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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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

PROTOCOL NUMBER: 718-CNA-202

Investigational Product	SAGE-718
Clinical Phase	2
Sponsor Contact	[redacted] Cambridge, MA 02142 Phone: [redacted]
Medical Monitor	[redacted], MD Cambridge, MA 02142 Phone: [redacted]
Date of Original Protocol	24 May 2022
Date of Amendment 1	22 December 2023

Confidentiality Statement

The confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose

the information contained herein to others without written authorization from Sage Therapeutics, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-718. I have read the 718-CNA-202 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD MMM YYYY)

CONTACT INFORMATION

Table 1: Contact Information

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SAE Reporting	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 e-mail: Sage.Safety@iqvia.com Fax: 1-855-638-1674 SAE Hotline: 1-855-564-2229
Product Complaints	Sage Therapeutics	e-mail: productcomplaints@sagerx.com Phone: 1-833-554-7243
Inspection Notification Contact	Sage Therapeutics	Email: InspectionNotification@sagerx.com

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Investigational Product:
SAGE-718 softgel lipid capsule

Name of Active Ingredient:
SAGE-718

Title of Study:
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

Number of Sites and Study Location: Approximately 40 sites in the United States.

Phase of Development: 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final Follow-up visit) for each participant is estimated to be 21 weeks, including an up to 4-week Screening Period, up to a 1-week Baseline Period, a 12-week Treatment Period, and a 4-week Follow-up Period.

Objectives and Endpoints:

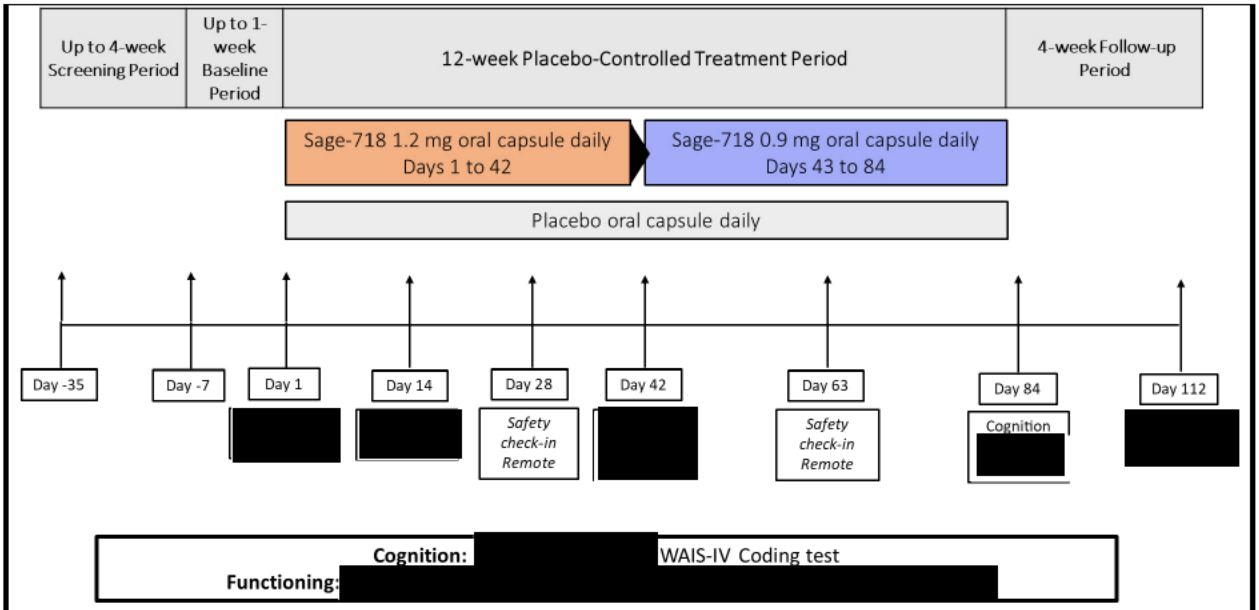
Objectives	Endpoints
Primary	
• To evaluate the effect of SAGE-718 on cognitive performance in participants with Alzheimer's Disease (AD)	• Change from baseline to Day 84 in the Wechsler Adult Intelligence Scale Fourth Edition-IV (WAIS-IV) Coding Test, total correct
Secondary	
• To evaluate the safety 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)
[redacted]	
• 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]

[redacted]

[redacted]

Study Description:

This is a randomized, double-blind, placebo-controlled study to evaluate the effects of SAGE-718 in participants with mild cognitive impairment (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 (Day 1 Visit to Day 42 Visit [±2 days]), followed by 0.9 mg of SAGE-718 for the remainder of the Treatment Period (ie, 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). All participants will self-administer investigational product (IP) in the morning.



Abbreviations: [redacted] WAIS-IV Coding Test = Wechsler Adult Intelligence Scale-IV Coding Test.

Assessments will be performed as outlined in the Schedule of Assessments (Table 2) [redacted].

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.

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] Participants and their study partners will receive training on the study procedures and devices. [redacted]

Treatment Period

The 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 (Day 1 Visit to Day 42 Visit [±2 days]) followed by 0.9 mg of SAGE-718 for the remainder of the Treatment Period (ie, 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 participants' treatment 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 consent or loses the capacity to grant consent. If a participant withdraws from the study/stops study participation early, an Early Termination Visit should be conducted. Treatment with SAGE-718 can be ended without down titration. Participants may be invited to screen for a subsequent SAGE-718 study (if available) after the Day 84 Visit.

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].

Number of Participants (planned): Approximately 150 participants will be randomized to obtain up to 60 evaluable participants per treatment arm.

Eligibility Criteria

Inclusion Criteria:

Participants must meet all of the following criteria to qualify for participation in this study:

1. Be capable of providing informed consent
2. Have signed an informed consent form (ICF) prior to any study-specific procedures being performed
3. Be willing and, in the opinion of the investigator, able to comply with study procedures
4. Be between the ages of 50 and 80 years, inclusive, at Screening
5. Meet the following criteria for MCI or mild dementia due to AD at Screening:
    a. A memory complaint reported by the participant or their study partner
    b. A Clinical Dementia Rating (CDR) score of 0.5 to 1.0 (inclusive) with a memory box score ≥0.5
    c. Essentially preserved activities of daily living, in the opinion of the investigator
    d. Brain MRI report, obtained within the 2 years preceding the Baseline Period, that is consistent with the diagnosis of AD with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment
6. Have a score of 15 to 25 (inclusive) on the MoCA with years of education adjustment at Screening
7. Have a study partner who, in the opinion of the investigator, is willing and able to provide informed consent, reliably support study-specific activities including IP adherence, be available by phone, and accompany the participant to study visits as needed
8. Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded) and able to travel to the study center
9. Have stable concomitant medication usage (dose and frequency) for at least 4 weeks prior to the first IP administration, and which is expected to remain stable for the duration of the study
10. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit
11. Agree, if female, to use an acceptable highly effective method of contraception during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and

confirmed by follicle stimulating hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy

12. Agree, if male, to use an acceptable method of highly effective contraception during the Treatment Period and for 21 days after receiving the last dose of IP, unless the participant does not engage in sexual relations that carry a risk of pregnancy
13. Agree, if male, to abstain from sperm donation during the Treatment Period and for 21 days after receiving the last dose of IP

Exclusion Criteria:

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer), unless the participant participated solely in the placebo arm of the study. Additionally, participants who have received treatment with antisense oligonucleotides (ASO) will be excluded
2. Have a condition that precludes undergoing an MRI, in accordance with standard operating procedures at the imaging facility (eg, ferromagnetic metal in the body, claustrophobia), in a participant requiring MRI during Screening
3. Have clinically significant comorbid medical conditions (eg, hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease), or a chronic condition that is unstable, or are taking concomitant medications that, in the opinion of the investigator, may make the participant unsuitable for inclusion or have the potential to compromise safety and/or compliance with study requirements
4. Have any medical or neurological condition (other than AD) that might be contributing to the participant's cognitive impairment or history of cognitive decline
5. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion, or other non-AD pathology) that is likely to call into question a primary clinical diagnosis of AD
6. Have a history, presence, and/or current evidence of
    a. Brain surgery, deep brain stimulation, or any history of hospitalization due to a brain injury
    b. Possible or probable cerebral amyloid angiopathy, according to the Boston Criteria (Greenberg 1995)
    c. Treatment with an anti-amyloid therapy (including biologics) without subsequent MRI demonstrating the absence of amyloid-related imaging abnormalities
    d. Seizures or epilepsy, with the exception of childhood febrile seizures
7. Have an alcohol or drug use disorder within the past 12 months as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria
8. Be receiving any of the following prohibited medications:
    a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine, within 4 weeks of IP administration and during the entire course of the study
    b. Medications that inhibit cholesterol absorption (eg, ezetimibe)
    c. Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)

d. Other medications or supplements given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance
e. Cannabis or other tetrahydrocannabinol (THC)-containing substances (any route of administration), regardless of whether or not they are prescribed

9. Participant has a history of suicidal behavior within 2 years or answers "YES" to Questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
10. Have any of the following medical conditions:
    a. Any clinically significant finding on 12-lead ECG during Screening in the opinion of the investigator
    b. Any clinically significant supine vital signs (heart rate, systolic and diastolic blood pressure) during Screening (note: vital sign measurements may be repeated once)
11. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1 or HIV-2, or hepatitis B or C
12. Have a positive pregnancy test, or be lactating, or intend to breastfeed during the study
13. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted)
14. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.
15. Plans to undergo elective surgery or procedures during participation in the study.
16. Have a history of gastric bypass

Investigational Product Dosage and Mode of Administration:

SAGE-718 or matching placebo, under double-blind conditions, will be self-administered as softgel lipid capsule orally once daily in the morning.

Duration of Treatment: IP will be administered once daily during the 12-week Treatment Period. Dosing ends at the Day 84 Visit (±7 days).

Statistical Methods:

A separate statistical analysis plan (SAP) will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock.

General Considerations

Unless otherwise specified, baseline is defined as the last measurement prior to the first dose of IP.

Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum, maximum, Q1, and Q3. In addition, change from baseline values will be calculated at each time point and will be summarized using the same summary statistics. Out of range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, summaries will include counts and percentages.

Analysis Sets

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

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

The Full Analysis Set (FAS) will include all participants in the Safety Set who have baseline and at least 1 postbaseline efficacy evaluation. The FAS will be used to describe the efficacy data. Analyses will be based on the randomized treatment.

[redacted]

Safety Analysis

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The proportion of participants experiencing TEAEs will be displayed by treatment group and by system organ class and preferred term. The frequency of TEAEs will also be presented by maximum severity and relationship to IP and by treatment group. Vital signs, laboratory parameters, ECGs, [redacted] data will be summarized by treatment group. Additional analyses will be detailed in the SAP.

Efficacy Analysis

The endpoints for each cognitive test, including WAIS-IV Coding Test, [redacted] are change from baseline scores at each postbaseline assessment. Descriptive statistics of scores and change from baseline scores will be summarized based on the Full Analysis Set. These endpoints will also be analyzed using a mixed effects model for repeated measures. The model will include change from baseline scores as dependent variable; treatment, visit, and visit by treatment interaction as fixed effects; participants as random effects; and baseline cognitive test scores as a covariate; Model-based point estimates (ie, least square means, 95% confidence intervals, and associated p values) at each time point (visit) will be reported where applicable. Line plots of change from baseline scores will be plotted with standard error bars. [redacted]

Sample Size Calculation

The sample size calculation is based on change from baseline in WAIS-IV Coding Test total correct score. Based on data in a previous study, we assume difference between placebo and the SAGE-718 group at the end of treatment (at Day 84) for primary endpoints of WAIS-IV Coding test total correct score is 2.5, 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 one interim analysis and one final analysis. This sample size and power are based on a two-sided test using an overall significance level of 0.05.One formal interim analysis may be conducted after approximately 60 participants have completed Week 12. The group sequential method by O'Brien and Fleming for the two-sided test will be used (O'Brien 1979). The significance level will be based on the type I error spending function of Lan and DeMets such that the overall significance level will be maintained at 0.05 (Lan 1983). 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%.

The table below summarizes operating characteristics of this design based on 120 evaluable participants.

Table Group Sequential Design

Repeated Analyses	Information Time	No of Participants	Boundaries for Efficacy	Boundary for Futility
Interim	0.5	60	2.796	0.4229
Final	1	120	1.977	

Table 2: Schedule of Assessments

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								
12-lead ECG[l]	X		X	X		X		X	X
MRI[m]	X								
Safety laboratory assessments[n]	X		X	X		X		X	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)
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]									
C-SSRS (Baseline/Screening Form)	X								
[redacted]									
WAIS-IV Coding test[r]		X	[redacted]					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)
[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] 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 at the Day 1 Visit 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 (ie, beginning the first day after the Day 42 Visit). Dosing ends at the Day 84 Visit (±7 days). The placebo arm will receive matching placebo throughout the Treatment Period (12 weeks).

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

[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 (eg, 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 the Day 84 Visit (±7 days; 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.

[redacted]

[redacted]

[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. At Day 14 Visit (±2 days), Day 42 Visit (±2 days), and Day 84 Visit (±7 days), 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 3: [redacted]

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol:

Abbreviation	Definition
24SHC	24(S)-hydroxycholesterol
AD	Alzheimer's Disease
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
[redacted]	[redacted]
ASO	antisense oligonucleotides
BMI	body mass index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CDR	Clinical Dementia Rating
COVID-19	coronavirus disease 2019
CS	clinically significant
DILI	drug-induced liver injury
[redacted]	[redacted]
ECG	electrocardiogram
ET	Early Termination
eCRF	electronic case report form
FAS	Full Analysis Set
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	identification

Abbreviation	Definition
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
LC-MS/MS	Liquid Chromatography with tandem Mass Spectrometry
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NCS	not clinically significant
[redacted]	[redacted]
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
[redacted]	[redacted]
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
US	United States
USM	urgent safety measure
WAIS-IV	Wechsler Adult Intelligence Scale-IV

5. INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and is projected to increase in incidence to >13 million in the United States by 2050 (Hebert 2013; Sharma 2019). Deficits in executive functioning (eg, problem solving) occur early in the disease, and are hypothesized to reflect prefrontal cortex pathology (Weintraub 2012). As AD progresses, deficits in learning and memory become more pronounced, and are coupled with impaired sustained attention and visuospatial abilities (Weintraub 2012).

The N-methyl-D-aspartate receptor (NMDAR) is a type of glutamate receptor that has a fundamental and well-documented role in regulating synaptic plasticity, as well as in memory and learning (Danysz 1998; Ghanavati 2022; Li 2009). NMDAR functioning is affected by AD (Mony 2009; Prasanth 2021; Taniguchi 2022), however the nature of this relationship may be a function of disease severity. In later stages of AD, memantine, an NMDAR antagonist, may protect against glutamate excitotoxicity (Gauthier 2013). In earlier stages of AD, however, NMDAR functioning may be impaired (Ortiz-Sanz 2022). Indeed, administration of a short-term NMDA partial agonist (D-cycloserine) has been shown to improve cognition in AD patients, as evidenced by scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale (Tsai 1999).

SAGE-718 is a novel NMDAR positive allosteric modulator that is being developed by Sage Therapeutics for the treatment of neurodegenerative disorders such as AD. Recently, a Phase 2 open-label study assessed the effects of SAGE-718 in an AD population (Study 718-CNA-201). In this seminal study, investigators assessed the safety and tolerability of SAGE-718, as well as its effects on cognitive and neuropsychiatric symptoms in participants with MCI or mild dementia due to AD (n=24). SAGE-718 had a well-tolerated safety profile, with no unexpected safety concerns. Over 14 days of open-label dosing with SAGE-718, improvement was observed on cognitive test performance in several key domains, including Global Cognition, Executive Function, Learning and Memory, Social Cognition, and Everyday Function.

The current study, 718-CNA-202, is a randomized, double-blind, placebo-controlled Phase 2 study designed to evaluate the effects of SAGE-718 in participants with MCI or mild dementia due to AD.

5.1. Overall Risk/Benefit Assessment

In addition to the study discussed above, SAGE-718 has been shown to improve cognition in other neurodegenerative disorders (for details refer to SAGE-718 Investigator's Brochure [IB]). The potential benefit of SAGE-718 is coupled with low risk of NMDAR-associated excitotoxicity. Indeed, SAGE-718 is oxysterol-based and acts on the 24(S) hydroxycholesterol (24SHC) binding site of NMDAR. SAGE-718 only modulates the response of NMDAR in the presence of endogenous glutamate. That is, SAGE-718 does not directly activate the receptor and thus, is not expected to cause NMDAR-associated glutamatergic excitotoxicity.

SAGE-718 has been well characterized in a comprehensive series of in vitro and in vivo nonclinical studies that have defined its key pharmacology, absorption, distribution, metabolism and excretion (ADME), drug-drug interaction, and toxicology findings, including compound-related effects and the reversibility of these changes. In a radiolabeled rat ADME study, there

was no selective distribution or retention of radioactive SAGE-718 to pigmented tissues and no quantifiable concentration of radioactivity was observed in the eye lens in Long Evans rats, implying that potential risk of phototoxicity is low.

Due to an unexplained mortality early in the 14-day oral repeat-dose rat study at 30 mg/kg/day, a human maximum concentration (C_{max}) cap for clinical studies was established from the Day 0 mean C_{max} (443 ng/mL) in female rats at the 15 mg/kg/day dose level. A 10-fold safety factor was used to derive the 45 ng/mL clinical exposure cap (see Section 5.2 Dose Justification). Across the nonclinical studies conducted with rats and dogs, a C_{max} threshold for observation of convulsions occurred at exposures 20 to 40 times greater than clinically relevant exposures.

No deaths, SAEs or TEAEs leading to discontinuation assessed as related to SAGE-718 were reported in the completed studies with SAGE-718. A maximum tolerated dose has not been identified and no characteristic safety signals have been identified to date. No clinically relevant mean changes from baseline have been observed in ECGs or EEGs. In addition, there were no SAEs or severe TEAEs reported in patients with AD that were enrolled in the completed Study 718-CNA-201.

There is no contraindication for use of the coronavirus disease 2019 (COVID-19) vaccination in the trial setting of SAGE-718. Vaccine status will be recorded as a concomitant medication and COVID-19 safety protocols will be incorporated in all studies, data collection, and operating procedures.

Based on the completed studies, the benefit-risk profile of SAGE-718 supports further development in an AD patient population.

5.2. Dose Justification

SAGE-718 has been well tolerated in both healthy participants and AD participants in previous clinical studies. However, based on nonclinical findings, the United States (US) Food and Drug Administration (FDA) imposed a median C_{max} cap of 45 ng/mL. To date, clinical studies have used doses that resulted in exposures within this cap; no IP-related SAEs or AEs leading to discontinuation have been reported. For additional information on exposure caps, see the SAGE-718 IB.

A daily dose of 1.2 mg from the Day 1 Visit to the Day 42 Visit (±2 days) followed by 0.9 mg until the Day 84 Visit (±7 days) (or ET) of SAGE-718 in a lipid-based softgel formulation or matching blinded placebo, will be taken by the participants each morning. The dose regimen is selected to provide PK exposures that are similar to those achieved in prior studies that have shown evidence of target engagement consistent with the NMDA hypothesis for pro-cognitive effects. [redacted]

In the completed SAGE-718 studies (718-EXM-101, 718-EXM-102 and 718-EXM-103), repeat doses of 1 mg and single doses of 3 mg, given as an oral solution to healthy volunteers, have demonstrated evidence consistent with NMDA target engagement in experimental medicine paradigms. A repeat dose of 1 mg daily of the oral solution in HD patients, and a solid tablet

taken with a moderate fat meal (containing approximately 30 g of dietary fat) in Parkinson's Disease patients, has shown beneficial effects on assessments of cognition in 14-day studies. Based on an approximately 3-fold accumulation of SAGE-718 at steady-state, the PK exposures in each of these scenarios was similar, with median AUC values ($AUC_{0-\infty}$ for single doses, and AUC_{0-24} for repeat doses, accordingly) ranging from 315 to 444 ng·h/mL and C_{max} values of 19.7 ng/mL to 29.7 ng/mL and these levels are expected to be achieved in the present study.

The effect of SAGE-718 will be evaluated in the current placebo-controlled study in participants with MCI or mild dementia due to AD. Additional data on the effects of SAGE-718 in participants with AD will be collected throughout, including the assessments of [redacted].

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of SAGE-718 on cognitive performance in participants with Alzheimer's Disease (AD)	• Change from baseline to Day 84 in the Wechsler Adult Intelligence Scale Fourth Edition-IV (WAIS-IV) Coding Test, total correct
Secondary	
• 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)
[redacted]	
• 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]

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled study to evaluate the effects of SAGE-718 in participants with mild cognitive impairment (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 softgel lipid capsule orally once daily in the morning 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 (ie, 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).

Assessments will be performed as outlined in the Schedule of Assessments (Table 2) [redacted].

7.1.1. 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.

7.1.2. 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 and functional data. Participants and study partners will receive training on the study procedures and devices. [redacted]

7.1.3. 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 (Day 1 Visit to Day 42 Visit [±2 days]) followed by 0.9 mg of SAGE-718 for the remainder of the Treatment Period (ie, beginning the first day after the Day 42 Visit). Dosing ends at the Day 84 Visit (±7 days). All participants will receive blinded investigational product (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.

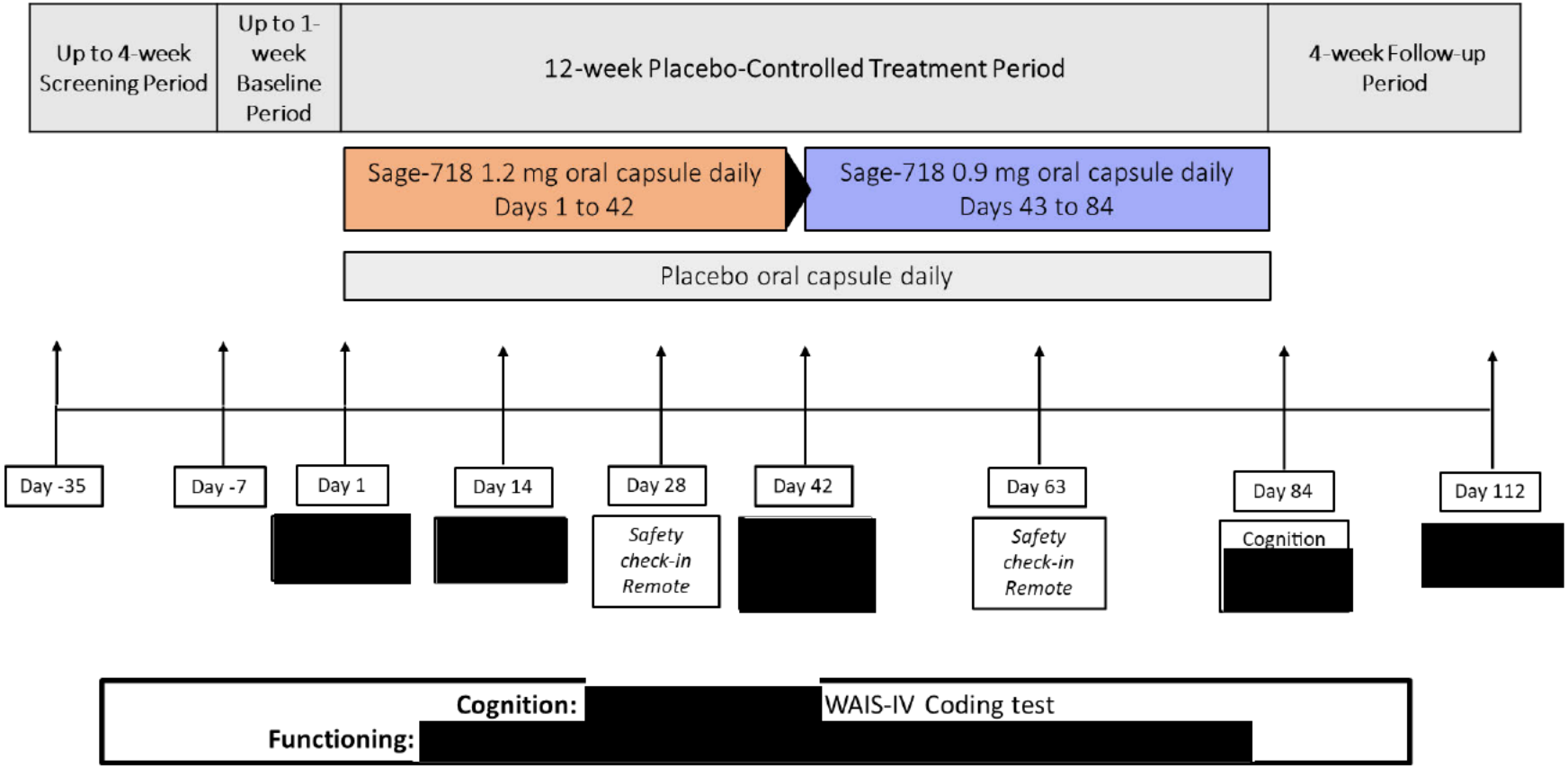
During the Treatment Period, participants will be able to receive IP if there are no dose limiting safety/tolerability concerns. Participants who discontinue IP should complete the remaining

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.

7.1.4. 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.

Note: See Table 2 for specific schedule of each test.

7.2. Number of Participants

Approximately 150 participants will be randomized to obtain up to 60 evaluable participants per treatment arm. Additional participants may be randomized if the early discontinuation rate is higher than expected. If the early discontinuation rate is lower than expected, enrollment may be closed once 120 evaluable participants have completed the study.

7.3. Treatment Assignment

Participants 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 softgel lipid capsule(s) orally once daily in the morning 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 (ie, 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).

7.4. Dose Adjustment Criteria

Individual dose reductions will be permitted.

During the Treatment Period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants who cannot tolerate 1.2 mg will receive 0.9 mg for the remainder of the Treatment Period.

If dose adjustment is deemed necessary by the investigator at any time during the Treatment Period, the participant will return to the site to return any remaining IP and for the adjusted dose to be dispensed.

At the discretion of the investigator, participants who cannot tolerate the 0.9-mg dose may be discontinued from further IP administration refer to Section 8.4 for procedures for early IP discontinuation). Participants will be encouraged to continue to come in for the remaining study-related periodic assessments even after the IP discontinuation.

7.4.1. Stopping Criteria

If clinical events suspicious for seizure occur after Screening, IP should be discontinued immediately with appropriate clinical follow-up, including electroencephalogram, serum chemistry, urinalysis, and drug/alcohol tests.

7.4.2. Dose Evaluation Committee

A Dose Evaluation Committee (DEC) will be convened at a reasonable time after the first 10 participants have completed the Treatment Period of the study [redacted]

[redacted]

A separate DEC charter will detail the data to be reviewed and will be agreed upon and signed prior to administration of the first dose of IP.

7.4.3. Criteria for Study Termination

Sage Therapeutics (The Sponsor) may terminate this study or any portion of the study at any time for safety reasons, including the occurrence of AEs or other findings suggesting unacceptable risk to participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their institutional review board (IRB)/independent ethics committee (IEC), where required, and initiate withdrawal procedures for participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Be capable of providing informed consent
2. Have signed an informed consent form (ICF) prior to any study-specific procedures being performed
3. Be willing and, in the opinion of the investigator, able to comply with study procedures
4. Be between the ages of 50 and 80 years, inclusive, at Screening
5. Meet the following criteria for MCI or mild dementia due to AD at Screening:
    a. A memory complaint reported by the participant or their study partner
    b. A Clinical Dementia Rating (CDR) score of 0.5 to 1.0 (inclusive) with a memory box score ≥0.5
    c. Essentially preserved activities of daily living, in the opinion of the investigator
    d. Brain MRI report, obtained within the 2 years preceding the Baseline Period, that is consistent with the diagnosis of AD with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment
6. Have a score of 15 to 25 (inclusive) on the MoCA with years of education adjustment at Screening
7. Have a study partner who, in the opinion of the investigator, is willing and able to provide informed consent, reliably support study-specific activities including IP adherence, be available by phone, and accompany the participant to study visits as needed
8. Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded) and able to travel to the study center
9. Have stable concomitant medication usage (dose and frequency) for at least 4 weeks prior to the first IP administration, and which is expected to remain stable for the duration of the study
10. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit
11. Agree, if female, to use an acceptable highly effective method of contraception during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy
12. Agree, if male, to use an acceptable method of highly effective contraception during the Treatment Period and for 21 days after receiving the last dose of IP, unless the participant does not engage in sexual relations that carry a risk of pregnancy
13. Agree, if male, to abstain from sperm donation during the Treatment Period and for 21 days after receiving the last dose of IP

8.2. Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer), unless the participant participated solely in the placebo arm of the study. Additionally, participants who have received treatment with antisense oligonucleotides (ASO) will be excluded
2. Have a condition that precludes undergoing an MRI, in accordance with standard operating procedures at the imaging facility (eg, ferromagnetic metal in the body, claustrophobia), in a participant requiring MRI during Screening
3. Have clinically significant comorbid medical conditions (eg, hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease), or a chronic condition that is unstable, or are taking concomitant medications that, in the opinion of the investigator, may make the participant unsuitable for inclusion or have the potential to compromise safety and/or compliance with study requirements
4. Have any medical or neurological condition (other than AD) that might be contributing to the participant's cognitive impairment or history of cognitive decline
5. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion, or other non-AD pathology) that is likely to call into question a primary clinical diagnosis of AD
6. Have a history, presence, and/or current evidence of
    a. Brain surgery, deep brain stimulation, or any history of hospitalization due to a brain injury
    b. Possible or probable cerebral amyloid angiopathy, according to the Boston Criteria (Greenberg 1995)
    c. Treatment with an anti-amyloid therapy (including biologics) without subsequent MRI demonstrating the absence of amyloid-related imaging abnormalities
    d. Seizures or epilepsy, with the exception of childhood febrile seizures
7. Have an alcohol or drug use disorder within the past 12 months as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria
8. Be receiving any of the following prohibited medications:
    a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine, within 4 weeks of IP administration and during the entire course of the study
    b. Medications that inhibit cholesterol absorption (eg, ezetimibe)
    c. Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)
    d. Other medications or supplements given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance

e. Cannabis or other tetrahydrocannabinol (THC)-containing substances (any route of administration), regardless of whether or not they are prescribed

9. Participant has a history of suicidal behavior within 2 years or answers "YES" to Questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
10. Have any of the following medical conditions:
    a. Any clinically significant finding on 12-lead ECG during Screening in the opinion of the investigator
    b. Any clinically significant supine vital signs (heart rate, systolic and diastolic blood pressure) during Screening (note: vital sign measurements may be repeated once)
11. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1 or HIV-2, or hepatitis B or C
12. Have a positive pregnancy test, or be lactating, or intend to breastfeed during the study
13. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted)
14. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.
15. Plans to undergo elective surgery or procedures during participation in the study.
16. Have a history of gastric bypass.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. Screen failure information will be collected, including, but not limited to demography, screen failure details, eligibility criteria, and any AE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, with the approval of the medical director or medical monitor. Rescreened participants will be assigned a new participant number.

8.4. Investigational Product Discontinuation and Early Termination from the Study

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study and/or from IP for safety, behavioral, compliance, or administrative reasons.

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's study record and in the participant's electronic case report form (eCRF).

8.4.1. Investigational Product Discontinuation

Participants who discontinue IP will be invited by the investigator to complete all of the scheduled study visits and assessments. Those who may decline to continue participation will be asked to complete an Early Termination Visit.

8.4.2. Early Termination from the Study

At the time of study withdrawal/stopping study participation, if possible, an early termination/end of treatment visit should be conducted. The participant will be permanently discontinued both from the IP and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.4.3. Lost to Follow-up

A participant will be deemed lost to follow-up after 3 attempts by different modes (eg, phone, email, letter) at contacting the participant have been made and it has been at least 1 month since the last participant contact. All attempts at contact and the reason for discontinuation will be documented. If the investigator becomes aware of a change in the participant's status or receives more information about a participant's disposition, this information will be documented.

8.4.4. Replacement of Participants

Participants who discontinue or withdraw from the study will not be replaced. However, additional participants may be dosed if the early discontinuation rate is higher than expected.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

SAGE-718 softgel lipid capsules are opaque, white to off-white, oval capsules containing either 1.2 mg or 0.9 mg of SAGE-718 Drug Substance. Placebo is matching in appearance.

9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements

9.2.1. Prior and Concomitant Medications and/or Supplements

All medications and supplements taken within 30 days prior to Screening, all medications used to treat AD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent [redacted] or cognitive manifestations of AD 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 collection at Screening and throughout the study.

At visits subsequent to Screening, all changes to any medication should be captured. All medications and/or supplements taken from the first dose of IP through the final study visit (including start and end dates, route, dose/units, frequency, and indication) will be recorded. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the Investigator at any time during the study.

Because this study aims to measure effects on cognitive performance, it is important to evaluate single or combined concomitant medications and their doses for their potential effects on cognition. Investigators will carefully review concomitant medications for possible cognitive effects at Screening and throughout the study, to determine participant eligibility.

9.2.2. Prohibited Medications

Treatment with an investigational drug, biologics or device is prohibited within the 30 days (or 5 half-lives of the IP, whichever is longer) prior to Screening and until the final Follow-up Visit.

During the course of the study, adjustment of medication or addition of medications that are known to affect cognitive performance (eg, stimulants, benzodiazepines, antipsychotics, anticholinergics) is to be avoided as much as possible. Any medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study, however, the use of any prohibited medications will be captured as a protocol deviation.

Use of the following medications is prohibited during the entire course of the study:

- Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine, within 4 weeks of IP administration and during the entire course of the study
- Medications that inhibit cholesterol absorption (eg, ezetimibe)
- Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)

- Other medications or supplements given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance
- Cannabis or other tetrahydrocannabinol (THC)-containing substances (any route of administration), regardless of whether or not they are prescribed

9.2.3. Other Restrictions

Participants must agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.

9.2.4. Acceptable Forms of Contraception

As per the Clinical Trials Facilitation and Coordination Group, a female is considered of childbearing potential eg, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by FSH >40 mIU/mL. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Acceptable forms of highly effective contraception (eg, can achieve a failure rate of <1% per year when used consistently and correctly) for participants of childbearing potential or for a male participant's partner of childbearing potential include:

- Sexual abstinence
- combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation;
- oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- intrauterine device;
- intrauterine hormone-releasing system;
- bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening);
- vasectomized partner (performed at least 3 months prior to Screening)
  (Note: vasectomy is a highly effective birth control method provided that partner is the sole sexual partner of the participants of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.)

Acceptable forms of contraception for male participants include:

- Sexual abstinence

- History of vasectomy (performed at least 3 months prior to Screening);
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods).

9.3. Intervention after the End of the Study

Not applicable.

9.4. Treatment Adherence

Beginning at the Day 1 Visit and continuing through the Day 84 Visit (±7 days), participants will self-administer blinded IP once per day in the morning.

At clinic visits, participants will self-administer the IP under staff supervision, followed by assessments of cognitive function, [redacted]. Study staff will dispense sufficient 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. This information will be documented along with any deviations from the prescribed dosage regimen. Details about IP accountability are included in Section 10.6.1.

9.5. Randomization and Blinding

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).

Participants, clinicians, and the study team will be blinded to treatment allocation. 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.

9.5.1. Emergency 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 Early Termination Visit should be completed after a participant's treatment assignment has been unblinded.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

SAGE-718 softgel lipid capsules are opaque, white to off-white, oval capsules containing 0.3, 0.6, 0.9, or 1.2 mg of SAGE-718 Drug Substance. The capsules are composed of SAGE-718 drug substance and butylated hydroxyanisole, gelatin, glycerin, glyceryl monocaprylate, glyceryl monolinoleate, lecithin, medium chain triglycerides, purified water, sorbitol, titanium dioxide, and vitamin E polyethylene glycol succinate as excipients.

Table 4: Investigational Product

Product Name:	SAGE-718 0.3 mg	SAGE-718 0.6 mg	SAGE-718 0.9 mg[a]	SAGE-718 1.2 mg[a]	Placebo
Dosage Form:	Softgel lipid capsule				
Unit Dose	0.3 mg	0.6 mg	0.9 mg	1.2 mg	Matching Placebo
Route of Administration	Oral				
Physical Description	Opaque, white to off-white, oval, softgel lipid capsule				
Manufacturer	[redacted]				

[a] SAGE-718 0.9 and 1.2 mg dose and matching placebo will be administered in this study.

10.2. Investigational Product Packaging and Labeling

SAGE-718 and matching placebo oral softgel lipid capsules are packaged in blisters using ACLAR® rigid barrier film and heat sealable foil lidding with an additional child resistant lid (refer to the pharmacy manual for further details).

The composition and pharmaceutical quality of the softgel lipid capsules will be maintained according to current Good Manufacturing Practice (GMP). Labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/Good Clinical Practice (GCP) guidelines and all other applicable regulations will be prepared by Sage Therapeutics.

10.3. Investigational Product Storage

Upon receipt of the IP, the Investigator, or the responsible pharmacist or designee, will inspect the product and acknowledge receipt in accordance with the study-specific process.

The IP must be carefully stored at the temperature specified in the SAGE-718 IB and (where applicable) in the pharmacy manual, securely and separately from other drugs. The IP may not be used for any purpose other than the present study. After the study is completed, all unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s). IP

may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding (if applicable), dispensing, inventory, and accountability of the IP. An accurate, timely record of the disposition of the IP must be maintained.

10.4. Investigational Product Preparation

SAGE-718 0.9 mg and 1.2 mg, or corresponding placebo will be provided as softgel lipid capsules for self-administration orally once daily in the morning through the Day 84 Visit (±7 days).

10.5. Investigational Product Administration

Each 0.9 or 1.2-mg dose of IP will be self-administered once daily in the morning.

Participants are to swallow the softgel lipid capsules whole with approximately 240 mL (8 fluid ounces) of water. For doses taken in the clinic, site staff will watch the participant self-administer the IP.

10.6. Investigational Product Accountability, Handling, and Disposal

10.6.1. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the Investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the SAGE-718 IB and (where applicable) in the pharmacy manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in Table 2.

Site staff will access the Interactive Response Technology (IRT) at the Screening Visit to obtain a participant identification (ID) number for each participant that has signed an ICF. On Day 1, site staff will access the IRT and provide the necessary participant-identifying information, including the participant ID number assigned at Screening, to randomize the eligible participant into the study and to obtain the medication ID number for the IP to be dispensed to that participant. The medication ID number and the number of softgel lipid capsules dispensed must be recorded.

At the subsequent IP-dispensing visits, the investigator or designee will access the IRT, providing the same participant ID number assigned at Screening, to obtain the medication ID number for the IP to be dispensed at that visit. The medication ID number, the number of softgel lipid capsules dispensed, and the number of softgel lipid capsules returned by the participant at this visit must be recorded.

If dispensing errors or discrepancies are discovered by site staff or Sponsor's designee, the Sponsor must be notified immediately.

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during and/or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP will be returned to Sage for destruction or destroyed locally per the site's procedures; disposition of IP will be documented.

More detailed information can be found in the SAGE-718 IB and (where applicable) in the pharmacy manual.

10.6.2. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY [redacted]

[redacted] cognitive function, [redacted]. All assessments are to be completed according to the Schedule of Assessments (Table 2) and [redacted].

An adult study partner is required for each participant to support completion of study activities and to answer questions about the participant's condition.

Participants will be required to take a short break (eg, 5 to 15 min) prior to beginning cognitive testing. The purpose of this break is to prepare for testing and to ensure maximal focus during the testing session. All cognitive assessments should be administered at approximately the same time of day (±2 hours) throughout the study in the following order: WAIS-IV Coding, [redacted]. When applicable, cognitive tests should be administered predose at the Day 1 Visit, [redacted] and Day 84 Visit (±7 days), and pre-laboratory assessments at the Day 112 Visit (±7 days). Cognitive, [redacted] assessments will be administered postdose during the rest of the Treatment Period. For clinician administered scales, the same individual should administer the scale when possible.

[redacted] It is recommended that the assessments are completed at approximately the same time each day, within 2 hours following IP administration. [redacted] If in conflict with clinic visit schedule, remote assessment may be completed in the clinic under observation by the study staff.

11.1. Cognitive Assessments

11.1.1. [redacted]

[redacted]

11.1.1.1. [redacted]

[redacted]

11.1.1.2. [redacted]

[redacted]

[redacted]

11.1.1.3. [redacted]

[redacted]

11.1.1.4. [redacted]

[redacted]

11.1.1.5. [redacted]

[redacted]

11.1.2. [redacted]

[redacted]

[redacted]

[redacted]

11.1.3. [redacted]

[redacted]

11.1.4. Wechsler Adult Intelligence Scale-IV Coding Test

The Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding Test is a valid and sensitive measure of cognitive dysfunction impacted by many domains (Erdodi 2020; Girard 2015; Wechsler 2009). 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 will be performed as outlined in Table 2.

11.2. [redacted]

11.2.1. [redacted]

[redacted]

11.2.2. [redacted]

[redacted]

11.2.3. [redacted]

[redacted]

11.3. [redacted]

11.3.1. [redacted]

11.3.1.1. [redacted]

[redacted]

11.3.2. [redacted]

11.3.2.1. [redacted]

[redacted]

11.3.2.2. [redacted]

[redacted]

11.3.2.3. [redacted]

[redacted]

11.3.2.4. [redacted]

[redacted]

[redacted]

11.3.3. [redacted]

11.3.3.1. [redacted]

[redacted]

11.3.3.2. [redacted]

[redacted]

11.3.3.3. [redacted]

[redacted]

11.4. [redacted]

11.4.1. [redacted]

[redacted]

[redacted]

[redacted].

11.4.1.1. [redacted]

[redacted]

[redacted]

[redacted]

11.4.1.2. [redacted]

[redacted]

11.4.2. [redacted]

[redacted]

11.4.3. [redacted]

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2) [redacted].

Abnormalities in physical examinations, vital signs, ECGs, MRI, and out of range values in laboratory test results will be interpreted by an investigator as clinically significant (CS) or not clinically significant (NCS) in the source documents.

Information about COVID-19 diagnosis, treatment, and quarantine status will be collected with medical history, AEs, and prior and concomitant medications.

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity, years of education, years of employment and current employment status) and a full medical history will be documented.

Full medical history of each participant will include history of AD (for participant and family), medications and supplements taken within 30 days prior to Screening, medications used to treat AD regardless of timing, and nonpharmacological methods (eg, 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.

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index (BMI) will be derived.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations.

A full physical examination will be conducted during Screening and at the Day 84 Visit (±7 days; End of Treatment). At other visits (Table 2), 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 abnormality in physical examinations will be interpreted by the investigator as abnormal, NCS, or abnormal, CS, in source documents.

12.1.4. COVID-19 Questions

Detailed information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 and COVID-19 vaccine history will be documented as part of medical history. In addition, information focused on COVID-19 (eg, AE collection, and prior/concomitant medication) will be collected at Screening and throughout the study.

12.1.5. Vital Signs

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.

Any abnormality in vital signs will be interpreted by an investigator as abnormal, NCS; or abnormal, CS in source documents.

12.1.6. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the time points described in Table 2. The standard intervals (heart rate, PR, QRS, QT, and QT corrected according to Fridericia's formula [QTcF]) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, procedures should be carried out in said order (vital signs, ECG, blood draw).

All abnormal ECGs will be interpreted by the investigator as CS or NCS in source documents.

12.1.7. Magnetic Resonance Imaging

Participants without documented MRI results that fulfill aforementioned entry criteria will undergo structural MRI of the brain. This assessment will be conducted according to the standard operating procedures (SOP) at the imaging center. The results will be reviewed by a qualified radiologist to assess for the presence of non-AD pathology that could account for the participant's observed cognitive impairment, and the site investigator will determine the clinical significance of these findings.

12.1.8. Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 5.

Table 5: Summary of Clinical Laboratory Analytes

Biochemistry	Renal Panel: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate Hepatic Panel: albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, total protein, lactate dehydrogenase, gamma glutamyl transferase Other: triglycerides, cholesterol (low density lipoprotein [LDL], high density lipoprotein [HDL]), creatine phosphokinase, thyroid stimulating hormone [TSH] and reflex to free triiodothyronine (T3) and thyroxine (T4) if TSH is abnormal.
Hematology	Red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]).

Urinalysis	Protein, glucose, pH, blood, leukocytes, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio
Serology (screening only)	Hepatitis B and C screening tests, human immunodeficiency virus (HIV)-1 and -2 antibody

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents.

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.

12.1.8.1. Drugs of Abuse, Alcohol

Separate urine samples for assessment of selected drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabis/THC, cocaine, and opiates) will be collected. A breath test for alcohol will be performed.

12.1.8.2. Pregnancy Testing

A serum pregnancy test will be conducted for all female participants at Screening; a urine pregnancy test will be conducted at other scheduled time points for female participants that are not postmenopausal or surgically sterile.

12.1.9. [redacted]

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no IP has been administered.

A TEAE is defined as an AE with onset after the start of IP, or any worsening of a pre-existing medical condition/AE with onset after the start of IP and throughout the study. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical study.

Laboratory abnormalities and changes from baseline in vital signs, and ECGs are considered AEs if they result in discontinuation or interruption of IP, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the Investigator considers them to be CS. Any abnormalities that meet the criteria for a SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs and ECGs that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the informed consent and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Participants who discontinue the IP due to an AE, regardless of Investigator-determined causality, should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer CS. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor or its representative retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event Definition

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

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the Investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an Investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

12.2.3. Definition of Urgent Safety Measure and Unanticipated Problem

In accordance with Article 10(b) of Directive 2001/20/EC, some reported events may result in an urgent safety measure, defined as an action that the sponsor and investigator may take in order to protect the participants of a study against any immediate hazard to their health or safety. Examples of USMs include:

- suspension of enrollment due to significantly higher incidence of death at one site
- additional clinical or non-clinical investigations performed due to increased frequency of AEs
- halting a clinical study for safety reasons

In accordance with Food and Drug Administration Guidance 21 Code of Federal Regulations Part 312.66, some reported events may qualify as an unanticipated problem, defined as any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (i) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (ii) the characteristics of the population being studied; related or possibly related to an individual's participation in the study; and
- suggests the study may place the participant or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the study than was previously known or recognized.

Any unanticipated problem must be reported within 24 hours via email to sage.safety@IQVIA.com upon discovery due to the urgent reporting requirements to regulators and IRB(s)/ECs(s).

12.2.4. Relationship to Investigational Product

The Investigator must make the determination of relationship to the IP for each AE (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this

	assessment include but are not limited to the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE.

12.2.5. Recording Adverse Events

AEs spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset date (and time, where applicable), resolution date (and time, where applicable), intensity, causality, action taken, outcome and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)
- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage and designee (see Table 1) within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage or designee.

Additional follow-up information, if required or available, should all be sent to Sage and designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

Serious adverse events occurring after the designated follow up time for the study, should be reported to Sage and designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage or designee, are responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site, as required by local law. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. IRBs/IECs will be notified of SAEs and/or SUSARs as required by local law.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARS to Investigators in a blinded fashion.

12.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the Pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy. The Investigator will also attempt to collect pregnancy information on any participant's partner who becomes pregnant after the participant has received the first administration of IP. After obtaining the necessary signed informed consent from the pregnant partner directly, the Investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

The participant or participant's partner will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The Investigator will collect follow-up information on the participant or participant's partner and the neonate, and the information will be forwarded to Sage or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, pre-eclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death,), the Investigator should follow the procedures for reporting an SAE.

The investigator will permanently withdraw the participant from IP if the participant becomes pregnant.

12.4. Special Considerations

Drug abuse is the persistent or sporadic, intentional excessive use of IP which is accompanied by harmful physical or psychological effects in the participant. If an event of drug abuse occurs during the study, it must be reported to the sponsor and designee (see Table 1) using the Special Considerations Form within 24 hours of the site becoming aware of the event(s). If the drug abuse results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

Drug misuse refers to situations where IP is intentionally and inappropriately used not in accordance with the intended use as specified in the protocol. If an event of drug misuse occurs during the study, it must be reported to the sponsor and designee using the Special Considerations Form within 24 hours of the site becoming aware of the event(s). If the drug misuse results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

An overdose is any dose of IP given to a participant or taken by a participant that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on the Special Considerations Form and sent to Sage and designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage and designee even if the overdose does not result in an AE. If an overdose results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

A medication error is any preventable event that may cause or lead to inappropriate medication use or participant harm while the medication is in the control of the healthcare professional, participant, or consumer. All medication errors must be recorded on the Special considerations form and sent to the sponsor and designee within 24 hours of the site becoming aware of the medication error. The medication error must be reported to the sponsor and/or designee even if the medication error does not result in an AE. If a medication error results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

13. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. Any changes/additions to the SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

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

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

The Full Analysis Set (FAS) will include all participants in the Safety Set who have baseline and at least 1 postbaseline efficacy evaluation. The FAS will be used to describe the efficacy data. Analyses will be based on the randomized treatment.

[redacted]

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all nonmissing data available. No imputation process will be used to estimate missing data. However, a sensitivity analysis will be used to investigate the impact of missing data if >5% of participants in any treatment group have missing data in the primary endpoint.

13.3. General Considerations

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 listings, 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.

Unless otherwise specified, baseline is defined as the last measurement prior to the first dose of IP.

Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum, maximum, Q1, and Q3. In addition, change from baseline values will be calculated at each time point and will be summarized using the same summary statistics. Out of range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, summaries will include counts and percentages.

Descriptive summary statistics will be provided for demographics, baseline characteristics, and total disposition, including the number of participants enrolled and the percentage of participants who discontinued from the study, along with reasons for discontinuations.

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, 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 the Safety Set.

Pregnancy test results and drug and alcohol test results will be listed but not summarized.

Medical history will be summarized and listed by participant.

13.5. Efficacy Analysis

Descriptive statistics of scores and change from baseline scores at each postbaseline assessment will be summarized based on the Full Analysis Set according to randomized treatment. Cognitive test scores endpoints will also be analyzed using a mixed effects model for repeated measures. The model will include change from baseline scores as dependent variable; treatment, visit, and visit by treatment interaction as fixed effects; participants as random effects; and baseline cognitive test scores as a covariate. An unstructured covariance matrix will be used to model the within-subject correlation. If the convergence criteria are not met, other covariance matrix will be used and more details will be described in the SAP. Model-based point estimates (ie, least square means, 95% confidence intervals, and associated p values) at each time point (visit) will be reported where applicable. Line plots of change from baseline scores will be plotted with standard error bars. [redacted]

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 participants with MCI or mild dementia due to AD.
3) The variable of interest is the change from baseline in WAIS-IV Coding Test total correct score at Day 84.
4) The intercurrent events could be:
    a) The premature discontinuation of treatment for any reason, thus not having a Day 84 WAIS-IV Coding Test total correct score available. The treatment policy strategy will be used.
    b) Certain medications including, but not limited to, medications with potent effects at the NMDA receptor, including memantine, medication that inhibit cholesterol absorption, bile acid sequestrants 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 tetrahydrocannabinol (THC)-containing substances.

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 total correct score at Day 84.

Additional analyses will be detailed in the SAP.

13.5.1. Multiplicity Adjustment

Not applicable.

13.5.2. Sensitivity Analyses

Sensitivity analysis is planned based on multiple imputation of missing values for different reason of discontinuation if >5% participants in any treatment group have missing data in primary endpoint, details will be provided in SAP.

13.6. Safety Analyses

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher. The proportion of participants experiencing TEAEs will be displayed by treatment group and by system organ class and preferred term. The frequency of TEAEs will also be presented by maximum severity and relationship to IP and by treatment group. Observed and change from baseline in vital signs, laboratory parameters, ECGs, [redacted] data will be summarized by treatment group. All safety summaries will be performed on the Safety Set.

Additional analyses will be detailed in the SAP.

13.6.1. Adverse Events

A TEAE is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by system organ class and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to discontinuation or interruption of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized.

All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

13.6.2. Clinical Laboratory Evaluations

Results of clinical laboratory parameters in each scheduled visit and mean changes from baseline will be summarized in standard units. Normal ranges for each parameter will be provided by the laboratory; shift from baseline to postbaseline values in abnormality of results will be provided. Potentially CS values will be summarized by treatment. Clinical laboratory results will be listed by participant and timing of collection.

13.6.3. Physical Examinations

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

13.6.4. Vital Signs

Vital sign results at each visit and mean changes from baseline will be summarized by scheduled visit. Potentially CS values will be summarized by treatment. Vital sign results will be listed by participant and timing of collection.

13.6.5. 12-Lead Electrocardiogram

Electrocardiogram data will be summarized by visit. Potentially CS values of QTcF will be summarized by treatment. ECG findings will be listed by participant and visit.

13.6.6. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary March 2021, or later.

All medications and supplements taken within 30 days prior to Screening, all medications used to treat AD regardless of timing, are to be recorded. Those medications taken prior to the first dose of IP will be denoted "Prior". Those medications taken prior to the first dose of IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted "Concomitant".

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

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

13.6.7. [redacted]

[redacted]

13.6.8. Other Safety Analysis

Not applicable.

13.7. [redacted]

[redacted]

13.8. 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 in a previous study, we assume difference between placebo and the SAGE-718 group at the end of treatment (at Day 84) for primary endpoints of WAIS-IV Coding test total correct score is 2.5, 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 one interim analysis and one final analysis. This sample size and power are based on a two-sided test using an overall significance level of 0.05. One formal interim analysis may be conducted after approximately 60 participants have completed 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 DeMets 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 6 summarizes operating characteristics of this design based on 120 evaluable participants.

Table 6: Group Sequential Design

Repeated Analyses	Information Time	No of Participants	Boundaries for Efficacy	Boundary for Futility
Interim	0.5	60	2.796	0.4229
Final	1	120	1.977	

13.8.1. [redacted]

[redacted]

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Unless otherwise waived or addressed in another forum (eg, investigator meeting), before an investigational site can enter a participant into the study, a representative of Sage will visit the investigational study site to:

- Confirm the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, IP management, GCP/ICH GCP compliance, and the responsibilities of Sage or its representatives. Agreed upon site responsibilities will be documented in a Clinical Trial Agreement between Sage and the investigator.

During the study, a monitor from Sage or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRF with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, medical records, source documents, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an IEC/IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP/ICH GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately at InspectionNotification@sagerx.com if contacted by a regulatory agency or IRB/IEC about an inspection.

14.3. Institutional Review Board or Independent Ethics Committee

The principal investigator must obtain IRB (or IEC) approval for the clinical study prior to enrolling a participant. Initial IRB (or IEC) approval, and all materials approved by the IRB (or IEC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 14.2 for more details regarding the audit process.

The investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Protocol deviations that harm or increase the possibility of harm to the rights and welfare of a participant, or a deviation made without prior IRB/IEC approval to eliminate an immediate hazard to the participant should be reported to the IRB/IEC per the IRB/IEC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site. When the investigator retains the services of any individual or party to perform study-related duties and functions, the investigator must ensure the individual or party is qualified to perform study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary to provide clarification.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be given a written and dated approval or favorable opinion by an IRB or IEC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or IEC must supply to the sponsor a list of the IRB/IEC membership and a statement to confirm that the IRB/IEC is organized and operates according to GCP and applicable laws and regulations.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/IEC and sponsor of any changes significantly affecting the conduct of the study and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

16.3. Written Informed Consent

Prior to enrolling a study participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the study, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent that is approved by the IRB/IEC for this protocol. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source records. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the study participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be

documented in the participant's source records, and when applicable, an updated ICF will be provided.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

Inspection of the study by a Regulatory Authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the Regulatory Authority representative(s).

17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

All information concerning SAGE-718 is considered confidential and shall remain the sole property of Sage Therapeutics. The investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the investigator.

19. LIST OF REFERENCES

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Protocol 718-CNA-202, Amendment 1

Date of Amendment: 22 December 2023

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

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to address the following recommendations, queries, emerging study results or correction of inadvertent errors, including:

- Increased the duration of the Screening Period to up to 4 weeks (Days -35 to Day -8) to increase flexibility for participants to complete the screening assessments within the time frame (Synopsis, Schedule of Assessments [Table 2]).
- Revised the duration of the Baseline Period to be "up to 1 week" to allow flexibility (Synopsis, Figure 1).
- The study schematic was updated to reflect changes in Screening Period and Baseline Period durations (Synopsis, Figure 1).
- [redacted]
- Increased the window for the Day 84 Visit and the Day 112 Follow-up Visit to ±7 days to increase flexibility and removed language that no dosing is permitted beyond Day 84 (Synopsis, Schedule of Assessments [Table 2], [redacted], Section 5.2, Section 7.1, Section 7.1.3, Section 7.3).
- Throughout the protocol, text referring to study days was updated to reflect the corresponding study visit and window for clarity.
- The optional, [redacted] was removed throughout the protocol (Synopsis, Schedule of Assessments [Table 2], previous Section 11.3.4). Based on resourcing and time considerations, the team is considering alternate options to collect participant experience data outside study protocol.
- Corrected the randomization text to state that approximately 150 participants will be randomized, instead of dosed, to obtain up to 60 evaluable participants per treatment arm (Synopis, Section 7.2).
- The following changes were made to the Inclusion and Exclusion Criteria (Synopsis, Section 8.1, Section 8.2):
  - Inclusion criterion #6 was revised to add years of education adjustment for Montreal Cognitive Assessment (MoCA).

  - Exclusion criterion #5 was revised to remove "clinically significant" from intracranial abnormality.
  - Exclusion criterion #9 was revised to ensure participants at risk are identified and to provide clarity to investigators on suicidal behavior and ideation that leads to exclusion.
  - Exclusion criterion #10b was revised to remove specific ranges for vital signs to ensure the vital signs are reviewed for clinical significance based on the population being studied by the investigator.
  - Exclusion criterion #15 was added to exclude participants to plan to undergo surgery during study participation.
  - Exclusion criterion #16 was added to excluded participants with a history of gastric bypass.
- Sample size text was revised to describe that an interim analysis may be performed, as one is not currently planned to perform due to fast participant enrollment (Synopsis, Section 13.8). The original protocol planned to perform one interim analysis and one final analysis using the group sequential method, and the significance level was based on the type I error spending function of Lan and DeMets to maintain the overall 0.05 significance level. Therefore, the interim analysis portion will remain in the sample size section of the protocol and will be addressed in the SAP. The original sample size was estimated based on two-sided test using an overall significance level of 0.05 and sample size will not be impacted by removing the interim analysis. The final analysis will be performed at the 2-sided significant level of 0.05.
- The description of the planned interim analysis was removed (Section 13.8.1).
- The data analysis set descriptions were updated to provide more detail (Synopsis, Section 13.1).
- An updated description of the results from Study 718-CNA-201 was added to the Introduction (Section 5).
- The description of adverse events was updated in the Benefit Risk section (Section 5.1).
- The description of the Follow-up Period was revised to include some cognition [redacted], which were inadvertently omitted (Section 7.1.4).
- Acceptable forms of contraception were updated to align with the SAGE-718 program (Section 9.2.4).
- [redacted]
- [redacted]

- The statement that body mass index "will be calculated" was changed to "will be derived" to indicate it will be done as part of the analyses (Section 12.1.4).
- The Overdose section was replaced with the Special Considerations section, which was implemented via Administrative Letter #1, and it is being formally added to the protocol with this amendment (Section 12.4).
- The Efficacy Analysis section was revised to simplify the list of endpoints and add a description of the covariance matrix (Section 13.5).
- Sunwoo et al, included in error, was removed from the list of references (Section 19).
- Minor textual changes have been made throughout the protocol to increase clarity on the procedures of the study.
- Study personnel and related administrative changes have been made based on changes to the study team.

Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting have been made.