Secondary Analysis – PDSS-2 Total Score

The CFB of PDSS-2 total score at each post-baseline visit up to Week 12, comparing treatments, is one of the secondary endpoints for the study. This secondary efficacy endpoint will be analyzed considering MMRM models based on the mITT analysis set as secondary analysis. All assumptions regarding dependent variable, covariate, fixed effects, repeated measure, interaction effects, covariance matrix and estimates remain the same as specified in Section 10.6.1.1. For baseline, the associated baseline will be considered as covariate.

10.6.7.1 Supplementary Analyses

Summary statistics for the observed and CFB values over time will be performed on this endpoint for mITT as supplementary analysis.

The PDSS-2 responses over time will be listed for the ITT analysis set with a flag for the mITT analysis set.

10.6.8 Exploratory Analyses

The tabulation for each exploratory endpoint analysis will be performed using the mITT analysis set.

The listings for each exploratory endpoint will be performed using the mITT analysis set.

10.6.8.1 The Modality System

10.6.8.1.1 Objective Speech and Facial Measures

Summary statistics for the observed and CFB values by time point will be performed for select Modality speech and facial metrics at Weeks 2, 4, 6, 8, 10 and 12.

The values over time will also be listed.

10.6.8.1.2 PD-PROP™

Summary statistics of predicted symptoms and domains corresponding to bothersome problems reported by patients related to their PD at baseline and Week 12 will be tabulated using count and percentage.

The PD-PROP™ responses over time will also be listed.

10.6.8.1.3 PWB-PROP™

Summary statistics of predicted symptoms and domains corresponding to bothersome problems related to personal well-being reported by patients at baseline and Week 12 will be tabulated using count and percentage.

The PD-PROP™ responses over time will also be listed.

10.6.8.1.4 S&E ADL

Counts and percentages for each individual response of S&E ADL at Weeks 4, 8 and 12 will be tabulated.

S&E ADL responses over time will also be listed.

10.6.8.2 Cogstate Digital Cognitive Testing Battery

Summary statistics for the observed and CFB values for Cogstate Digital Cognitive Testing Battery parameters/tests over time will be performed.

The Cogstate Digital Cognitive Testing Battery assessment responses over time will be listed.

10.6.8.3 SAS

Summary statistics for the observed and CFB values over time will be performed for the SAS total score at Weeks 2, 4, 8 and 12. The number of subjects with a SAS total score more than 14 at each timepoint will also be tabulated.

SAS responses (individual and SAS total score) will be listed.

10.6.8.4 Beacon Dreem Overnight EEG

Summary statistics for the observed and CFB values over time will be performed for the EEG parameters and Sleep stage transitions.

EEG responses will also be listed.

10.7 PK

All displays (tables, listings, and figures) for PK analysis will be presented for PKS.

For PK analysis, descriptive summary statistics along with the geometric mean (GM), geometric standard deviation (GSD), arithmetic coefficient of variation (CV%), and geometric coefficient of variation (GCV%) for plasma concentrations of CVN424 over time (per timepoints indicated in the SoA (Appendix 1)), will be presented. First and third athematic quartiles (Q1 and Q3) will also be presented along with median. Also, the 95 % CI for the mean using t-statistics approximation will also be presented.

The above-mentioned descriptive statistics will be repeated for the following subgroups:

- Sex (Male and Female)
- Weight group (< median weight at baseline and ≥ median weight at baseline)

Figures of the following PK items are planned for presentation:

- Overlaid individual plasma concentration versus time plot (linear and semi-logarithmic scale)
- Mean plasma concentration versus time plot (linear scale with and without SD)
- Mean plasma concentration versus time plot (semi-logarithmic scale with and without SD)

The three set of plots will be repeated for the above specified subgroup classifications.

Individual CVN424 plasma concentration levels over time (per timepoints indicated in the SoA, Appendix 1), will be listed. The actual time of collection will also be displayed along with nominal timepoints.

10.8 Safety and Tolerability

All displays (tables, listings, and figures) for the safety analysis will be presented for SFAS.

10.8.1 Adverse Events

The following items are planned to be presented in summary tables showing event incidence (n) and corresponding event counts E:

- AE overview, including row items for frequency of subjects {n (%)} experiencing:
  - At least one TEAE
  - TEAEs by relationship with study drug:
    - Related TEAEs
    - Unrelated TEAEs
  - TEAEs by severity:
    - Mild TEAEs
    - Moderate TEAEs
    - Severe TEAEs
    - Moderate or severe TEAEs
  - Serious TEAEs
  - TEAEs leading to study drug interruption/suspension
  - TEAEs leading to study drug discontinuation

  - TEAEs leading to death
  - TEAEs reported as life threatening
  - TEAEs requiring an inpatient hospitalization or prolongation of existing hospitalization
  - TEAEs resulting in persistent disability or incapacity
  - TEAEs associated with a congenital anomaly or birth defect
  - TEAEs that are medically important events not covered by other serious criteria
  - AESI
  - Abuse-related TEAEs
- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs related to study drug by SOC and PT
- TEAEs related to study drug by PT
- AESI by SOC and PT
- Abuse-related TEAEs by PT
- Serious TEAEs by SOC and PT
- Serious TEAEs by PT
- TEAEs resulting in study drug interruption/suspension by PT
- TEAEs resulting in study drug discontinuation by PT
- TEAEs resulting in death by PT

The SOCs will be sorted alphabetically, and PTs will be sorted by number of decreasing frequencies in the total arm.

To study temporal profile of the following events, post first study drug administration, overlayed plot of cumulative number and absolute number of subjects with events over time will be plotted separately for each treatment:

- First TEAE

- First severe TEAE
- First serious TEAE
- First related TEAE

The following AE items will be listed:

- All AEs
- Serious TEAEs
- Study drug related TEAEs
- Abuse-related TEAEs
- Hospitalization due to TEAE
- TEAEs leading to study drug interruption/suspension
- TEAEs leading to study drug discontinuation
- TEAEs leading to death

10.8.2 Clinical Laboratory

The following central laboratory result items are planned for table presentation, for each applicable visit:

- Chemistry:
  - Summary statistics for observed and CFB values over time
  - Shift from baseline to post-baseline in reference range limits over time
- Hematology:
  - Summary statistics for observed and CFB values over time
  - Shift from baseline to post-baseline in reference range limits over time
- Urinalysis:
  - Summary statistics for observed and CFB values over time – quantitative results
  - Incidence of results over time – qualitative results
- Incidence of marked abnormalities for the following parameters at any timepoint:

- Alanine aminotransferase (ALT) > 2 x upper limit of normality (ULN)
- ALT > 3 x ULN
- Aspartate aminotransferase (AST) > 2 x ULN
- AST > 3 x ULN
- Total bilirubin > 1.5 x ULN
- Total bilirubin > 2 x ULN
- (ALT OR AST > 2 x ULN) AND total bilirubin > 1.5 x ULN
- Alkaline phosphatase (ALP) < 2 x ULN
- (ALT OR AST > 3 x ULN) AND total bilirubin > 2 x ULN AND ALP < 2 x ULN (Hy's law)
- Creatinine clearance ≤ 50 mL/min

For computing percentages for the shift tables, the denominator will be the total number of subjects with a non-missing baseline and post-baseline value for the respective laboratory parameter, post-baseline timepoint and treatment group.

The following subject safety laboratory results are planned to be listed:

- Chemistry
- Hematology
- Urinalysis (Quantitative and Qualitative results)
- Drug and alcohol screening
- Abnormal laboratory results
- Pregnancy test

10.8.3 Vital Signs

The following listings will be presented for vital sign measurements:

- Observed vital sign parameters
- Abnormal vital sign results, including:
  - Increase/decrease in SBP by 20 mm Hg from Baseline

- Increase/decrease in DBP by 10 mm Hg from Baseline
- Increase/Decrease in HR by 15 bpm from Baseline
- Decrease in SBP by 20 mm Hg from pre-dose assessment to first three minutes at dosing visit.
- Decrease in DBP by 10 mm Hg from pre-dose assessment to first three minutes at dosing visit.

Note: Each range limits are included in abnormality criteria outlined above.

The following vital sign tables are planned to be presented:

- Summary statistics for observed and CFB over time
- Summary statistics for postural change in SBP and DBP over time
- Incidence of abnormal vital sign results at any post baseline assessment

10.8.4 ECG

The following listings will be presented for ECG measurements:

- Observed ECG parameter values
- Abnormal ECG results
  - Abnormal but clinically significant
  - Abnormal but clinically not significant
  - QT interval, corrected using Fridericia's formula (QTcF) > 470 msec for female subjects; > 450 msec for male subjects at any post-baseline timepoint
  - QTcF CFB > 60 msec

The following ECG tables are planned to be presented:

- Summary statistics for observed and CFB values of numerical ECG parameters over time
- Incidence (n) and percentage (%) of abnormal ECG interpretation at any post baseline assessment
- Time-matched placebo adjusted QT interval, corrected using Bazett's formula (QTcB) and QTcF summary statistics over time

The following figures are planned for presenting ECG parameters QTcB and HR:

- Mean observed QTcB over time
- Mean CFB QTcB over time (including visits with a pre-dose, following the first dose, and 2-hour post dose administration)
- Mean observed HR over time
- Mean CFB HR over time

10.8.5 Physical Examinations

The following physical and neurological examination measurements will be tabulated by treatment:

- Physical examination results over time
- Incidence of abnormal physical examination results over time
- Neurological examination results over time
- Incidence of abnormal in neurological examination results by neurological examination part, classification over time

The following listings are planned for physical and neurological examination measurements:

- Observed physical examination results
- Observed neurological examination results

10.8.6 C-SSRS

The suicidal behavior, suicidal ideation, suicidal behavior, OR suicidal ideation at Baseline and over time will be tabulated using number of subjects and percentage for each treatment.

The C-SSRS response over time will be listed.

11 REFERENCES

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12 APPENDICES

Appendix 1. Schedule of Assessments and Procedures

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 Appendix 4)									
Clinical Laboratory Tests[g]	X			X		X		X	X[f]
Urine Drug Screen	X	X							
Pregnancy test[h]	X	X		X		X		X	X
Plasma Pharmacokinetics;									
[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

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
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-SSR“ ("Lifetime”)	X								
C-SSRS (“Since Last Visit”)		X	X	X		X		X	X
Modality Assessments[i]		X	X	X	X	X	X	X	X
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 of Severity Scale; 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-2 = Parkinson’s Disease Sleep Scale-2; PGI-S = Patient Global Impression of Severity Scale; PWB-PROP™ = Personal Wellbeing Patient Report of Problems; 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 of protocol 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 Appendix 4 for a list of all hematology, chemistry, and urinalysis tests to be performed. Coagulation studies 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 of Protocol 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 of Protocol 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. Quality check (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 ogstate Computerized Battery testing will be conducted twice at Screening for familiarization.

n Beacon Dreem Overnight EEG recordings 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 8.2.8.5 of Protocol for details.

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

Appendix 2. Imputation of Partial Dates

Missing or partial AE start dates will be imputed for the purpose of determining whether the AEs are treatment emergent as per start date imputation rules outlined in Table 25.

The start date of medical history related to PD will also be imputed using Table 25. The imputed dates will be used only for the calculation of time since PD diagnosis.

For medication/therapy, missing and partial start dates or stop dates, both will be imputed for the purpose of determining whether the medication/therapy is prior or concomitant. Detailed data handling rules for missing or partial start/stop date for medications/therapies are described in Table 25. The missing or partial dates will be displayed in the data listings as reported on the eCRF rather than the imputed dates.

Table 25. Imputation Rules for Partial Dates

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y same as M and Y of first study drug administration	Date of first study drug administration
		M and/or Y not the same as M and Y of first study drug administration	First day of indicated month
	M and D	Y same as Y of first study drug administration	Date of first study drug administration
		Y not the same as Y of first study drug administration	01 January of indicated year
	M, D, and Y	--	Date of first study drug administration
End Date	D only	M and Y same as M and Y of last study drug administration	Date of last study drug administration
		M and/or Y not the same as M and Y of last study drug administration	Last day of indicated month
	M and D	Y same as Y of last study drug administration	Date of last study drug administration
		Y not the same as Y of last study drug administration	31 December of indicated year
	M, D, and Y	Date completely missing	Date of last study drug administration

D = day; M = month; Y = year.
Note: The imputation of end date must be later than start date.

No imputed dates will be reported. The imputed dates will only be used for flagging of treatment-emergent AEs and determining prior and concomitant medications. If still there is not clarity on flagging treatment-emergent AEs and determining prior and concomitant medications, consider event/medication as TEAE or concomitant medication taking a conservative approach.

The start date of medical history related to PD will be imputed using Table 25. The imputed dates will be used only for the calculation of time since PD diagnosis.

Appendix 3. Summary of Efficacy Analyses

Parameter	Analysis Set	Statistical Method	Missing Data/ Subgroup	Interpretation	Table Number
MDS – UPDRS Part II+ Part III sum score	mITT	MMRM	NA	Primary	14.2-1.1
	ITT	MMRM (Hypothetical Scenario for Medication for PD Motor Features)	MAR	Sensitivity	14.2-1.2.1
	ITT	MMRM (Hypothetical Scenario for Medication for PD Motor Features)	MNAR (Copy-Reference)	Sensitivity	14.2-1.2.2
	ITT	MMRM (All available data)	MAR	Sensitivity	14.2-1.2.3.
	ITT	MMRM (All available data)	MNAR (Copy-Reference)	Sensitivity	14.2-1.2.4
	ITT	MMRM (Hypothetical Scenario for Medication for PD Motor Features)	MNAR (Tipping Point)	Sensitivity	14.2-1.2.5
	Completer	MMRM	NA	Supplementary	14.2-1.3.1
	PPS	MMRM	NA	Supplementary	14.2-1.3.2
	mITT	MMRM	Age group 1	Subgroup	14.2-1.4.1
	mITT	MMRM	Age group 2	Subgroup	14.2-1.4.2
	mITT	MMRM	Sex group	Subgroup	14.2-1.4.3
	mITT	MMRM	MDS – UPDRS Part II + Part III sum score group	Subgroup	14.2-1.4.4
	mITT	MMRM	MDS – UPDRS Part II group	Subgroup	14.2-1.4.5
	mITT	MMRM	MDS – UPDRS Part III sum score group	Subgroup	14.2-1.4.6
	mITT	Summary statistics	NA	Supplementary	14.2-1.5.1
	ITT	Summary statistics	Considering intercurrent events	Supplementary	14.2-1.5.2
CGI-S Responder	mITT	Chi Square	NA	Secondary	14.2-2.1
	ITT	GLIMMIX	NA	Supplementary	14.2-2.2
	mITT	Count and percentage	NA	Supplementary	14.2-2.3
CGI-S Score	mITT	Summary statistics	NA	Supplementary	14.2-2.4
PGI-S Responder	mITT	Chi Square	NA	Secondary	14.2-3.1
		GLIMMIX	NA	Supplementary	14.2-3.2

Parameter	Analysis Set	Statistical Method	Missing Data/ Subgroup	Interpretation	Table Number
	mITT	Count and percentage	NA	Supplementary	14.2-3.3
PGI-S Score	mITT	Summary statistics	NA	Supplementary	14.2-3.4
MDS – UPDRS Part II sum score	mITT	MMRM	NA	Secondary	14.2-4.1
	mITT	Summary statistics	NA	Supplementary	14.2-4.2
MDS – UPDRS Part III sum score	mITT	MMRM	NA	Secondary	14.2-5.1
	mITT	Summary statistics	NA	Supplementary	14.2-5.2
MDS – UPDRS Part I sum score	mITT	MMRM	NA	Secondary	14.2-6.1
	mITT	Summary statistics	NA	Supplementary	14.2-6.2
ESS total score	mITT	MMRM	NA	Secondary	14.2-7.1
	mITT	Summary statistics	NA	Supplementary	14.2-7.3
NMSS total score	mITT	MMRM	NA	Secondary	14.2-8.1
	mITT	Summary statistics	NA	Supplementary	14.2-8.2
Total MDS – UPDRS score	mITT	MMRM	NA	Secondary	14.2-9.1
	mITT	Summary statistics	NA	Supplementary	14.2-9.2
PDSS-2 total score	mITT	MMRM	NA	Secondary	14.2-10.1
	mITT	Summary statistics	NA	Supplementary	14.2-10.2
Objective Speech and Facial Measures	mITT	Summary statistics	NA	Exploratory	14.2-11.1
PD-PROP™ responses over time	mITT	Count and percentage	NA	Exploratory	14.2-11.2
PWB-PROP™ responses over time	mITT	Count and percentage	NA	Exploratory	14.2-11.3
S&E ADL over time	mITT	Count and percentage	NA	Exploratory	14.2-11.4
Cogstate Digital Cognitive Testing Battery parameters over time	mITT	Summary statistics	NA	Exploratory	14.2-12
SAS total score over time	mITT	Summary statistics	NA	Exploratory	14.2-13
Beacon Dreem EEG parameters over time	mITT	Summary statistics	NA	Exploratory	14.2-14.1
Sleep stage transitions over time	mITT	Summary statistics	NA	Exploratory	14.2-14.2

ADL = Activities of Daily Living; CGI-S = Global Impression of Severity Scale; EEG = electroencephalogram; ESS = Epworth Sleepiness Scale; GLIMMIX = Generalized linear mixed model; ITT = Intent-to-treat; MAR = Missing at random; MDS – UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale; mITT = Modified intent-to-treat; MMRM = Mixed model repeated measure; MNAR = Missing not at random; NA = Not applicable; NMSS = Non-motor Symptoms Scale; PDSS-2 = Parkinson's Disease Sleep Scale-2; PGI-S = Patient Global Impression of Severity Scale; PD = Parkinson's Disease; PD-PROP™ = Parkinson's Disease Patient Report of Problems; PPS = Per protocol analysis set; PWB-PROP™ = Personal Wellbeing Patient Report of Problems; S&E = Schwab and England; SAS = Starkstein Apathy Scale.

Appendix 4. Planned Laboratory Assays

Laboratory Category	Laboratory Tests		
Hematology	• Hematocrit • Hemoglobin • Platelet count • RBC count	• RBC indices: ○ MCH ○ MCHC ○ MCV ○ %/nL reticulocytes	• WBC count with differential: ○ Neutrophils ○ Lymphocytes ○ Monocytes ○ Eosinophils ○ Basophils
Clinical Chemistry	• Albumin • Alkaline phosphatase • ALT/SGPT • AST/SGOT • BUN • Calcium	• Bicarbonate • Chloride • Creatinine • Creatinine kinase • GGT • Glucose [non fasting] • LDH	• Potassium • Sodium • Total bilirubin • Direct bilirubin • Total protein
Coagulation	• INR • PT • PTT/aPTT		
Urinalysis	• Specific gravity • By dipstick ○ pH ○ Glucose ○ Protein ○ Blood ○ Ketones ○ Nitrite	• Microscopic examination (if blood or protein is abnormal): ○ RBC/high power field ○ WBC/high power field ○ Epithelial cells, ○ casts, etc.	
Diagnostic Screening in Serum	• Serum hCG[a] • FSH[b]	• Hepatitis panel including: ○ HBsAg ○ Anti-HCV • HIV • COVID-19	
Diagnostic Screening in Urine/ Blood	• Drug screen including ○ Amphetamines ○ Barbiturates ○ Benzodiazepines ○ Cocaine ○ Opiates ○ Methadone	○ MDMA ○ Phencyclidine (PCP) ○ THC • Urine Pregnancy Test[a]	

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; MDMA = Methylenedioxymethamphetamine; PCP = Phencyclidine; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; THC = Tetrahydrocannabinol; WBC = white blood cell.

a Serum pregnancy test at Screening and urine pregnancy test at all other indicated visits for women of childbearing potential only.

b For women of child-bearing potential only.

E20007_CVN424-203_SAP Ver Final 2.0 16Jan2025

Final Audit Report 2025-01-17

Created:	2025-01-16
By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAAJfIsHGOtdlz1024xPoyOc5GZuJvTR0hX

"E20007_CVN424-203_SAP Ver Final 2.0 16Jan2025" History

Document created by [redacted]
2025-01-16 - 11:28:37 AM GMT

Document emailed to [redacted] for signature
2025-01-16 - 11:30:48 AM GMT

Document emailed to [redacted] for signature
2025-01-16 - 11:30:48 AM GMT

Document emailed to [redacted] for signature
2025-01-16 - 11:30:49 AM GMT

Document emailed to [redacted] for signature
2025-01-16 - 11:30:49 AM GMT

Document emailed to [redacted] for signature
2025-01-16 - 11:30:49 AM GMT

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2025-01-16 - 11:33:30 AM GMT

Email viewed by [redacted]
2025-01-16 - 11:34:12 AM GMT

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2025-01-16 - 11:34:41 AM GMT

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user clicked on the signature field: 'Signature Field 5'.
2025-01-16 - 11:35:30 AM GMT

Signer [redacted] entered name at signing as [redacted]
2025-01-16 - 11:35:56 AM GMT

Document e-signed by [redacted]
Signing reason: I approve this document
Signature Date: 2025-01-16 - 11:35:58 AM GMT - Time Source: server

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user clicked on the signature field: 'Signature Field 1'.
2025-01-16 - 11:37:20 AM GMT

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2025-01-16 - 11:39:09 AM GMT

Email viewed by [redacted]
2025-01-16 - 11:39:53 AM GMT

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user clicked on the signature field: 'Signature Field 1'.
2025-01-16 - 11:40:03 AM GMT

Document e-signed by [redacted]
Signing reason: I am the author of this document
Signature Date: 2025-01-16 - 11:40:14 AM GMT - Time Source: server

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user opened the agreement.
2025-01-16 - 11:40:57 AM GMT

[redacted] authenticated with Adobe Acrobat Sign.
Challenge: The user clicked on the signature field: 'Signature Field 2'.
2025-01-16 - 11:41:47 AM GMT

Document e-signed by [redacted]
Signing reason: I have reviewed this document
Signature Date: 2025-01-16 - 11:41:56 AM GMT - Time Source: server

Email viewed by [redacted]
2025-01-16 - 6:18:25 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2025-01-16 - 6:19:00 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user clicked on the signature field: 'Signature Field 3'.

2025-01-16 - 6:19:54 PM GMT

Document e-signed by [redacted]

Signing reason: I approve this document

Signature Date: 2025-01-16 - 6:20:02 PM GMT - Time Source: server

Email viewed by [redacted]

2025-01-17 - 8:51:31 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user opened the agreement.

2025-01-17 - 8:51:55 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.

Challenge: The user clicked on the signature field: 'Signature Field 4'.

2025-01-17 - 8:52:30 PM GMT

Document e-signed by [redacted]

Signing reason: I approve this document

Signature Date: 2025-01-17 - 8:52:40 PM GMT - Time Source: server

Agreement completed.

2025-01-17 - 8:52:40 PM GMT