Official Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effects of SAGE-718 in Parkinson's Disease Cognitive Impairment

NCT ID: NCT05318937

Document Date: SAP Version 1.0: 15 March 2024

STATISTICAL ANALYSIS PLAN

METHODS

PROTOCOL NUMBER 718-CNP-202

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effects of SAGE-718 in Parkinson's Disease Cognitive Impairment

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Version: 1.0

Version Date of SAP: 14 March 2024

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1. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this Statistical Analysis Plan (SAP).

Table 1. Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse Event
AR	Autoregressive
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CR	Controlled Release
CS	Clinically Significant
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DD	Daily Dose
DSST	Digit Symbol Substitution Test
EBT	Emotional Bias Task
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ER	Extended Release
ERT	Emotion Recognition Task
ET	Early Termination
FAS	Full Analysis Set
[redacted]	[redacted]
GEE	Generalized Estimating Equation

Abbreviation	Definition
IADL	Instrumental Activities of Daily Living
IP	Investigational Product
IR	Immediate Release
IRT	Interactive Response Technology
LD	Levodopa Dose
LED	Levodopa Equivalent Dose
LFT	Liver Function Test
LSM	Least Square Mean
MAR	Missing at random
Max	Maximum
MCI	Mild Cognitive Impairment
MDS	Movement Disorder Society
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed-effects model for repeated measures
MNAR	Missing not at random
MoCA	Montreal Cognitive Assessment
MTT	Multitasking Test
[redacted]	[redacted]
NCS	Not Clinically Significant
[redacted]	[redacted]
[redacted]	[redacted]
OTS	One Touch Stockings of Cambridge
PAL	Paired Associates Learning
PCS	Potentially Clinically Significance
PD	Parkinson's Disease
[redacted]	[redacted]
PDAQ-15 KI	Penn Parkinson's Daily Activities Questionnaire-15 Knowledgeable Informant
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
PO	Orally
PPS	Per Protocol Set
PRM	Pattern Recognition Memory
PT	Preferred Term
PVT	Psychomotor Vigilance Task
Q1	25th Percentile
Q3	75th Percentile
RL	Reaction Latency
RTI	Reaction Time Index
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SSP	Spatial Span
SWM	Spatial Working Memory
TEAE	Treatment-emergent Adverse Event
UN	Unstructured
VRM	Verbal Recognition Memory
WAIS-IV	Wechsler Adult Intelligence Scale-IV

2. INTRODUCTION

This SAP is for the final analysis and is based on the following approved study documents:

- Study Protocol, Version 3.0 (09 August 2022)
- electronic Case Report Form (eCRF), Version 8.0 (December 2023)

This SAP addresses the objectives of the study and describes the planned statistical analyses and data presentations. All analyses and data presentations will be generated using SAS® Version 9.4 or higher Software (SAS Institute, Cary, North Carolina, USA). This SAP will be finalized and approved before the clinical database lock. Any changes made to the SAP after the clinical database lock will be documented and discussed in the clinical study report for this study.

[redacted] Analyses of biomarkers and [redacted].

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the effect of SAGE-718 on cognitive performance in participants with Parkinson's Disease (PD) Mild Cognitive Impairment (MCI).

3.2. Secondary Objectives

- To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with PD-MCI.

[redacted]

4. STUDY ENDPOINTS

4.1. Efficacy Endpoint

4.1.1. Primary Efficacy Endpoint

The primary endpoint is change from baseline to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test.

4.2. Safety Endpoints

- To evaluate the safety and tolerability of SAGE-718 in participants with PD-MCI
  - Proportion of participants experiencing treatment-emergent adverse events (TEAEs) and severity of TEAEs.
  - Number of participants who withdraw due to adverse events (AEs).
- To evaluate the safety and tolerability of SAGE-718 on other safety parameters.
  - Change from Baseline in vital signs, clinical laboratory parameters, electrocardiograms (ECGs), and [redacted].

[redacted]

5. STUDY DESIGN

5.1. Overall Design

This is a randomized, placebo-controlled, double-blind study to evaluate the effects of SAGE-718 in PD-MCI.

The Screening Period begins with the informed consent process for prospective participants, including optional caregivers. Subsequent screening assessments will be performed between Day -28 and Day -8 to determine eligibility, including assessments of cognitive and motor function. An adult caregiver is optional but highly recommended for each participant to support completion of study activities and to answer questions about the participant's condition.

The Baseline Period will occur from Day -7 through Day -1. On Day -7, participants will visit the clinic for confirmation of continued eligibility and collection of baseline cognitive and safety data. Participants and caregivers will receive training on the study procedures and devices. Participants will continue to complete daily assessments of cognitive performance using the mobile device during the Baseline Period.

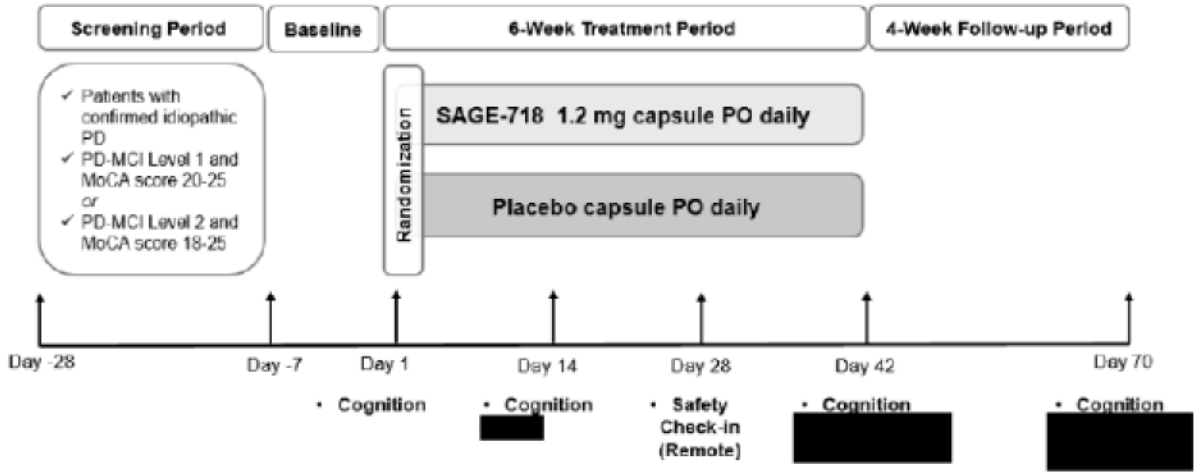
Eligible participants with a confirmed diagnosis of idiopathic PD by 2015 Movement Disorder Society (MDS) criteria at Screening and who meet MDS Task Force Criteria for MCI in PD (excluding requirement for United Kingdom PD Brain Bank diagnostic criteria) will receive a 1.2 mg dose of SAGE-718 or placebo daily for 6 weeks (42 days). Beginning on Day 1 and continuing through Day 42, participants will self-administer blinded investigational product (IP) once per day in the morning. No dosing will be permitted beyond Day 42.

At scheduled clinic visits during the Treatment Period, safety, efficacy, and [redacted] will be performed, and study staff will dispense a sufficient amount of blinded IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by examination of the used packaging and counting any returned capsules.

During the treatment period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants who discontinue IP early should complete the remaining study visits as scheduled unless the participant withdraws consent or loses the capacity to grant consent. If a participant withdraws from the study/stops study participation early, an early termination (ET) visit should be conducted. Treatment with SAGE-718 can be ended without down titration.

After completing the treatment period, participants will return to the clinic for a follow-up visit on Day 70 to collect continued safety, efficacy, and [redacted].

Figure 1. Study Schematic



Abbreviations: Cognition = Cognitive assessments (includes Wechsler Adult Intelligence Scale-IV [WAIS-IV] Coding test; [redacted] and Montreal Cognitive Assessment [MoCA]. [redacted]
PDMCI = Parkinson's Disease Mild Cognitive Impairment; [redacted]; PO = orally.
See Appendix A for the specific schedule of each test.

5.2. Sample Size and Power

Assuming a placebo-adjusted treatment effect size of 0.75 (Burdick 2014; the estimated treatment difference in z-score was 0.8 with a standard deviation of 1.07) in the WAIS-IV Coding test, a total sample size of 60 evaluable participants (30 per arm) will provide 80% power at a two-sided significance level α=0.05.

Adjusting for an anticipated 20% dropout rate, approximately 76 participants will be randomly assigned in a 1:1 ratio to either SAGE-718 or placebo.

5.3. Randomization

This is a randomized, placebo-controlled, double-blind study. Eligible participants will be randomized 1:1 to receive SAGE-718 or placebo for 42 days.

Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to treatment group will be based on the randomization schedule. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

5.4. Blinding and Unblinding

Participants, clinicians, and the study team are blinded to treatment allocation during the study. The randomization schedules are kept strictly confidential, accessible only to authorized personnel until the time of unblinding.

During the study, the blind can be broken by the investigator via the IRT system only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make attempts to contact Sage prior to unblinding the study treatment administered to a participant. The responsibility to break the treatment code in emergency situations resides solely with the investigator. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records. The ET visit should be completed after a participant's treatment assignment has been unblinded.

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

- Protocol does not specify the analysis objective of Daily (Mobile Phone-based) Assessments including Psychomotor Vigilance Task (PVT), Digit Symbol Substitution Test (DSST), and National Sleep Foundation Sleep Diary. They will be analyzed to evaluate the below objectives.
    - PVT: To evaluate the effect of SAGE-718 on motor symptoms in participants with PD-MCI.
    - DSST: To evaluate the effect of SAGE-718 on additional measures of global and domain-specific cognitive performance in participants with PD-MCI.
    - National Sleep Foundation Sleep Diary: To evaluate the effect of SAGE-718 on functioning in participants with PD-MCI.
- Protocol Section 10.6.1: [redacted]
- Protocol Section 11.3.2.2: [redacted]

6.2. Modifications from the Approved Statistical Analysis Plan

Not applicable.

6.3. Modifications from the Approved DMC Charter

Not applicable.

7. ANALYSIS SETS

7.1. All Randomized Set

The All Randomized Set will include all participants who have been randomized and will be used to describe participant disposition.

7.2. Safety Set

The Safety Set will include all participants who were administered at least one dose of the IP. The Safety Set will be used to describe the safety data and analyses will be based on actual treatment received.

7.3. Full Analysis Set

The Full Analysis Set (FAS) will include all participants in the Safety Set who have baseline and at least 1 post-baseline efficacy evaluation. FAS will be used to describe the efficacy data, which is based upon the Intent-to-Treat principle. Analyses will be based on the planned treatment.

7.4. Per Protocol Set

The Per Protocol Set (PPS) is defined as a subgroup of participants in FAS excluding:

- participants with major protocol deviations that could affect efficacy
- participants who consumed less than 80% of IP
- participants who consumed incorrect IP at any time during study
- participants or study partner who were unblinded to treatment assignment prior to the database lock.

For further details see Section 8.2.2. A supportive analysis will be performed on the PPS to assess the robustness of the study conclusions to the choice of analysis set for the primary efficacy variable.

[redacted]

8. STATISTICAL ANALYSIS

8.1. General Considerations

Continuous data will be summarized in terms of the number of participants, mean, standard deviation (SD), minimum value (min), maximum value (max), median, 25th percentile (Q1), and 75th percentile (Q3). The minimum and maximum will be reported with the same number of decimal places as the source (raw) data. Mean, median, Q1, and Q3 will be reported to 1 decimal place more than the source (raw) data. SD and standard error (SE), if applicable, will be reported to 2 decimal places more than the source (raw) data. Least Square Means (LSM) will be reported to 1 decimal place more than the source (raw) data. Confidence intervals (CI) will be presented to one more decimal place than the associated parameter estimate. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts, and percentages. Percentages will be presented to 1 decimal place unless otherwise specified. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will not be presented for zero counts. Percentages will be calculated using the number of participants (n) as the denominator. A missing category shall be included only for categorical variables where no data is available. The missing category will be omitted if there are no missing values for that variable.

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. All summaries will be provided by treatment – either by randomized treatment or actual treatment received.

If a participant takes any dose of SAGE-718, the participant's actual treatment is considered as SAGE-718, regardless of the treatment to which the participant has been randomized.

P-values will be reported to four decimal places, with p-values less than 0.0001 reported as "<0.0001". P-values larger than 0.9999 will be reported as ">0.9999".

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data unless otherwise specified.

General definitions are defined as below:

- Baseline is defined as the last non-missing measurement prior to the first dose of IP, unless stated otherwise. If the time of an assessment is collected, baseline will be the latest assessment prior to first dose of IP administration time; if the time of an assessment is not collected, the assessment on Day 1 is assumed to be prior to dosing

if the protocol mentions that this assessment needs to be before dosing or it is collected as "pre-dose".

- Study day 1 is defined as the date of randomization for untreated randomized participants or the date of first dose for treated participants.
- Study day will be calculated relative to the date of randomization for untreated randomized participants and relative to the date of first dose for treated participants.
  - If event is prior to randomization or the first dose, then study day is calculated as:

    Date of Event – Date of Randomization or First Dose
  - If event is after randomization or the first dose, then study day is calculated as:

    Date of Event – Date of Randomization or First Dose + 1

8.2. Background Characteristics

8.2.1. Participant Disposition

This analysis will be based on all screened participants (i.e., all participants who have signed an informed consent).

Summaries will be provided for all screened participants in the study including participants screened, screen-failed, randomized, randomized but not dosed, received at least one dose of IP, completed IP, discontinued study treatment with primary reasons for discontinuing treatment, completed study, and discontinued study with primary reasons for early discontinuation. Numbers of participants and percentages will be based on the participants who were randomized and received IP (Safety Set). In addition, summary of analysis sets including Safety Set, FAS, PPS, and [redacted] will be provided for participants randomized. Treatment arm assignment will be summarized according to the randomized treatment.

If a participant is rescreened because the participant has been a screen failure the first time, the status of the participant will be determined from the second screening. In the count of screened participants, this participant will be counted only once.

Listings by treatment group will be provided for disposition of participants: screen failures, inclusion/exclusion criteria, completion and discontinuation from study treatment and study participation, and inclusion in analysis sets.

8.2.2. Protocol Deviations

Protocol deviations will be classified as "major" or "minor" on ongoing basis by the clinical study team and sponsor.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the participant's rights, safety, well-being, and/or the validity of the data for analysis. Minor protocol deviations include all deviations from the protocol excluding the major protocol deviations.

Major protocol deviations and any action to be taken regarding the exclusion of participants or affected data from specific analyses are defined in the project-specific Protocol Deviation Assessment Plan.

The study team will identify the major protocol deviations related to efficacy or that may have impact on efficacy to determine the participants in the FAS to be excluded from the PPS prior to database lock in a blinded fashion. Some major protocol deviations may not lead to participants' data being excluded from the PPS.

The number and percentage of participants with a major protocol deviation in the FAS will be summarized by randomized treatment group. A by-participant listing of all protocol deviations will also be provided.

8.2.3. Demographics and Baseline Characteristics

This analysis will be based on the Safety Set and FAS.

Demographic data, such as age at randomization, sex, race, and ethnicity, years of education, employment history, current employment status, and baseline characteristics, such as height, weight, and body mass index (BMI) will be summarized using descriptive statistics by treatment group and overall.

Baseline characteristics related to the diagnosis and treatment of PD, cognitive performance and motor symptoms will also be summarized for:

- Years since initial diagnosis of PD (continuous)
- Diagnosis Criteria Level for PD-MCI (categorical: Level 1 [abbreviated], Level 2 [comprehensive])
- Medication for treating PD symptoms (categorical: No, Yes)
    - If yes, Clinical Status (categorical: On, Off)
        - *Note:* On is the typical functional state when patients are receiving medication and have a good, and Off is the typical functional state when patients have a poor response despite taking medications.
- WAIS-IV Coding test score (continuous)
- [redacted]
- Total daily Levodopa Equivalent Dose (LED) at Screening (continuous)

Total daily LED at Screening will be calculated based on the conversion factor presented in Appendix D.

By-participant listing of all demographics and baseline characteristics will also be provided by treatment group.

8.2.4. Medical History

This analysis will be based on the Safety Set.

Medical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0 or higher. Medical history data will be summarized by system organ class (SOC) and preferred term (PT).

Medical history will be listed by treatment group. Also, by-participant listing of Parkinson's disease history will be provided.

8.2.5. Prior and Concomitant Medications/Procedures

This analysis will be based on the Safety Set.

Medications and procedures will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary September 2015, or later and MedDRA Version 22.0 or higher, respectively.

All medications/procedures taken within 60 days prior to Screening through the duration of the study will be recorded, as well as all medications/procedures used to treat PD regardless of timing. Those medications/procedures taken and ended prior to the first dose of IP will be denoted "Prior". Those medications/procedures taken prior to the first dose of IP and continuing beyond the initiation of the IP or those medications/procedures started at the same time or after the initiation of the IP will be denoted "Concomitant".

Medications/procedures will be presented according to whether they are "Prior" or "Concomitant" as defined above. If medication/procedures dates are incomplete and it is not clear whether the medication/procedures are concomitant, it will be assumed to be concomitant.

Missing or partial dates will be imputed for medication/procedures. Algorithm for missing or partial start /end date is documented in Appendix C.

Concomitant medications/procedures are further categorized as on-treatment and post-treatment as follows:

- On-treatment concomitant medications/procedures are those that have been used between first and last dose of IP (both inclusive) as well as medications started prior to first dose of IP and continue beyond the initiation of IP.
- Post-treatment medications/procedures are those that have been started after the last dose of IP.

Concomitant medications will be summarized on the Safety Set using Anatomical Therapeutic Chemical (ATC) level 1 and Standard Medication Name by actual treatment group. Concomitant procedures will be summarized on the Safety Set using SOC and PT by actual treatment group. By-participant listings of prior and concomitant (on-treatment and post-treatment) medications as well as procedures will also be provided.

8.2.6. Investigational Product Exposure

This analysis will be based on the Safety Set.

Total exposure duration to IP (in days), total drug exposure (in mg), and percent of planned exposure received (in %) will be summarized by actual treatment group.

Total exposure duration to IP (in days) is defined as the date of the last dose minus the date of first dose plus 1. Note that this does not exclude days when the dose has been missed.

Total drug exposure (in mg) is defined as the total IP in mg for SAGE-718 that was taken during the study. Total drug exposure for participants randomized to placebo is zero unless the participant has taken SAGE-718 by mistake, in which case the total exposure comes from SAGE-718 exposure. The dose taken will be considered as 0 mg on days the participant skips a dose.

Percent of the planned exposure received (in %) is defined as the total drug exposure, divided by planned exposure, times 100%.

- For participants randomized to SAGE-718 who complete the treatment period, the planned exposure is calculated as follows:
    - 40 days times 1.2 mg if Study Day of Day 42 Visit < 40
    - (Date of Day 42 visit – First Dose Date + 1) times 1.2 mg if Study Day of Day 42 Visit is 40 or 41
    - 42 days times 1.2 mg if Study Day of Day 42 Visit ≥ 42
- For participants randomized to SAGE-718 who discontinue the treatment earlier than Day 42 Visit, the planned exposure is (Last Dose Date – First Dose Date + 1) times 1.2 mg for participants randomized to SAGE-718.
- For participants randomized to placebo, this measure is not applicable.

By-participant listing of IP administration and exposure will also be provided including participant ID, date of dose, planned exposure (mg), and actual exposure (mg).

8.2.7. Investigational Product Adherence

This analysis will be based on the FAS.

IP adherence (%) is defined as the number of capsules taken, divided by the number of capsules planned to be taken, times 100%. The planned number of capsules is defined as similar way as planned exposure.

- For participants who complete the treatment period, the planned number of capsules taken is defined as follows:
  - 40 if Study Day of Day 42 Visit < 40
  - (Date of Day 42 visit – First Dose Date + 1) if Study Day of Day 42 Visit is 40 or 41
  - 42 if Study Day of Day 42 Visit ≥ 42
- For participants who discontinue the treatment earlier than Day 42 Visit, the planned exposure is (Last Dose Date – First Dose Date + 1).

Number and percentage of participants with IP adherence in categories (<80%, 80-100%, >100%) will be provided. By-participant listing of IP adherence will be provided.

8.3. Efficacy Analysis

The FAS and PPS will be used for all efficacy summary and analysis tables. Participants will be analyzed according to randomized treatment.

8.3.1. Definition of Efficacy Variables

8.3.1.1. Primary Efficacy Assessment

The WAIS-IV Coding test is a valid and sensitive measure of cognitive dysfunction impacted by many domains that correlates with real-world functional outcomes (e.g., the ability to accomplish everyday tasks) and recovery from functional disability. In-clinic administration of the WAIS-IV Coding test will use the traditional paper-and-pen format, in which the participant is required to identify the symbols matched to numbers using a key and write in the symbol beneath the associated number. The score is based on the total number of codes correctly completed over a 120 second time limit (higher scores reflecting better performance).

WAIS-IV Coding Test is collected at Baseline (Day -7), Day 1 (pre-dose), Day 14, Day 42 and Day 70.

[redacted]

[redacted]

[redacted]

8.3.1.2.5. Penn Parkinson's Daily Activities Questionnaire-15 Knowledgeable Informant

Penn Parkinson's Daily Activities Questionnaire-15 Knowledgeable Informant (PDAQ-15 KI) is a caregiver-reported outcome that measures the cognitive IADL in PD. The instrument is completed by a KI to the patient. The PDAQ-15 KI was created as an abbreviated version of the PDAQ-50 consisting of 15 of the original 50 items and demonstrates strong psychometric properties across the spectrum of cognitive impairment. The items are scored for difficulty in performing each IADL on a "none" (4), "a little" (3), "somewhat" (2), "a lot" (1) and "cannot do" (0) with the total score ranging from 0 to 60 (higher scores indicating better IADL function). PDAQ-15 KI is collected on Baseline (Day -7), Day 42 and Day 70.

The key outcome measure is a total score. Other outcome measures are each individual items.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.3.1.2.13. Daily (Mobile Phone-Based) Assessments

Daily assessments will be derived for Baseline, Day 14, and Day 42 using the mean of non-missing assessments for 7 days as descripted in the Table 2 below. The baseline measurement will be calculated as the mean of days immediately preceding to first dose day. The precision level of averages is to keep one decimal place. Table 2 lists visit deviation. If there are missing assessments for more than 4 days among 7 days, the derived mean will be considered as missing.

Table 2. Analysis Visit Derivation for Daily Mobile Assessments

Scheduled Visit	Derivation for averaging
Baseline *	> Day -7 and ≤ Day 1
Day 14	> Day 7 and ≤ Day 14
Day 42	> Day 35 and ≤ Day 42

* Day 1 assessment will be collected prior to the first dosing per protocol. For PVT and DSST, if Day 1 assessment is collected after the first dose or not available, available non-missing assessments for 7 days prior to the first dose will be used (i.e., > Day -8 and ≤ Day -1).

8.3.1.2.13.1. Psychomotor Vigilance Task

The PVT has participants press a button in response to a simple visual stimulus provided at random intervals. The primary measure is the number of missed responses, which describes the participant's sustained attention. This test will be administered each morning during the Treatment Period using a mobile device. At scheduled clinic visits, the task will be performed in the clinic under observation by study staff, otherwise the participant will perform this task remotely (at home).

The key outcome measures are:

- PVT Total False Positives
- PVT Total Timeouts
- PVT Slope of Linear Fit
- PVT Reaction Latency (mean)
- PVT Reaction Latency (Coefficient of Variation)
- PVT Total Hits

Other outcome measures are:

- PVT Reaction latency (variance)
- PVT Mean Press Length

8.3.1.2.13.2. Digit Symbol Substitution Test

The DSST is widely used to monitor changes in cognitive function over time and for early detection of cognitive dysfunction. The task requires participants to use a reference key to pair specific numbers with geometric figures. The number of correct pairings achieved within 90 seconds is summed to generate a total score. This test will be administered each morning during the Treatment Period using a touch screen mobile device. At scheduled clinic visits, the task will be performed in the clinic under observation by study staff, otherwise the participant will perform this task remotely (at home).

The key outcome measures are:

- DST Total Correct
- DST Total Incorrect
- DST Correct Movement Latency Mean
- DST Incorrect Movement Latency Mean
- DST Correct Response Latency Mean
- DST Incorrect Response Latency Mean

Other outcome measures are:

- DST Correct Movement Latency SD
- DST Incorrect Movement Latency SD
- DST Correct Response Latency SD
- DST Incorrect Response Latency SD

8.3.1.2.13.3. National Sleep Foundation Sleep Diary

Once daily in the morning, participants will briefly answer 5 questions about sleep length, sleep latency, night awakenings, and sleep quality. These questions have been modified from version 6 of the National Sleep Foundation Sleep Diary. This diary will be completed each morning during the Treatment Period using a mobile device. At scheduled clinic visits, the task will be performed in the clinic under observation by study staff, otherwise the participant will perform this task remotely (at home).

Outcome measures are individual items for sleep length, sleep latency, night awakenings, and sleep quality. Sleep length (minutes) is computed as participant get out of bed this morning – time participant went to bed last night. There is no key outcome measure.

8.3.2. Visit Windows for Efficacy Analyses

The scheduled visits will not be windowed and will be used at nominal visit value for analysis purposes. The unscheduled and ET visit will be mapped to a scheduled visit for analysis. In order to accommodate as much data as possible into analysis, the executive windows have been defined as shown in below tables, which have been widened, compared to protocol-specified operational windows. These windows will be used for analysis purposes only. Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the "analyzed record" within the analysis window; a participant's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If the data from the scheduled visit is available, then the scheduled visit data will be used.
- If no data from the scheduled visit is available, the data from unscheduled visit closest to the scheduled study day for that window will be used.
- If there is a tie before and after the scheduled day, the later data will be used.

Table 3. Analysis Visit Windows for WAIS-IV Coding Test, [redacted]

Scheduled Visit (+/1 window days) in protocol	Target Study Day	Study Day Window for Visit in Analysis
Baseline	Day 1 (pre-dose)	Day 1 (pre-dose) or last non-missing assessment before the first dose of IP
Day 14 (±2days)	Day 14	Day 2 – Day 28
Day 42 (-2 days)	Day 42	Day 29 – Day 56
Day 70 (±4 days)	Day 70	Day 57 – End of study

[redacted]

[redacted]

[redacted]

[redacted]

8.3.3. Analysis of Primary Efficacy Variable

8.3.3.1. Primary Analysis

Participants will be analyzed according to randomized treatment. Descriptive statistics of WAIS-IV Coding test score, percent change from baseline and change from baseline will be summarized by treatment group and by visit.

The primary endpoint is change from baseline to Day 42 in the WAIS-IV Coding test and this primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include baseline WAIS-IV Coding test score as a continuous explanatory variable, treatment, visit, and visit-by-treatment interaction as categorical explanatory variables. The Kenward-Roger correction to degrees of freedom will be applied. All explanatory variables will be treated as fixed effects in the model, and all post-baseline time points will be included in the model. An unstructured (UN) covariance matrix with the default Newton-Raphson algorithm used by SAS PROC MIXED will be used to model the within-subject correlation. If this model fails to converge – or, if the convergence criteria is met but the final Hessian is not positive definite - the Fisher Scoring algorithm (via the SCORING option of the PROC MIXED statement), the no-diagonal factor analytic structure (via the TYPE=FA0(T) option of the REPEATED statement, where T is the total number of time points), Toeplitz, Autoregressive (1) [AR (1)], Compound symmetry (CS) covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with CS structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance-covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS. The primary comparison will be between SAGE-718 and placebo at the Day 42. LSM and SE with 95% CI for each treatment group as well as difference in LSM and SE with 95% CI will be summarized, and the p-value from the hypothesis test of no difference between the treatment groups will be also presented.

Line plots with LSM and SE bars of change from baseline in WAIS-IV Coding test score over time by treatment group will be provided.

By-participant listing of WAIS-IV Coding test score by treatment group and by visit will be produced.

8.3.3.2. Multiplicity adjustment:

Not applicable.

8.3.3.3. Sensitivity Analysis of Primary Endpoint

If any of the sensitivity analyses yields a result that is in a different direction from the result of the primary analysis, the nature of the discrepancy will be examined to clearly explain the discrepancy based on statistical principles and discrepancy will be discussed in the CSR.

8.3.3.3.1. Control-Based Pattern Mixture Model Multiple Imputation

If ≥10% of participants have missing data in the primary endpoint, a sensitivity analysis using control-based Pattern Mixture Model Multiple Imputation (PMM-MI) under the missing not at random (MNAR) assumption will be used to investigate the impact of missing data (Lingling 2019, SAS Institute Inc.). MNAR assumes the missingness depends on the unobserved study data and cannot be predicted solely based on participant's observed data.

In cases where there is a missing baseline value, the missing baseline value will not be imputed with control-based PMM-MI. Instead, the average of all available baseline values (regardless of treatment group) will be populated for the missing baseline value. After this step, the control-based PMM-MI will be applied. Control-based PMM-MI under MNAR involves four steps as described below.

Step 1. Assessing the pattern of missing data.

To investigate the pattern of missing data, "ods output misspattern" will be used in the MI procedure of the SAS system (PROC MI). The imputation method will be based on the observed pattern of missing data and amount of missing data. The pattern of missing data will be assessed as monotone or arbitrary.

Step 2. Turning the arbitrary missing patterns to monotone missing patterns under missing at random (MAR) assumption.

If a mixture of non-monotone and monotone missing patterns exist in the data with majority of monotone missing patterns, then the arbitrary missing patterns will be converted to monotone missing patterns under MAR assumption.

Step 3. Generation of imputed datasets for AVAL using control-based pattern imputation under MNAR.

PROC MI will be used to generate *m* complete datasets. The selection of *m* depends on the required computing time and will be determined based on the amount of missing information prior to the last patient last visit but has been recommended varying from 5 to 100.

Step 4. Convert datasets into long format in which CHG variable represents all change from baseline with different values of avisit.

Step 5. Conducting model-based analysis using each imputed dataset.

The *m* complete datasets are analyzed using MMRM.

Step 6. Pooling the results from the imputed *m* datasets for inference.

The results from the m complete datasets are combined to produce inferential results.

8.3.3.3.2. Tipping Point Analysis

If ≥10% of participants have missing data in the primary endpoint, another sensitivity analysis – tipping point analysis – will be considered to investigate the robustness of the result to departures from the MAR assumption of the MMRM model and to identify the tipping point

where the treatment effect in participants with missing data overturns the treatment effect from statistically significant to statistically non-significant.

Hence the tipping point analysis will only be performed if the primary efficacy analysis is statistically significant in treatment effect.

Implementing the tipping point approach includes the following steps (Yuan 2014, SAS Institute Inc.):

Step 1. Missing baseline will be imputed as the mean of non-missing baseline for all other participants. For post-baseline, under the MNAR assumption, missing WAIS-IV Coding test score up to Day 70 will be imputed using PROC MI under MNAR.

Step 2. The imputed values for observations in SAGE-718 treatment group will be adjusted directly using the shift parameter (δ).

Step 3. The imputed datasets with the shift parameter applied will be analyzed using PROC MIXED.

Step 4. The results will be combined for the inference using PROC MIANALYZE.

Step 5. Step 1-4 will be repeated until the result is not statistically significant.

Step 6. If needed, step 1-5 will be repeated with more stringent shift parameter applied until the result is not statistically significant.

The shift parameter (δ) value will be progressively decreased, and process repeated until non-significant p-value is achieved. One hundred datasets will be generated.

The tipping point summary for each pairwise comparison will include LSM difference, the 95% CI, and p-value for each of δ value. Iterations including the tipping point will be summarized.

8.3.3.3.3. Complete Data Analysis

If ≥10% of participants have missing data in the primary endpoint, a sensitivity analysis using only participants who have at least baseline and Day 42 values will be performed. The MMRM analyses proposed for the analysis of the primary outcome will be provided for change from baseline to Day 42.

8.3.3.4. Supportive Analysis of Primary Endpoint

The primary analysis will be repeated based on the PPS. The WAIS-IV coding score after taking the prohibited medication will not be included in the analysis. No sensitivity analysis will be performed based on the PPS.

8.3.3.5. Subgroup Analyses of Primary Analysis

The primary endpoint will be analyzed for the following subgroups:

- Baseline Modified Hoehn and Yahr Stage: ≤2, >2

- [redacted]
- Age at randomization: ≤65, >65

Subgroup analyses will only occur if there are at least 10 participants for each subgroup.

[redacted]

By-participant listing by visit will be provided.

[redacted]

8.3.4.6. Penn Parkinson's Daily Activities Questionnaire-15 Knowledgeable Informant

For each PDAQ-15 KI item and total score, a summary using descriptive statistics on observed values and changes from baseline will be provided.

The change from baseline to Day 42 and Day 70 on the PDAQ-15 KI total score will be analyzed using a similar MMRM model described in Section 8.3.3.1. A plot showing the LSM ± SE bar over time within each treatment group will also be provided.

By-participant listing by visit will be provided.

[redacted]

[redacted]

8.3.4.14. Daily (Mobile Phone-Based) Assessments

For PVT and DSST, invalid data will be flagged after science team review by the vendor and will not be used for the analysis.

For key outcome measures specified in Section 8.3.1.2.13, the change from baseline to Day 14 and Day 42 will be summarized using descriptive statistics and analyzed using a similar MMRM model described in Section 8.3.3.1. A plot showing the LSM ± SE bar over time within each treatment group will also be provided.

Other outcome measures specified in Section 8.3.1.2.13 will be summarized by visit using descriptive statistics.

By-participant listing by visit will be provided.

8.4. Safety Analysis

All safety summaries will be performed on the Safety Set using treatment received.

Safety and tolerability of SAGE-718 oral capsule in participants with PD-MCI is the secondary objective of this study and will be evaluated by the frequency and severity of TEAEs and withdrawal due to AEs. Other safety endpoints include change from baseline in vital signs, clinical laboratory analytes, ECGs, and [redacted].

The safety endpoints evaluated at scheduled visits are taken as done in nominal visit, without any windowing. If a value is available for a nominal scheduled visit, that value will be used in summary by visit. Unless specified, unscheduled measurement and ET measurement will be included only if a scheduled measurement is not available, and the unscheduled measurement and ET measurement falls within the visit window for the scheduled visit (same as WAIS-IV Coding Test in Table 3). If there are two or more measurements in a visit window, the measurement taken closest to the study day target will be used in analysis. If the two have same distance from the target study day, the latter one will be used.

Anytime on treatment, last value on treatment and last value on study will be included in the summaries, unless specified. Anytime on treatment is defined as measurement on or after first dose, on or before the date of last dose. Last value on treatment is defined as the last post-baseline value between first dose of IP and up to the date of last dose of IP (inclusive). Last value on study is defined as the last post-baseline value on or after the first dose of IP and on or before the last date of the study.

No statistical hypothesis testing will be conducted.

Safety data will be listed by treatment group and participant and summarized by treatment group.

Table 8. Summary of Safety Analysis

Safety Evaluation	Incidence	Source Data	Change from Baseline	Shift from Baseline	Potentially Clinically Significant	Abnormality/ Clinical Significance
AEs	X					
Clinical Laboratory		X	X	X	X	*
ECG		X	X		X	*
Vital Signs		X	X		X	
Physical Exam		*				
[redacted]						

ECG = Electrocardiograms; [redacted]

X = Safety Assessment will be summarized in tables

* = Safety Assessment will be listed in individual participant data listings

8.4.1. Adverse Events

AEs will be coded using MedDRA version 22.0 or higher. Intensity/severity and relationship of AE will be evaluated by the investigator.

A TEAE is defined as any AE on or after the first dose of IP or any worsening of a pre-existing medical condition/AE with onset after the start of IP and throughout the study. The analysis of AEs will be based on the concept of TEAEs. Where the AE start date is missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the first dose of study treatment. Missing or partial dates will be imputed for AE. The algorithm for missing or partial start /end date is documented in Appendix C.

Adverse events are assigned an AE period based on the onset date/time. AE periods are defined as follows:

- Pre-treatment AE: AE onset date/time before first IP dosing date/time
- TEAE: AE onset date/time on or after the first IP dose date/time (If an AE start date same as IP first dose date, but no time either in AE start or treatment start, then consider this AE to be in treatment period TEAE.)

- On-treatment TEAE: AE onset date/time on or after first IP dose date/time and on or before IP last dose date + 30 days (Note that time does not matter for the end of this period. i.e., if AE occurred after the last dose but on the same date of last dose, it is considered as on-treatment TEAE)
- Post-treatment TEAE: AE onset date on or after IP last dose date + 31 days

An overall summary of TEAEs will include the number and percentage of participants in the following categories:

- Any TEAE (On-treatment, Post-treatment)
- TEAEs by maximum severity (severe > moderate > mild)
- Any related TEAEs
- Any related TEAEs by maximum severity
- Any serious TEAEs
- Any serious related TEAEs
- Any TEAEs leading to death
- Any TEAEs leading to IP withdrawal
- Any TEAEs leading to withdrawal from the study
- Any TEAEs leading to IP interruption.

Incidence of TEAEs in following categories will be provided by SOC and PT. A participant is counted only once under each SOC and PT in case of multiple occurrences of the same AE. These tables will be sorted by decreasing frequency of SOC in SAGE-718 group, then in placebo group, then alphabetically first within SOC, then within PT.

- TEAEs
- On-treatment TEAEs
- Post-treatment TEAEs
- TEAEs by maximum severity
- TEAEs by causality (related, not related) to IP
- TEAE by maximum severity and causality to IP
- Serious TEAEs
- TEAEs leading to IP withdrawal
- TEAEs leading to withdrawal from the study
- TEAEs leading to IP interruption.

Additionally, incidence of TEAEs will be summarized by PT. Most frequent TEAEs reported >5% in PT of the combined treatment group will also be summarized by PT.

For maximum severity, participants will be counted only once within each SOC and PT at the maximum severity in the following order: severe > moderate > mild; an AE with missing severity will be omitted from severity presentation and will not be imputed. For relationship to IP, participant will be counted only once within each SOC and PT with the strongest relationship to IP in the following order: related > not related; an AE with relationship missing is treated as related. For seriousness, an AE with missing seriousness will not be imputed. The incidences will be presented by descending frequency of SOC and then, within a SOC, by descending frequency of PT based on the participant count, and in alphabetical order of PT if the incidence within a PT is a tie.

In addition, TEAE summaries by SOC/PT will also be presented by the following subgroups:

- Race (Black or African American, White, Other)
- Sex (Male, Female)
- BMI (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2; Categories are defined after rounding)
- Age at randomization: ≤65, >65 years

A by-participant listing of all AEs, SAEs (including those with onset or worsening before the start of IP), TEAEs leading to death, TEAEs leading to IP withdrawal through the end of the study, and most frequent (5%) TEAEs will be provided.

8.4.2. Clinical Laboratory

Any lab results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

For the laboratory results that are "≤ x" or "≥ x", where x is a number as collected in the data, the numeric part of the result will be used in the calculation in the summary tables. If a laboratory value is reported as "< y" then y minus the minimum value with the same precision as y (e.g., if y = 1.345, then use y - 0.001) will be used for the analysis. If a laboratory value is reported as "> y" then y plus the minimum value with the same precision as y will be used for the analysis. The same is true if the result is presented as below limit of quantification (BLQ) and a lower limit of quantification (LLOQ) value is provided; the LLOQ value will be used for calculation in the summary tables. The actual results as collected will be displayed in the listings.

Results of continuous clinical laboratory parameters for hematology, biochemistry, coagulation, and urine samples for urinalysis at each scheduled visit and mean changes from baseline will be summarized in standard units. In addition, it will also include the summary of the last value on treatment and the last value on study.

Normal ranges for each parameter will be provided by the laboratory. Shift from baseline to post-baseline values in abnormality of hematology and biochemistry results will be

summarized. In addition, shift from baseline to worst post-baseline values in abnormality of results at any time on treatment, the last value on treatment (on or after first dose, on or before last dose) and the last value on study (after last dose, on or before last day of the study) will be summarized. If a participant has both low and high post-baseline records, the participant will be counted twice for each low and high cell.

Clinical laboratory results will be listed by participant and timing of collection for each treatment group.

The number and percentage of participants with potentially clinical significance (PCS) values for each laboratory parameter will be summarized by treatment for anytime on treatment, the last value on treatment and the last value on study. Sponsor determined PCS values will be identified for specific laboratory parameters as outlined in Table 9 below.

Table 9. Potentially Clinically Significant Values for Specific Laboratory Parameters

Laboratory Parameter	**Sex**	**Units**	**Criteria for PCS Values (Observed values)**	
			High	**Low**
Hematology				
Hemoglobin	Male	g/L	>185	<115
	Female	g/L	>170	<100
Hematocrit	Male	Fraction of 1	>0.55	<0.385
	Female	Fraction of 1	>0.49	<0.345
Platelet count		10^9/L	>600	<125
White blood cell		10^9/L	>15	<2.5
Basophils		10^9/L	>0.5	NA
Eosinophils		10^9/L	>1.5	NA
Neutrophils		10^9/L	NA	<1.5
Lymphocytes		10^9/L	>6.0	<0.5
Monocytes		10^9/L	>1.4	NA
Serum Chemistry				
Albumin		g/L	>70	<28
Blood urea nitrogen		mmol/L	>10.71	NA
Calcium		mmol/L	>2.75	<2.0
Chloride		mmol/L	>120	<90

Laboratory Parameter	**Sex**	**Units**	**Criteria for PCS Values (Observed values)**	
			High	**Low**
Creatinine		mmol/L	>3xULN or >3x Baseline	
Gamma Glutamyl Transferase			>3xULN	
Glucose		mmol/L	>13.9	<2.8
Sodium		mmol/L	>150	<132
Potassium		mmol/L	>5.4	<3.3
Protein		g/L		<45
Bicarbonate		mmol/L	>34	<18
Phosphorus		mmol/L	>1.94	<0.61
Coagulation				
Prothrombin time			≥1.11xULN	NA
Partial thromboplastin time			>1.5 xULN	NA

Liver function tests will be monitored closely for PCS values, and will be summarized for occurrence any time post-baseline for the following parameters for these PCS threshold:

- Alanine Aminotransferase: >3xULN, >5xULN, >10xULN
- Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
- Alanine Aminotransferase or Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
- Alkaline Phosphatase: >1.5xULN, >2xULN
- Total Bilirubin: >1.5xULN, >2xULN
- Total Bilirubin >2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN) [any time post-baseline, does not need to be measured at the same time point of assessment]
- [(Total Bilirubin >2xULN) **AND** Alkaline Phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)] **AND** [(ALT or AST >3xULN) **AND** Alkaline Phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)]

  Note: The conditions in the first pair of brackets do not need to occur at the same timepoint as the conditions in the second pair of brackets.

By-participant listing of FSH and serology test results at screening will be provided.

By-participant listing of urine drug screen and breath alcohol test will also be provided.

8.4.3. 12-Lead Electrocardiogram

A single 12-lead ECG under Protocol Amendment 2 and triplicate 12-lead ECG under Original Protocol and Protocol Amendment 1 will be performed after the participant has been resting in the supine position for at least 5 minutes. If the multiple 12-lead ECG are performed, the average of all values on the same date will be used in the summary. If there are both scheduled visit and unscheduled visit on the same date, all the assessments on that date are considered as the scheduled visit for the summary. A summary of the observed values (raw values for the single ECG; average values for the multiple ECG on the same date) and change from baseline values will be summarized by each scheduled visit for the following ECG parameters: heart rate, PR, QRS, QT, and QTcF interval. This summary will also include the last values on treatment and on study. A by-participant listing of 12 lead ECG will also be provided for each of the ECG measurements.

ECG is evaluated by investigator as "normal", "abnormal, not clinically significant" and "abnormal, clinically significant". The number and percentage of participants with each category will be provided at baseline and each post-baseline scheduled assessment time point. If there are more than one evaluation at the same time point, the latest assessment from ECG vendor will be used for the summary.

Potentially clinically significant values of QTcF as outlined in Table 10 will be summarized by treatment for anytime on treatment, the last value on treatment and the last value on study.

Table 10. Potentially Clinically Significant (PCS) Values for 12-Lead ECG Parameter

12-Lead ECG	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline)	
		High	Low	Increase	Decrease
QTcF	msec	>450 but ≤480 >480 but ≤500 >500	NA	≥30 to 60 >60	NA

8.4.4. Vital Signs

Vital signs will include oral temperature (˚C), respiratory rate (breaths per minute), heart rate (beats per minute [bpm]), and blood pressure (mmHg). Heart rate and blood pressure were collected in supine position and standing position at all scheduled time points.

Vital sign results and mean changes from baseline will be summarized by scheduled visit. It will also include the summary of last values on treatment and on study assessments. Potentially clinically significant values as outlined in Table 11 will be summarized by treatment for

anytime on treatment, the last value on treatment and the last value on study. By-participant listing of vital signs will also be provided.

Table 11. Potentially Clinically Significant (PCS) Values for Vital Sign Parameters

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCS values (Change from Baseline values)	
		High	Low	Increase	Decrease
Heart rate (supine and standing)	Beats/min	>120	<40	NA	NA
Respiratory rate	Breaths/min	>20	<8		
Systolic blood pressure (supine and standing)	mmHg	>180	<90	≥30	≥30
Diastolic blood pressure (supine and standing)	mmHg	>110	<50	≥20	≥20
Supine – Standing* Systolic Blood Pressure	mmHg	≥20			
Supine – Standing* Diastolic Blood Pressure	mmHg	≥10			
Orthostatic hypotension: supine – standing* SBP and DBP	mmHg	SBP ≥20 and DBP ≥10			
Possible orthostatic hypotension: supine – standing* SBP and DBP	mmHg	SBP ≥20 or DBP ≥10			

* Supine – Standing means the difference of results between supine and standing positions.

8.4.5. Physical Examination

A full physical examination is to be conducted during Screening and at Day 42 (End of Treatment). At other visits, an abbreviated physical examination will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical assessment as determined by the investigator. Unscheduled, symptom directed examinations may be conducted at any time at the discretion of the investigator. Any baseline abnormalities will be recorded on the medical history form. Any post-baseline abnormalities or baseline conditions that worsened post-baseline will be recorded on the adverse events form.

The occurrence of a physical examination (yes/no) and the date performed will be listed by participant.

[redacted]

[redacted]

[redacted]

8.4.7. Other Safety Analysis

Not applicable.

[redacted]

9. SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable.

10. REFERENCES

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11. LIST OF APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS

Table 12. Schedule of Assessments

	Screening Period	Baseline	Treatment Period				Follow-Up Period
Assessments[a]	**Days -28 to -8**	**Day -7 (±2 days)**	**Day 1[b]**	**Day 14 (±2 days)**	**Day 28[c] (±2 days) Phone Call**	**Day 42[d] (-2 days)**	**Day 70 (±4 days) or ET**
Informed consent[e]	X						
Inclusion/exclusion criteria	X	X	X				
Randomization			X				
Medical history and demographics[f]	X						
Participant training[g]	X	X					
Body weight	X		X			X	X
Body height	X						
Vital signs (including orthostatics)[h]	X		X	X		X	X
Physical examination[i]	X		X	X		X	X
FSH test[j]	X						
Serology test[k]	X						
12-lead ECG[l]	X			X		X	X

Assessments[a]	Screening Period	Baseline	Treatment Period				Follow-Up Period
	Days -28 to -8	Day -7 (±2 days)	Day 1[b]	Day 14 (±2 days)	Day 28[c] (±2 days) Phone Call	Day 42[d] (-2 days)	Day 70 (±4 days) or ET
Clinical laboratory assessments[m]	X		X	X		X	X
Urine drug test	X		X	X		X	X
Alcohol breath test	X		X	X		X	X
Pregnancy test[n]	X		X				X
[redacted]							
Optional biochemical research sample[o]	X			X		X	
Optional genetic research sample[o]	X						
[redacted]							
Modified Hoehn and Yahr stage scale	X						
[redacted]							

Assessments[a]	Screening Period	Baseline	Treatment Period				Follow-Up Period
	Days -28 to -8	Day -7 (±2 days)	Day 1[b]	Day 14 (±2 days)	Day 28[c] (±2 days) Phone Call	Day 42[d] (-2 days)	Day 70 (±4 days) or ET
[redacted]							
WAIS-IV Coding Test		X	X	X		X	X
[redacted]							
[redacted] and PDAQ-15 [redacted] Knowledgeable Informant)[r]		X				X	X
[redacted]							

Assessments[a]	Screening Period	Baseline	Treatment Period				Follow-Up Period
	Days -28 to -8	Day -7 (±2 days)	Day 1[b]	Day 14 (±2 days)	Day 28[c] (±2 days) Phone Call	Day 42[d] (-2 days)	Day 70 (±4 days) or ET
[redacted]							
Daily mobile assessment[t] (DSST, PVT, sleep diary)		X					
IP self-administration[u]			X (once daily in the morning)				
IP dispensation[v]			X	X			
IP accountability/return[w]			X	X		X	
AEs/SAEs[x]	X	X	X	X	X	X	X
Prior and concomitant medications[y]	X						

Abbreviations: AE = adverse event, [redacted] COVID-19 = coronavirus disease 2019; [redacted] DSST = Digit Symbol Substitution Test; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; [redacted] PD = Parkinson's Disease; [redacted]; PDAQ-15 KI = Penn Parkinson's Disease Activities Questionnaire-15 Knowledgeable Informant; [redacted]; PRO = patient-reported outcome; PVT = Psychomotor Vigilance Task; SAE = serious adverse event; [redacted] WAIS-IV = Wechsler Adult Intelligence Scale-IV.

[a] The scales are to be administered after the daily dose of IP during the Treatment Period, and at approximately the same time of day (±2 hours) throughout the study. For participants receiving medication for PD symptoms, the scales are to be administered in the "On" state (defined as the period in which motor symptoms are mitigated due to the effects of PD medication). For clinician administered scales, the same individual should administer the scale whenever possible.

[b] All tests on Day 1 will be conducted predose.

[c] Phone check-in only for AEs/SAEs and changes to medical history or medications.

[d] Dosing ends on Day 42

[e] Both participants and caregivers (if applicable) will be consented during the Screening Period.

[f] In addition to full medical history, including family history of PD, all medications and supplements taken within 60 days prior to Screening, all medications used to treat PD regardless of timing, and all nonpharmacological methods (e.g., psychosocial, psychotherapeutic) used to treat or prevent [redacted], and cognitive manifestations of PD are to be recorded. Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

[g] Participants and caregivers (if applicable) will be trained by study staff on the use of software applications and devices necessary for the conduct of the study.

[h] Vital signs include body temperature, respiratory rate, heart rate, and blood pressure. Vital signs will be measured prior to dosing on days when IP is administered. Blood pressure and heart rate will be measured after the participant has been in the supine position for at least 5 minutes and then repeated approximately 1 and 3 minutes after standing, at all scheduled time points.

[i] A full physical examination will be conducted during Screening and at Day 42 (End of Treatment). At other visits, an abbreviated physical examination will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical assessment as needed. A symptom directed examination may be conducted at any time at the discretion of the investigator.

[j] Serum FSH test will be conducted at Screening for the female participants who are not surgically sterile to confirm whether female participants with ≥12 months of spontaneous amenorrhea meet the protocol-defined criteria for being postmenopausal.

[k] To include hepatitis B and C screening tests, HIV-1 and -2 antibody.

[l] A single ECG will be measured after the participant has been in the supine position for at least 5 minutes.

[m] Clinical laboratory assessments will include blood samples for hematology, biochemistry, coagulation, and urine samples for urinalysis. Samples will be collected prior to dosing on days when IP is administered. On nondosing days, collection may occur at any time.

[n] Serum pregnancy tests will be conducted for all female participants at Screening; urine pregnancy tests will be conducted at other scheduled time points for female participants who are not postmenopausal or surgically sterile.

[o] Refer to Table 13 for details.

[redacted]

[r] PDAQ-15 Knowledgeable Informant is provided by caregiver.

[redacted]

[t] Daily reminders will be sent to participants via a mobile device to complete assessments on remote device. Daily assessments include the [redacted] DSST, PVT, and the National Sleep Foundation Sleep Diary. It is recommended that assessments are completed at approximately the same time each day, within 1 hour following IP administration. Daily mobile assessments should be completed in a quiet area of participant's home. On dosing days the remote assessment will be completed in the clinic following dosing under observation by the study staff.

[u] On Days 1, 14, and 42, the participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing and all scheduled cognitive tests will be administered postdosing.

[v] Study staff will dispense enough IP for the participant to take daily at home until the next scheduled visit.

[w] Participants will bring all used packaging and unused IP to the clinic at each visit for study staff to review and document.

[x] AEs/SAEs collected from time of ICF throughout the duration of participation.

[y] At Screening, to include all medications and supplements taken within 60 days and all medications used to treat PD regardless of timing. At subsequent visits, all changes to any medication should be captured.

Table 13. Schedule of [redacted], Biochemical, and Genetic Sampling

Assessments	Screening	Baseline	Treatment			Follow-Up
	Days -28 to -8	Day -7 (±2 days)	Day 1	Day 14 (±2 day)	Day 42 (-2 day)	Day 70 (±4 days) or ET
[redacted]						
Predose				X	X	X
Optional blood collection: biochemical research[b]						
	X			X	X	
Optional blood collection: genetic research						
	X					

Abbreviations: ET = early termination; IP = investigational product; [redacted]

[b] Biochemical samples will be collected at any time during Screening. On Days 14 and 42, the samples will be collected at times corresponding with the [redacted] blood draw.

APPENDIX B. DETAILS OF STATISTICAL METHODOLOGY

Sample SAS Code for MMRM

```
proc mixed data= data;
    class trt01pn(ref='1') avisitn usubjid;
    model CHG = trt01pn base avisitn trt01pn *avisitn/ddfm=kr;
    repeated avisitn / subject= usubjid type=UN;
    lsmeans trt01pn*avisitn / diff=all cl alpha=0.05;
run;
```

Sample SAS Code for GEE

```
proc genmod data= data;
    class trt01pn(ref='1') avisitn usubjid;
    model AVALC = base trt01pn avisitn trt01pn *avisitn / dist=bin link=logit;
    repeated avisitn /subject= usubjid type=UN;
    lsmeans treatment*avisit / diff exp cl;
run;
```

Sample SAS Code for ANCOVA

```
proc mixed data= data;
    class trt01pn(ref='1');
    model CHG = trt01pn base / solution cl;
    lsmeans trt01pn / cl diffs;
run;
```

Sample SAS Code for PMM-MI under MNAR

Step 1. Assessing the pattern of missing data

```
proc mi data=non_mono seed=xxx nimpute=0;
    var trt01pn base y1-y3; *y1=Day 14, y2=Day 42, y3=Day 70;
    ods output misspattern=pattern;
run;
```

Step 2. Turning the arbitrary missing patterns to monotone missing patterns under MAR assumption

```
proc mi data=non_mono out=mono seed=xxx nimpute=m
    min=. . x x x
    max=. . y y y; * period (.) means no imputation needed;
    var trt01pn base y1 y2 y3;
    mcmc chain=multiple impute=monotone;
run;
```

Step 3. Generation of imputed datasets for AVAL using control-based pattern imputation under MNAR

```
proc mi data=mono seed=xxx nimpute=m out=imputed;
    min=. . x x x;
    max=. . y y y;
    by _imputation_;
    class trt01pn;
    var y1 y2 y3;
    monotone reg(/details);
    mnar model(y1 y2 y3/ modelobs=(trt01pn='1')); *only control group is used to derive
the imputation model;
run;
```

Step 4-1. Calculate CHG14, CHG42, and CHG70.

Step 4-2. Convert datasets into long format in which CHG variable represents all change from baseline with different values of avisit.

Step 5. Conducting model-based analysis using each imputed dataset

```
proc mixed data= imputed;
    by _imputation_;
    class subjid trt01pn(ref='1') avisitn;
    model chg = trt01pn base avisitn trt01pn*avisitn / ddfm=kenwardroger;
    repeated avisitn / subject=usubjid type=UN;
    lsmeans trt01pn*avisitn / diff=all cl alpha=0.05;
    ods output lsmeans=lsmeans diffs=diffs;
run;
```

Step 6. Pooling the results from the imputed *m* datasets for inference

```
proc sort data=lsmeans;
by trt01pn avisitn _imputatoin_;
run;

proc mianalyze parms=lsmeans;
modeleffects estimate;
ods output ParameterEstimates=lms;
by treatment avisit;
run;

proc sort data=diffs;
by avisit _imputatoin_;
run;

proc mianalyze parms=diffs;
```

```
    modeleffects estimate;
    ods output ParameterEstimates=dif;
    by avisit;
    run;
```

Sample SAS Code for Tipping Point Analysis

```
/*----------------------------------------------------------------*/
/*--- Generate imputed data set for specified shift parameters ---*/
 /*--- data= input data set ---*/
 /*--- smin= min shift parameter ---*/
 /*--- smax= max shift parameter ---*/
/*--- sinc= increment of the shift parameter ---*/
 /*--- out= output imputed data set ---*/
/*----------------------------------------------------------------*/
%macro midata( data=, smin=, smax=, sinc=, out=);
    data &out;
     set _null_;
run;

/*------------ # of shift values ------------*/
    %let ncase= %sysevalf( (&smax-&smin)/&sinc, ceil );
/*------- Imputed data for each shift -------*/
%do jc=0 %to &ncase;
    %let sj= %sysevalf( &smin + &jc * &sinc);
    proc mi data=&data seed=xxx nimpute=m out=outmi;
        class trt01pn;
        monotone reg(y1 y2 y3);
        mnar adjust( y1 y2 y3 / shift=&sj adjustobs=(trt01pn='1') ); *active treatment is used;
        var trt01pn y1 y2 y3;
    run;

    data outmi;
        set outmi;
        Shift= &sj;
    run;

    data &out;
        set &out outmi;
    run;
%end;
    %mend midata;
```

APPENDIX C. HANDLING OF MISSING DATES

Adverse Events

If the AE start date is completely missing, do not impute a date but consider it as TEAE, unless the AE end date is before the initiation of treatment, in which case the AE will be considered prior.

For partial AE start dates:

- When the year is present, but the month and day are missing, then:
  - If the year is the same as the year of the first dose date, then impute as the month and day of the first dose date.
  - Otherwise, impute the month and day as January 1st.
- If the year and month are present, but the day is missing, then:
  - If the year and month of AE start are the same as the year and month of initiation of the treatment, the impute as the date of the first dose.
  - Otherwise, impute as the 1st day of the month.
- If the imputed AE start date is after the AE end date, then the start date will be set to the end date.
- When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for "year is present, but the month and day are missing".

For partial AE end dates:

- Do not impute the AE end date.

Dates in Disease History (Dates of diagnosis, current episode, first episode)

- If the year is present and the month and day are missing, then the month and day will be set to January 1st.

  –If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.

Prior and Concomitant Medications/Procedures

If the medication start date is completely missing, do not impute a date but consider it as concomitant, unless the medication end date is before the initiation of treatment, in which case the medication will be considered prior. Apply the same rule to the completely missing case of medication end date.

For the partial start date of medication:

- If the year is present, but the month and day are missing, then the month and day will be set to January 1st unless the year is the same as the first dose date, then impute the first dose.

  –If the year and day are present, but the month is missing, then treat it as if the day is missing and only year is present. Follow the imputation rule for "the year is present, but the month and day are missing".

- If the year and month are present and the day is missing, then the day will be set to the 1st day of month, unless the year and month are the same as the year and month of the first dose, then impute as the date of the first dose.

  –If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

For the partial end date of medication:

- If the year is present, but the month and day are missing, then the month and day will be set to December 31st.

  –If the year and day are present, but the month is missing, then treat it as if the day is missing and only year is present. Follow the imputation rule for "the year is present, but the month and day are missing".

- If the year and month are present, but the day is missing, then the day will be set to the last day of the month.

Apply the same rule to the procedures with missing or partial dates.

APPENDIX D. CONVERSION FACTORS FOR CALCULATING LED

Table 14. Conversion factors for calculating LED

Drug Class	Generic Name	Trade Name	Conversion Factor/Ratio
L-dopa IR	Carbidopa-levodopa	Sinemet	DD × 1
	Carbidopa-levodopa (orally disintegrating tablet)	Parcopa IR	DD × 1
	Levodopa Inhalation powder	Inbrija	DD x 0.69
	Carbidopa/Levodopa Entacapone	Stalevo	DD x 1.33
	Carbidopa-levodopa-entacapone (enteral suspension)	Duopa (US) Duodopa (EU)	DD x 1.11 (morning dose); DD x 1.46 (maintenance and extra doses)
L-dopa CR	Carbidopa-levodopa (controlled release)	Sinemet CR	DD × 0.75
L-dopa ER	Carbidopa-levodopa (extended release capsules)	Rytary	DD × 0.5
	Carbidopa-levodopa (extended release)	Not Rytary	DD × 0.75
Catechol-o-methyl-transferase inhibitors	Entacapone	Comtan	LD × 0.33
	Tolcapone	Tasmar	LD × 0.5
	Opicapone	Ongentys	LD × 0.5
Monoamine oxidase-B inhibitors	Selegiline	Eldepryl	DD × 10
	Selegiline (orally disintegrating tablet)	Zelapar	DD × 80
	Rasagiline	Azilect	DD × 100

Drug Class	Generic Name	Trade Name	Conversion Factor/Ratio
Monoamine oxidase-B inhibitors	Safinamide	Xadago	LED = 150 mg
Dopamine Agonists	Pramipexole	Mirapex	DD x 100
	Pramipexole (extended release)	Mirapex ER	DD x 100
	Ropinirole	Requip	DD x 20
	Ropinirole (extended release)	Requip XL	DD x 20
	Apomorphine (subcutaneous injection)	Apokyn	DD x 10
	Apomorphine sublingual film	Kynmobi	DD x 1.5
	Rotigotine (transdermal patch)	Neupro	DD x 30.3
Adenosine 2A antagonist	Istradefylline	Nourianz	LD x 0.2
Anticholinergic	Trihexyphenidyl	Artane	LED = 100 mg
	Benztropine	Cogentin	LED = 100 mg
Other	Amantadine	Amantadine	DD × 1
	Zonisamide	Zonisamide	LED = 100 mg

Note: IR = immediate release, CR = controlled release, ER = extended release, DD = daily dose, LD = levodopa dose, LED = levodopa equivalent dose. LD is the subtotal LED of levodopa-containing medications.

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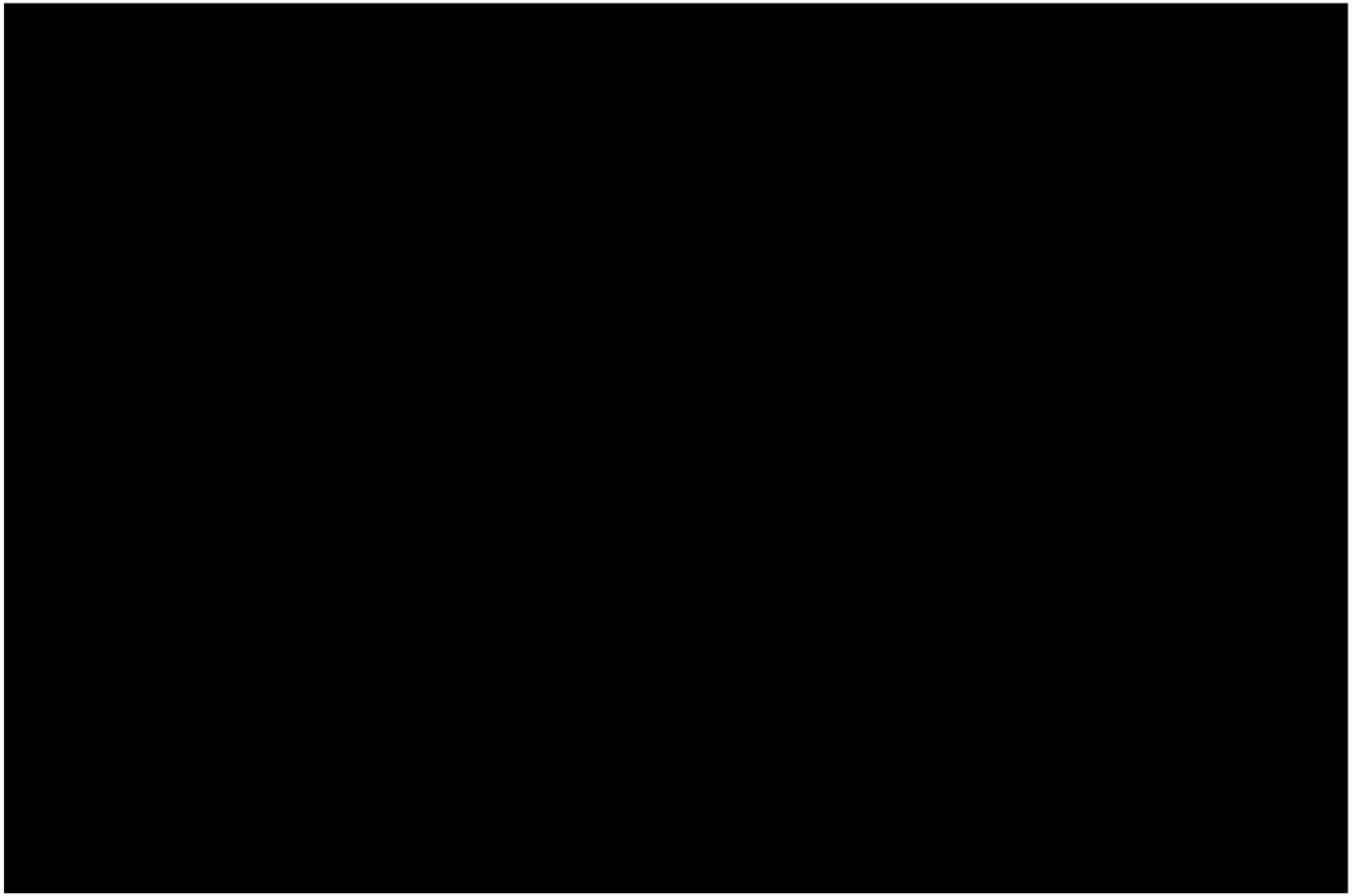

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Approval Signatures

Document Name: Statistical Analysis Plan 15 Mar 2024 718-CNP-202

Document Number: VV-TMF-6527794

Parexel Version Number:

System Version Number: 1 .0

Document Approvals	
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 14-Mar-2024 16:37:29 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 14-Mar-2024 18:11:03 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 14-Mar-2024 18:13:41 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 14-Mar-2024 20:37:51 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 15-Mar-2024 16:54:51 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: [redacted] Date of signature: 15-Mar-2024 18:30:13 GMT+0000