Official Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effects of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

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STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER: 718-CNA-202

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effects of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

Author of SAP: [redacted]

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Sponsor:
Sage Therapeutics, Inc.
55 Cambridge Parkway
Cambridge, Massachusetts 02142

AUTHORIZATION SIGNATURE PAGE

Protocol Number: 718-CNA-202

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Author:

[redacted] Date

Approved by:

[redacted] Date

Parexel International

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

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1. LIST OF ABBREVIATIONS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation	Definition
AD	Alzheimer's Disease
AE	adverse event
[redacted]	[redacted]
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical code
BMI	Body Mass Index
BLQ	Below Limit of Quantification
[redacted]	[redacted]
CDR	Clinical Dementia Rating
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence Intervals
COVID-19	Coronavirus Disease 2019
CS	Clinically Significant
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ET	Early Termination
eCRF	electronic Case Report Form
[redacted]	[redacted]
FAS	Full Analysis Set
[redacted]	[redacted]
IA	Interim Analysis
IP	Investigational Product
IRT	Interactive Response Technology
[redacted]	[redacted]
LSM	Least Squares Means
MAR	Missing At Random
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed-effects Model for Repeated Measures

Abbreviation	Definition
MNAR	Missing Not At Random
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
[redacted]	[redacted]
PCS	Potentially Clinically Significant
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PMM	Pattern Mixture Model
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
[redacted]	[redacted]
[redacted]	[redacted]
Q1	25th percentile
Q2	75th percentile
[redacted]	[redacted]
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Events
WAIS-IV	Wechsler Adult Intelligence Scale Fourth Edition-IV

2. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis, and is based on the following approved study documents:

- Study Protocol, Version 2.0 (22 December 2023)
- electronic Case Report Form (eCRF), Version 7.0 on 29 April 2024

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 the SAS Software Version 9.4 or higher (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.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the effect of SAGE-718 on cognitive performance in participants with Alzheimer's Disease (AD)

3.2. Secondary Objectives

- To evaluate the safety and tolerability of SAGE-718 softgel lipid capsule in participants with AD

3.3. [redacted]

- To evaluate the safety and tolerability of SAGE-718 softgel lipid capsule on other safety parameters

[redacted]

4. STUDY ENDPOINTS

4.1. Efficacy Endpoint

4.1.1. Primary Efficacy Endpoint

The primary endpoint is the change from baseline to Day 84 in the Wechsler Adult Intelligence Scale Fourth Edition-IV (WAIS-IV) Coding Test, total correct score.

4.1.2. [redacted]

[redacted]

[redacted]

4.2. Safety Endpoints

- To evaluate the safety and tolerability of SAGE-718 softgel lipid capsule in participants with AD
  - 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 softgel lipid capsule on other safety parameters
  - Change from baseline in vital signs, clinical laboratory parameters, electrocardiograms (ECGs), [redacted]

4.3. [redacted]

[redacted]

5. STUDY DESIGN

5.1. Overall Design

This is a randomized, double-blind, placebo-controlled study to evaluate the effects of SAGE-718 in participants with MCI or mild dementia due to AD. Eligible participants with a confirmed diagnosis and who meet the criteria for MCI or Mild Dementia due to AD at Screening will be randomized to receive either SAGE-718 or matching placebo. Within the SAGE-718 treatment arm, participants will receive 1.2 mg of SAGE-718 as a softgel lipid capsule orally once daily for the first 6 weeks (Days 1 Visit to 42 Visit [±2 days]), followed by 0.9 mg of SAGE-718 for the remainder of the Treatment Period (i.e., beginning the first day after the Day 42 Visit). Dosing ends at the Day 84 Visit (±7 days). The placebo arm will receive placebo throughout the Treatment Period (12 weeks).

5.1.1. Screening Period

The Screening Period will begin with the informed consent process for prospective participants and their study partners. Subsequent screening assessments will be performed between Day -35 and Day -8 to determine eligibility, including assessments of cognitive function. An adult study partner is required to support completion of study activities and to answer questions about the participant's condition.

5.1.2. Baseline Period

The Baseline Period will occur from Day -7 through Day -1. During the Baseline Period, participants will visit the clinic for collection of baseline cognitive, [redacted] data. Participants and their study partners will receive training on the study procedures and devices. [redacted]

5.1.3. Treatment Period

The blinded Treatment Period will occur from the Day 1 Visit through the Day 84 Visit (±7 days). Eligible participants will be randomized 1:1 to receive either SAGE-718 or matching placebo. Participants who are randomized to SAGE-718 will receive 1.2 mg of SAGE-718 for the first 6 weeks (Days 1 Visit to 42 Visit [±2 days]) followed by 0.9 mg of SAGE-718 for the remainder of the Treatment Period (i.e., beginning the first day after the Day 42 Visit). Dosing ends at the Day 84 Visit (±7 days). All participants will self-administer blinded IP once per day in the morning, orally.

At scheduled clinic visits during the Treatment Period, safety, efficacy, [redacted] will be performed. Participants will self-administer IP in the clinic under the supervision of study staff. Participants will receive a sufficient amount of IP for daily administration until the next scheduled clinic visit, at which time study staff will assess participant adherence by examining used packaging and counting returned capsules.

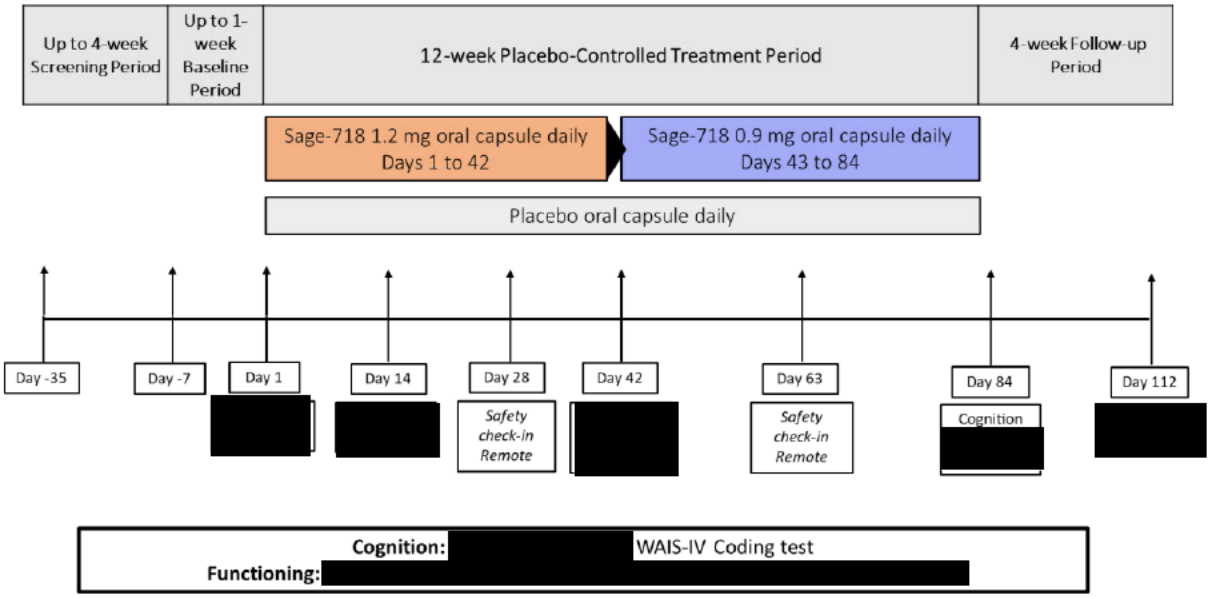
During the Treatment Period, participants will be able to receive IP if there are no dose-limiting safety/tolerability concerns. Participants who discontinue IP should complete the

remaining study visits as scheduled unless the participant chooses to withdraw their consent or loses the capacity to grant consent. If a participant withdraws from the study/stops study participation early, an Early Termination Visit will be conducted. Treatment with SAGE-718 can be ended without down titration.

5.1.4. Follow-up Period

After completing the Treatment Period, participants will return to the clinic for a Follow-up Visit on Day 112 (±7 days) to collect safety, some cognition, [redacted].

Figure 1: Study Schematic



Abbreviations: [redacted] WAIS-IV Coding Test = Wechsler Adult Intelligence Scale-IV Coding Test.
See Appendix A for specific schedule of each test.

5.2. Sample Size and Power

The sample size calculation is based on change from baseline in WAIS-IV Coding Test total correct score. Based on data from a previous study (718-CNA-201), the assumed difference between placebo and the SAGE-718 group at the end of treatment (at Day 84) for the primary endpoint of WAIS-IV Coding test total correct score is 2.5, and the standard deviation is 4.2.

The total sample size of 120 evaluable participants will provide 90% power to detect the treatment difference of 2.5 in change from baseline in WAIS-IV Coding Test total correct score while allowing for 1 interim analysis (IA) and 1 final analysis. This sample size and power are based on a 2-sided t-test using an overall significance level of 0.05. One formal IA

may be conducted after approximately 60 participants as total have completed Day 84 (Week 12). The group sequential method by O'Brien and Fleming for the two-sided test will be used. The significance level will be based on the type I error spending function of Lan and DefsMets such that the overall significance level will be maintained at 0.05. Assuming a 20% dropout and a 1:1 randomization ratio, approximately 150 randomized participants (75 per treatment group) will be required to obtain 60 evaluable participants per treatment group. Evaluable participants are defined as those randomized participants who receive IP and have a valid baseline and at least 1 postbaseline WAIS-IV Coding test assessment. Additional participants may be randomized if the dropout rate is higher than 20%. Table 2 summarizes operating characteristics of this design based on 120 evaluable participants.

Table 2: Group Sequential Design

Repeated Analyses	Information Time	Number of Participants	Boundaries for Efficacy (Z-score)	Boundary for Futility (Z-score)
Interim	0.5	60	2.796	0.4229
Final	1	120	1.977	

* Using the SAS Software Version 9.4

5.3. Randomization

This is a randomized, double-blind, placebo-controlled study. Eligible participants will be randomized 1:1 to receive SAGE-718 or placebo for 84 days (±7 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.

5.4. Blinding and Unblinding

Participants, clinicians, and the study team will be blinded to treatment allocation. 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 for the final analysis. In addition, only the designated personnel approved by Sage will be unblinded to the treatment allocation for the participants included in the IA, should one occur.

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. In the case of emergency

unblinding, the Early Termination Visit should be completed after a participant's treatment assignment has been unblinded.

If a participant becomes unblinded to the participant's treatment assignment before database lock, the participant will be excluded [redacted], but will be included in the Full Analysis Set (FAS) (see Section 7.3)

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

Not applicable

6.2. Modifications from the Approved Statistical Analysis Plan

This is the first version of the SAP.

6.3. Modifications from the Approved DMC Charter

Not applicable

7. ANALYSIS SETS

7.1. Randomized Set

The Randomized Set will include all participants who have been randomized to the investigational product (IP) and will be used to describe participant's background characteristics.

7.2. Safety Set

The Safety Set will include all participants who were administered at least 1 dose of the IP. The Safety Set will be used to describe the safety data and analyses will be based on the 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 randomized treatment.

[redacted]

7.5. [redacted]

[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, Least squares Means (LSM), 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. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision. 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.

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.

Participants who are randomized to 1.2 mg treatment and received 0.9 mg dose due to dose reduction will be summarized under the same SAGE-718 treatment group. For efficacy data analysis, participants' data are analyzed by randomized treatment. For safety data analysis, participants' data are analyzed per the actual treatment received, and this is determined as follows: if a participant received any dose of SAGE-718 at any point of time, the participant is assigned to actual treatment of SAGE-718, regardless of the treatment to which the participant has been randomized.

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.

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 as 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 on or after date of 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 participants enrolled in the study including:

- Participants screened
- Participants screen-failed
- Participants screened but neither screen failed nor randomized
  Note: Due to enrolment closed, participants were discontinued from the study prior to inclusions/exclusions criteria reviewed
- Participants randomized
- Participants randomized but not dosed
- Participants received at least 1 dose of IP
- Number of participants randomized to placebo but received SAGE-718
- Participants who had dose reduction before Visit Day 42
- Participants completed IP
- Participants discontinued from IP and primary reasons for discontinuing IP
- Participants completed the study
- Participants discontinued from the study and primary reasons for early discontinuation

Numbers of participants and percentages for study or treatment completion or discontinuation as well as the reason for discontinuation will be based on the participants

who were randomized and received IP. Treatment arm assignment will be according to the randomized treatment.

In addition, summary of analysis sets including Safety Set, FAS, [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 and inclusion/exclusion criteria for all screened participants, and completion and discontinuation from study treatment and study participation, and inclusion in analysis sets for Randomized Set.

[redacted]

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 (continuous and categorical: ≤65, >65), sex, childbearing status, race (both from CRF and derived categorical: Black or African American, White, Other), and ethnicity, years of education, years of employment, 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 will also be summarized for:

- WAIS-IV Coding test score (continuous)

- WAIS-IV total correct Score (<Median, ≥Median)
- Clinical Dementia Rating (CDR) score (continuous)
- Clinical Dementia Rating (CDR) score (categorical: 0.5, 1)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- BMI (categorical: ≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2)
- Years of Education (<Median, ≥Median)

Median categories are calculated from the overall baseline value and rounded to the nearest integer.

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

8.2.4. Medical/Surgical 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 24.1 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 AD history will be provided separately. Listings will be provided for Randomized Set.

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 the World Health Organization Drug dictionary September 2021 B3, or later and MedDRA Version 24.1 or higher, respectively.

All medications/procedures taken within 30 days prior to Screening, all medications used to treat AD regardless of timing, and all nonpharmacological methods used to treat or prevent [redacted], or cognitive manifestations of AD are to be recorded. 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 Safety Set using System Organ Class (SOC) and preferred term 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 for Randomized Set.

8.2.6. Investigational Product Exposure

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

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 and is summarized under SAGE-718 as the actual treatment. If a participant skips a dose on any of the days, the dose taken is 0 mg.

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.

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

- For participants who complete the treatment period, planned exposure is (Date of Day 42 visit – First Dose Date of 1.2 mg + 1) times 1.2 mg for participants randomized to SAGE-718 plus (Date of Day 84 visit – Date of Day 42 visit) times 0.9 mg for participants randomized to SAGE-718. For 0.9 mg exposure, with consideration of the Day 84 visit windows (+/- 7 days),
    - If Study Day of Day 84 Visit > 91, use the First Dose Date of 1.2 mg + 90 instead of Date of Day 84 visit. i.e. (Date of Day 84 visit – Date of Day 42 visit) = First Dose Date of 1.2 mg + 90 – Date of Day 42 visit.

  - If Study Day of Day 84 Visit < 77, use the First Dose Date of 1.2 mg + 76 instead of Date of Day 84 visit. i.e. (Date of Day 84 visit – Date of Day 42 visit) = First Dose Date of 1.2 mg +76 – Date of Day 42 visit.

- For participants who discontinue the treatment prior to 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 who discontinue the treatment on or after Day 42 visit but prior to Day 84 visit, the planned exposure is (Date of Day 42 visit – First Dose Date of 1.2 mg + 1) times 1.2 mg plus (Last Dose Date of 0.9 mg – Date of Day 42 visit) times 0.9 mg for participants randomized to SAGE-718.
- For participants who cannot tolerate 1.2 mg prior to Day 42 visit therefore received 0.9 mg for the remainder of the treatment period, the planned exposure is (First Dose Date of 0.9 mg – First Dose Date of 1.2 mg) times 1.2 mg plus (Date of Day 84 visit – First Dose Date of 0.9 mg + 1) times 0.9 mg for participants randomized to SAGE-718. For 0.9 mg exposure, refer to the first bullet for participants who complete the treatment period.
- For participants who never received SAGE-718, this measure is not applicable.

By-participant listings 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 taken is defined as similar way as planned exposure, with consideration of the Day 84 visit windows (+/- 7 days).

- For participants who complete the treatment period, the planned number of capsules taken is defined as follows:
  - 77 if Study Day of Day 84 Visit < 77
  - (Date of Day 84 visit – First Dose Date + 1) if Study Day of Day 84 Visit is between 77 and 91 (inclusive)
  - 91 if Study Day of Day 84 Visit > 91
- For participants who discontinue the treatment earlier than Day 84 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 will be used for all efficacy summary and analysis tables. [redacted]

8.3.1. Definition of Efficacy Variable(s)

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. 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. The WAIS-IV Coding Test will be performed as outlined in Table 12.

8.3.1.2. [redacted]

8.3.1.2.1. [redacted]

8.3.1.2.1.1. [redacted]

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8.3.1.2.1.2. [redacted]

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8.3.1.2.1.3. [redacted]

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8.3.1.2.1.3.1. [redacted]

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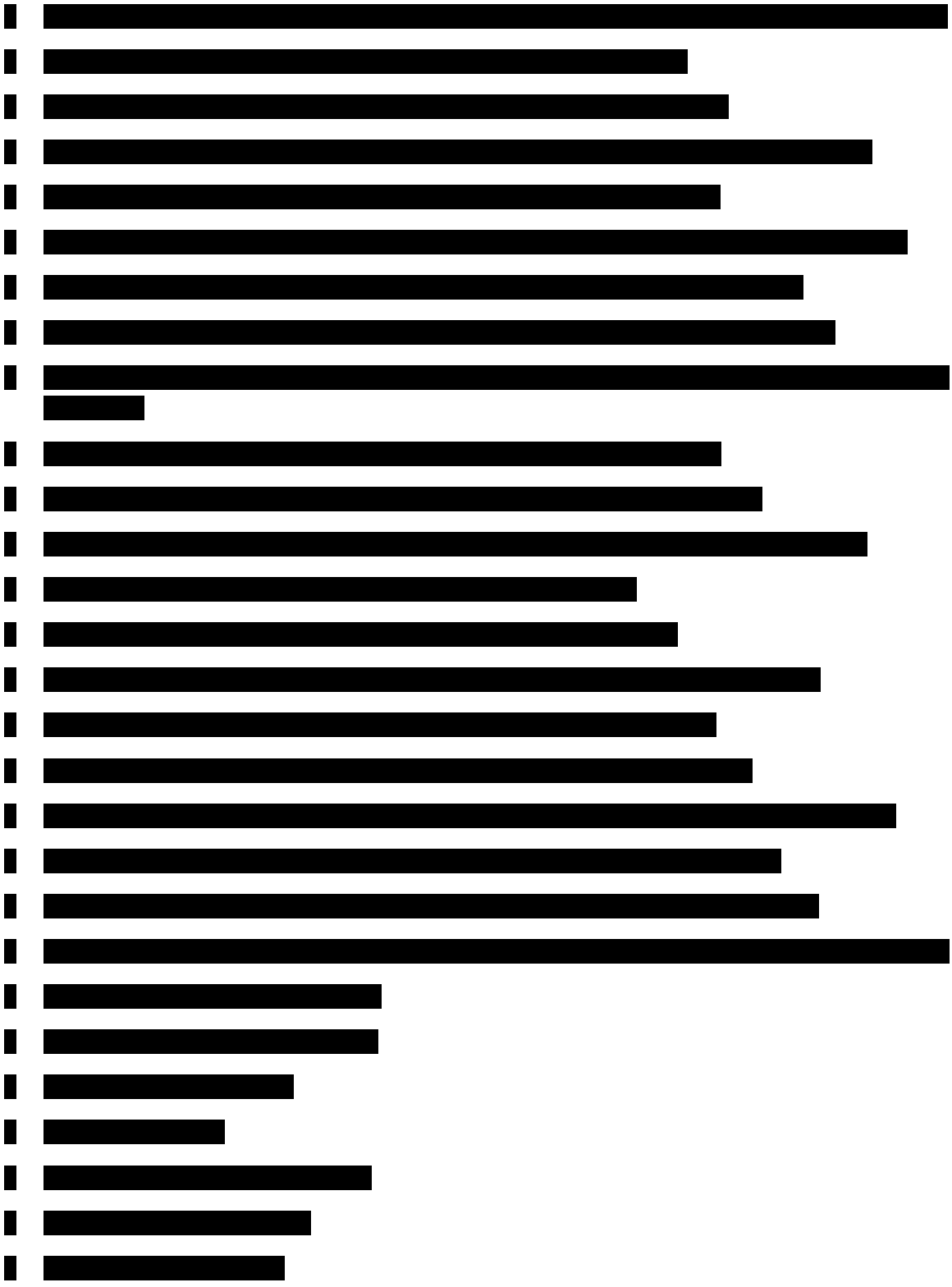

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8.3.1.2.2. [redacted]

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Table 3. [redacted]

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8.3.1.2.3.6. [redacted]

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[redacted]

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 early termination (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 4. Analysis Visit Windows for WAIS-IV Coding Test

Scheduled Visit	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
[redacted]		
Day 84 (±7 days)	Day 84	Day 64 – Day 98
[redacted]		

Table 5. [redacted]

[redacted]

Table 6. [redacted]

[redacted]

Table 7. [redacted]

[redacted]

8.3.3. Analysis of Primary Efficacy Variable(s)

8.3.3.1. Primary Analysis and Estimand

The estimand for the primary efficacy analysis is defined as follows:

1) The treatment regimen for participants is placebo or SAGE-718 for 84 days.
2) The target population is adult participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease.

3) The variable of interest is the change from baseline in WAIS-IV Coding test score at Day 84.
4) The intercurrent events could be:
    a) The premature discontinuation of treatment for any reason. The treatment policy strategy will be used.
    b) Taking certain medications including, but not limited to, medications with potent effects at the NMDA receptor, including memantine, amantadine, ketamine, or related compounds or other medications, given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance, or prescribed cannabis or other THC-containing substances. The treatment policy strategy will be used.
5) The population summary level deals with the difference between SAGE-718 and placebo treatments in mean change from baseline in WAIS-IV Coding test score at Day 84.

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 84 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 as implemented in the SAS procedure PROC MIXED will be used to model the within-subject correlation. If this model fails to converge, 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 (TOEP), 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 84. The 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.

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.

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.

[redacted]

[redacted]

[redacted]

8.3.3.4. Supportive Analysis of Primary Endpoint

The primary analysis will be repeated [redacted]. The WAIS-IV coding score after taking the prohibited medication will not be included in the analysis. No sensitivity analysis will be performed [redacted].

8.3.3.5. Subgroup Analyses of Primary Analysis

Primary endpoint will be analyzed using a similar MMRM model in Section 8.3.3.1 for the following subgroups:

- Baseline MoCA: 15-17, ≥18
- Baseline CDR: 0.5, 1
- Age: ≤65, >65
- Race (Black or African American, White, Other)
- Sex (Male, Female)
- Baseline WAIS-IV (<Median, >=Median)
- Baseline RBANS (<Median, >=Median)
- Years of Education (<Median, >=Median)

Median categories are calculated from the overall baseline value and rounded to the nearest integer.

A summary using descriptive statistics on observed values, percent change from baseline and change from baseline by treatment group and subgroup will be provided. The primary endpoint by subgroup will be analyzed using MMRM only if there are at least 10 participants per subgroup. A forest plot showing the LSM and 95% CI bar at Day 84 within each subgroup and treatment group will be provided.

8.3.4. Analysis of Secondary Efficacy Variables

Not applicable.

8.3.5. [redacted]

[redacted]

8.3.5.1. [redacted]

[redacted]

8.3.5.2. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.3.5.3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.3.5.4. [redacted]

[redacted]

[redacted]

[redacted]

8.3.5.5. [redacted]

[redacted]

8.3.5.6. [redacted]

[redacted]

8.3.5.7. [redacted]

[redacted]

8.3.5.8. [redacted]

[redacted]

8.3.5.9. [redacted]

[redacted]

8.3.5.10. [redacted]

[redacted]

8.3.5.11. [redacted]

[redacted]

8.4. Safety Analysis

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

Safety and tolerability of SAGE-718 softgel lipid capsule

in participants with AD 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, [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. For the summary of the scheduled visits, unscheduled measurements and ET measurement, unless specified, 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 4). 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. 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 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		*				

Safety Evaluation	Incidence	Source Data	Change from Baseline	Shift from Baseline	Potentially Clinically Significant	Abnormality/ Clinical Significance
[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 Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Intensity 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. 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 TEAEs (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
- Any TEAEs leading to dose reduction before Day 42

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 System Organ Class (SOC) in SAGE-718 group, then in placebo group, then alphabetically first within SOC then within preferred term.

- 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 any 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 summary 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 group (≤65, >65 years)

A by-participant listing of all AEs, SAEs (including those with onset or worsening before the start of IP), AEs leading to death, AEs 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.

Laboratory values contain '≥ x' or 'x ≤' will be taken as the value of x in the analysis. If a laboratory value is reported as '<y' then y minus the minimum value with the same precision as y (ex. 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 – 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 post-baseline values in abnormality of results at anytime on treatment where the worst value is used, the last value on treatment and the last value on 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 (PCS) 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
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
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		second	>=1.11 x ULN	NA

Laboratory Parameter	Sex	Units	Criteria for PCS Values (Observed values)	
			High	Low
Partial thromboplastin time		second	>1.5 x ULN	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 (for condition involving more than one parameter, the results need to be from the same timepoint):

- 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]

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

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

8.4.3. Electrocardiogram

A 12-Lead ECG will be performed after the participant has been resting in the supine position for at least 5 minutes. 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 raw values 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 Parameters

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 height, weight, oral temperature(˚C), respiratory rate (breaths per minute), heart rate (beats per minute [bpm]), and blood pressures (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	Beats/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			

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCS values (Change from Baseline values)	
		High	Low	Increase	Decrease
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 and neurological examination are to be conducted during Screening and at Day 84 (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. 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 to confirm the examination was done. A separate listing for the neurological examination will be provided.

8.4.6. Magnetic Resonance Imaging

By-participant listing of MRI at screening will be provided.

8.4.7. [redacted]

[redacted]

[redacted]

8.4.8. Other Safety Analysis

Not applicable.

8.5. Other Analysis

[redacted] will be described and reported separately.

8.5.1. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10. REFERENCES

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[redacted]

APPENDIX A. SCHEDULE OF ASSESSMENTS

Table 12. Schedule of Assessment

Assessments	Screening Period	Baseline Period	Treatment Period						Follow-Up Period
	Days -35 to -8	Days -7 through -1	Day 1[a]	Day 14 (±2 days)	Day 28 (±2 days) safety phone call[b]	Day 42 (±2 days)[c]	Day 63 (±2 days) safety phone call[b]	Day 84 (±7 days)[d] or ET	Day 112 (±7 days)
Informed consent[e]	X								
Inclusion/exclusion criteria	X		X						
Randomization			X						
Medical history and demographics[f]	X								
Participant training[g]		X							
Body weight	X		X			X		X	X
Body height	X								
CDR	X								
Vital signs (including orthostatic)[h]	X		X	X		X		X	X
Physical examination[i]	X		X	X		X		X	X
FSH test[j]	X								
Serology test[k]	X								

Assessments	Screening Period	Baseline Period	Treatment Period						Follow-Up Period
	Days -35 to -8	Days -7 through -1	Day 1[a]	Day 14 (±2 days)	Day 28 (±2 days) safety phone call[b]	Day 42 (±2 days)[c]	Day 63 (±2 days) safety phone call[b]	Day 84 (±7 days)[d] or ET	Day 112 (±7 days)
12-lead ECG[l]	X		X	X		X		X	X
MRI[m]	X								
Safety laboratory assessments[n]	X		X	X		X		X	X
Urine drug test	X		X	X		X		X	X
Alcohol breath test	X		X	X		X		X	X
Pregnancy test[o]	X		X					X	
[redacted]									

Assessments	**Screening Period**	**Baseline Period**	**Treatment Period**						**Follow-Up Period**
	Days -35 to -8	**Days -7 through -1**	**Day 1[a]**	**Day 14 (±2 days)**	**Day 28 (±2 days) safety phone call[b]**	**Day 42 (±2 days)[c]**	**Day 63 (±2 days) safety phone call[b]**	**Day 84 (±7 days)[d] or ET**	**Day 112 (±7 days)**
WAIS-IV Coding test[r]		X						X	
[redacted]									
IP self-administration[u]			X (once daily in the morning)						
IP dispensation[v]			X	X		X			
IP accountability[w]			X						
IP return[x]				X		X		X	
Safety call assessment[b]					X		X		
AEs/SAEs[y]	X								
Prior and concomitant medications[z]	X								

Abbreviations: AD = Alzheimer's Disease; AE = adverse event, [redacted] CDR = Clinical Dementia Rating; [redacted] COVID-19 = coronavirus disease 2019; [redacted] ECG = electrocardiogram; ET = early termination; [redacted] FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; [redacted] MRI = magnetic resonance imaging; [redacted] SAE = serious adverse event; WAIS-IV Coding Test = Wechsler Adult Intelligence Scale-IV Coding Test.

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

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

[c] Within the SAGE-718 treatment arm, participants will receive 1.2 mg of SAGE-718 daily for the first 6 weeks (Day 1 Visit to Day 42 Visit [±2 days]), followed by 0.9 mg of SAGE-718 for the remainder of the Treatment Period (Days 43 to 84 [±7 days]). The placebo arm will receive matching placebo throughout the Treatment Period (12 weeks).

[d] Dosing ends on Day 84 (±7 days). Participants who terminate early should perform all of the assessments that are scheduled for Day 84.

[e] Both participants and their study partners will provide informed consent at screening. Participants and study partners will consent to participation in the study, and any optional assessments [redacted].

[f] Includes full medical history (including family history of AD), medications and supplements taken within 30 days prior to Screening, medications used to treat AD regardless of timing, and nonpharmacological methods (e.g., psychosocial, psychotherapeutic) used to treat or prevent [redacted], or cognitive manifestations of AD. 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 collection at Screening and throughout the study.

[g] Participants and study partners will be trained by study staff on the use of software applications and devices necessary for the conduction of the study.

[h] Vital signs include body temperature, respiratory rate, heart rate, and blood pressure. On dosing days, vital signs will be measured prior to dosing. 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. Vital signs can be repeated once if out of range.

[i] A full physical and neurological examination will be conducted during Screening and at Day 84 (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 and who have ≥12 months of spontaneous amenorrhea to confirm postmenopausal state as defined in protocol.

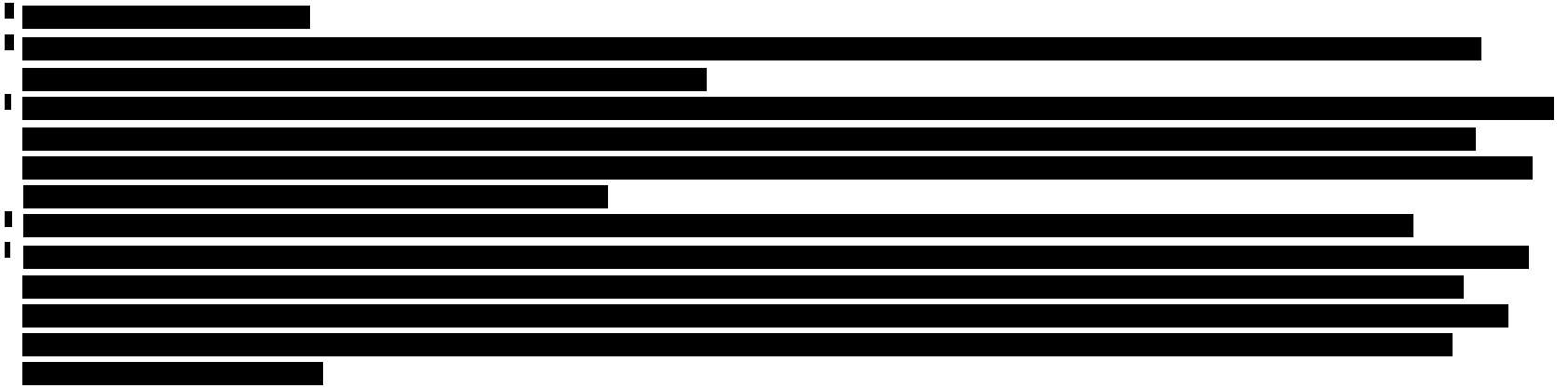
[k] To include hepatitis B and C screening tests, HIV-1 and -2 antibody.

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

[m] Only in participants without an MRI report obtained within the 2 years preceding the Baseline Period.

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

[o] 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 do not meet the protocol definition of postmenopausal or surgically sterile.



[u] On Day 1, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments and cognitive tests will be administered prior to dosing. On Days 14, 42, and 84, cognitive tests will be administered postdose.

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

[w] IP dosing date and time will be recorded by participant remotely using mobile device.

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

[y] AEs/SAEs will be collected beginning with completion of ICF through end of study participation.

[z] At Screening, to include all medications and supplements taken within 30 days of signing ICF and all medications used to treat AD. At visits subsequent to Screening, all changes to any medication should be captured.

Table 13: [redacted]

[redacted]

APPENDIX B. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX C. [redacted]

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APPENDIX D. LIST OF DISPLAYS

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[redacted]		
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[redacted]		
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[redacted]		

Type	Number	Title
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Type	Number	Title
[redacted]		

Type	Number	Title
[redacted]		
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[redacted]		
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[redacted]		

Type	Number	Title
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[redacted]		
Listing	16.2.6.1	Wechsler Adult Intelligence Scale – IV (WAIS-IV) Coding Test (Full Analysis Set)
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Type	Number	Title
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