Official Title:	**An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease**
NCT Number:	NCT04602624
Document Date:	Protocol Version 2.0: 24 September 2020

1. PROTOCOL AND AMENDMENTS

Version Number	Date	Title
2.0	23 Sep 2020	An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease V
2.0 SOC		Amendment 1 Summary of Changes
Admin. Letter #1	19 May 2021	Administrative Letter #1
1.0	11 May 2020	An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

AN OPEN-LABEL EVALUATION OF THE SAFETY AND TOLERABILITY OF SAGE-718 IN PARTICIPANTS WITH MILD COGNITIVE IMPAIRMENT OR MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE

PROTOCOL NUMBER: 718-CNA-201

Investigational Product	SAGE-718
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact and Medical Monitor	[redacted], MD [redacted] e-mail: [redacted] Phone: [redacted]
Date of Original Protocol	11 May 2020
Date of Amendment 1	23 September 2020

SPONSOR APPROVAL

Protocol Number: 718-CNA-201

Study Title: An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

Protocol Version and Date: Version 2, 23 September 2020

DocuSigned by: [redacted] 9/23/2020

[redacted], PhD Date (DD MMM YYYY)

[redacted]

DocuSigned by: [redacted] 9/23/2020

[redacted], MD Date (DD MMM YYYY)

[redacted]

DocuSigned by: [redacted] 9/23/2020

[redacted], MS Date (DD MMM YYYY)

[redacted]

DocuSigned by: [redacted] 9/23/2020

[redacted], MLA Date (DD MMM YYYY)

[redacted]

DocuSigned by: [redacted] 9/24/2020

[redacted] Date (DD MMM YYYY)

[redacted]

DocuSigned by: [redacted] 9/23/2020

[redacted], MD Date (DD MMM YYYY)

[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-718. I have read the 718-CNA-201 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

Role in Study	Name	Contact Details
Sage Study Physician	[redacted], MD	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142 [redacted] Phone: [redacted]
SAE Reporting	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 e-mail: [redacted] Fax: [redacted] SAE Hotline: [redacted]
Product Complaints Sage Therapeutics	Product Complaints Sage Therapeutics	e-mail: [redacted] Phone: [redacted]

2. SYNOPSIS

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

Name of Investigational Product:
SAGE-718 Oral Tablet

Name of Active Ingredient:
SAGE-718

Title of Study:
An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

Number of Sites and Study Location: Approximately 5 sites in the US

Phase of Development: 2

Planned Duration for each Study Participant: Each participant's involvement will be approximately 7 weeks, including a maximum 2-week Screening Period, a 1-week Baseline Period, a 2-week Treatment Period, and a 2-week Follow-up Period.

Objectives:

Primary Objective

- To evaluate the safety and tolerability of orally administered SAGE-718 in participants with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD)

[redacted]

Endpoints:

Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)

Secondary Endpoint

- Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms (ECGs), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS)

[redacted]

Study Description:

This is an open-label study evaluating the safety and tolerability of SAGE-718 and its effects on [redacted] in participants with MCI or mild dementia due to AD. Eligible participants will have a confirmed diagnosis of MCI or mild dementia due to AD, according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines, which will be confirmed via the Clinical Dementia Rating Dementia Staging Instrument® (CDR). Participants will self-administer 3.0 mg of SAGE-718 once daily in the morning for 14 days within 1 hour after initiating a meal containing approximately 30 g of fat. Dosing and morning food intake will be tracked in a participant diary. Assessments will be performed as outlined in the Schedule of Assessments (Table 2) [redacted]

In the setting of public health advisories due to COVID-19, assessments scheduled to be conducted at the study site may be performed via telephone/video if feasible. For assessments that cannot be conducted by phone or video, an in-home visit may be conducted.

Screening Period

The Screening Period will begin with the informed consent process for prospective participants, including study partners. Subsequent screening assessments will be performed between Day -21 and Day -8 to determine eligibility, including but not limited to: assessments of [redacted], vital

signs, clinical laboratory tests, electrocardiogram (ECG), magnetic resonance imaging (MRI) of the brain, and C-SSRS.

An electroencephalogram (EEG) will also be performed for all participants during Screening.

Baseline Period

The Baseline Period will occur from Day -7 through Day -1. During this period, each participant will receive dietary counseling to aid in choosing a morning meal containing approximately 30 g of fat to consume prior to dosing. On Day -7 (±1 day), participants will visit the clinic for confirmation of continued eligibility and collection of baseline [redacted] safety data. Additionally, participants will be trained on the use of a mobile data capture device to perform [redacted] and to document [redacted]. Participants will continue to complete these assessments daily during the Baseline Period, using the mobile device remotely (at home), with the support of a study partner. On Day -1, participants will return to the study site for confirmation of continued eligibility and collection of further baseline [redacted] safety data.

Treatment Period

Beginning on Day 1 and continuing through Day 14, participants will self-administer 3.0 mg of SAGE-718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after initiating a meal containing approximately 30 g of fat, in accordance with the guidelines provided in a nutritional information brochure. During this period, participants will continue to complete daily assessments of [redacted] via mobile device either remotely (at home) or in the clinic (at scheduled in-clinic visits) and will track investigational product (IP) dosing and predose food intake in a participant diary.

On Day 1, Day 7 (±1 day), and Day 14, participants will arrive at the clinic in the morning prior to IP dosing and completion of daily mobile device tasks. Following predose procedures (ie, body weight, vital signs, ECG, followed by blood and urine collection for clinical laboratory analyses, [redacted] and [redacted]), participants will eat a morning meal, then take the IP and complete the mobile device tasks under staff supervision.

At scheduled clinic visits during the Treatment Period, study staff will dispense a sufficient amount of SAGE-718 for daily administration until the next scheduled study visit. In addition to the clinic visits, study staff will contact participants by telephone on Day 4 to document any TEAEs and/or changes in concomitant medications.

Follow-up Period

Study staff will contact participants by telephone on Day 21 (±1 day) to document any TEAEs and/or changes in concomitant medications. Participants will return to the clinic on Day 28 (±2 days) for a follow-up visit.

Dose Evaluation Committee

At any time during the study, Sage may elect to form a Dose Evaluation Committee (DEC). If convened, this DEC will review the available data and provide recommendations for adjusting the dose, administration schedule, and/or food intake and make adjustments for subsequent participants, if appropriate (see Section 7.4.2).

Number of Participants (planned): Up to 22 participants will be dosed to obtain up to 20 participants that complete 14 days of dosing in this study. Additional participants may be dosed if the early discontinuation rate is >10%.

Eligibility Criteria:

Inclusion criteria

Each eligible participant must:

1. Be capable of providing informed consent

2. Have signed an informed consent form 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 his/her study partner
   b. A 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-MCI with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment
6. Have a score of 15 to 24 (inclusive) on the Montreal Cognitive Assessment at Screening
7. Have an estimated premorbid IQ ≥85 (as assessed by the Test of Premorbid Functioning, performed at Screening)
8. Have a study partner who is reliable, competent, at least 18 years of age, willing to be available to the study center by phone, support study-specific activities, and accompany the participant to study visits as needed
9. Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded), able to travel to the study center, and in the opinion of the investigator likely to be able to continue to travel to the study center to complete study visits for the duration of the study
10. Have stable concomitant medication usage per the following criteria:
    a. For psychotropic medications, including acetylcholinesterase inhibitors and other medications that are likely to have an effect on cognitive performance, the dose and frequency must remain stable for at least 12 weeks prior to the first IP administration and be expected to remain stable for the duration of the study
    b. For all other concomitant medications, the dose and frequency must remain stable for at least 4 weeks prior to the first IP administration and be expected to remain stable for the duration of the study
11. Agree, if female, to use an acceptable highly effective method of contraception (as defined in Section 9.2.4) 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 >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 (as defined in Section 9.2.4) during the 14-day Treatment Period and for 2 weeks 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 14-day Treatment Period and for 2 weeks after receiving the last dose of IP
14. Agree to refrain from drugs of abuse and alcohol for the duration of the study

Exclusion Criteria

Each eligible participant must not:

1. Have participated previously in a clinical study of SAGE-718, or have used any other investigational drug, biologic, or device or have participated in a clinical drug, biologic, or device study within 30 days or 5 half-lives (whichever is longer) prior to Screening
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, a chronic condition that is unstable or requires more than 2 medications to be controlled, or be 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 of brain surgery, deep brain stimulation, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury
6. Have a history, presence, and/or current evidence of a clinically significant 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 Alzheimer's Disease.
7. Have a history of possible or probable cerebral amyloid angiopathy, according to the Boston Criteria (Greenberg 1995)
8. Have a history of treatment with an anti-amyloid therapy (including biologics) without subsequent MRI demonstrating the absence of amyloid-related imaging abnormalities
9. Be receiving any of the following prohibited medications:
    a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including amantadine, ketamine, cycloserine, or related compounds
    b. Memantine within the 4 weeks prior to IP administration
    c. Medications that inhibit cholesterol absorption (eg, ezetimibe)
    d. Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)
    e. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as described in the 2019 American Geriatrics Society Updated Beers® Criteria for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019)
    f. Prescribed cannabis or other THC-containing substances
10. Have an alcohol or drug use disorder within the past 12 months, as per DSM-5 criteria
11. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood
12. Have current or recent suicidality, defined as follows:
    a. Suicidal ideation within the past month, as evidenced by a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) on the C-SSRS during Screening or Baseline

b. Suicidal behavior within the past year, as evidenced by a "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) on the C-SSRS during Screening or Baseline
c. Participant presents a serious risk of suicide in the opinion of the investigator

13. Have any of the following clinically significant medical conditions:
    a. Any clinically significant finding on 12-lead ECG during Screening or Baseline
    b. Supine vital signs outside of the following ranges during Screening or Baseline; vital sign measurements may be repeated once for initial values outside these ranges:
    c. Heart rate <50 or >100 bpm
    d. Systolic blood pressure <100 or >160 mmHg
    e. Diastolic blood pressure <60 or >100 mmHg
14. Have a history, presence, and/or current evidence of serologic positive results for HIV-1 or HIV-2
15. Have a positive pregnancy test or be lactating at Screening or Day -1
16. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted)

Investigational Product Dosage and Mode of Administration: SAGE-718 3.0 mg will be -self-administered as six 0.5-mg oral tablets, once daily in the morning within 1 hour after initiating a meal containing approximately 30 g of fat.

Duration of Treatment: 14 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 and 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

Safety Set will include all participants who were administered IP and will be used to describe the safety data.

[redacted]

Safety Analysis

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities with the overall incidence of AEs displayed by System Organ Class and preferred term. Incidence of TEAEs will also be presented by maximum severity, and relationship to IP. Data from vital signs, clinical laboratory analytes, ECGs, and C-SSRS will be summarized using descriptive statistics.

[redacted]

Sample Size Calculation

No formal sample size calculation was made for this study. Up to 20 participants completing 14 days of dosing are considered sufficient to assess preliminary safety and tolerability and for signal-finding of [redacted] after 14 days of repeated daily dosing with SAGE-718.

Assuming a 10% dropout rate, approximately 22 total participants will be required to obtain 20 completers. Additional participants may be dosed if the early discontinuation rate is >10%.

Table 2: Schedule of Assessments

Study Period	Screening	Baseline		Treatment				Follow Up	
Study Day	D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 [a]	D 7 (±1 d)	D 14 or ET	D 21 [a] (±1 d)	D 28 (±2 d)
Informed consent [b]	X								
Inclusion/exclusion criteria	X	X	X						
Medical history and demographics [c]	X								
Body weight	X			X		X	X		X
Body height	X								
CDR	X								
[redacted]									
Test of Premorbid Functioning	X								
Vital signs [d]	X	X	X	X		X	X		X
Physical examination [e]	X	X	X				X		
EEG [f]	X								
12-lead ECG [g]	X		X	X		X	X		X
C-SSRS [h]	X	X	X	X		X	X		X
Clinical laboratory tests [i]	X		X			X	X		X
Alcohol test [j]	X	X							
Urine drug test	X	X	X	X		X	X		
FSH test [k]	X								
Pregnancy test [l]	X		X				X		X
Serology test [m]	X								
MRI [n]	X								
[redacted]									
Participant training [p, q]		X	X						
[redacted]									

Study Period	Screening	Baseline		Treatment				Follow Up	
Study Day	D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 [a]	D 7 (±1 d)	D 14 or ET	D 21 [a] (±1 d)	D 28 (±2 d)
[redacted]									
Remote assessments [v]		X							
IP self-administration [w]				X (once daily)					
IP dispensation [x]				X		X			
IP accountability [y]				X					
Safety telephone call					X			X	
TEAEs/SAEs	X								
Concomitant medications [z]	X								

Abbreviations: CDR = Clinical Dementia Rating Dementia Staging Instrument®; C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; ECG = electrocardiogram; EEG = electroencephalogram; ET = early termination; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; IP = investigational product; MRI = magnetic resonance imaging; PET = positron emission tomography; [redacted]; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Notes: In the event of ET, efforts should be made to collect the Day 14 visit assessments.

When scheduled for the same time point, procedures should be performed in the following order: vital signs, ECG, blood draws, morning meal, IP dosing, then any scheduled postdose and/or [redacted].

In the setting of public health advisories due to COVID-19, assessments scheduled to be conducted at the study site may be performed via telephone/video if feasible. For assessments that cannot be conducted by phone or video, an in-home visit may be conducted. Information about COVID-19 diagnosis, treatment, and quarantine status will be collected with medical history, AEs, and prior and concomitant medications.

a Day 4 and Day 21 visits will occur via scheduled telephone calls.

b Both study partners and participants are to be consented during the Screening Period.

c In addition to full medical history, all nonpharmacological methods ([redacted]) used to treat or prevent [redacted] of AD are to be recorded.

d Vital signs to include temperature, respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position and standing position at all scheduled time points (see Section 12.1.4).

e Full physical examination to be conducted at Screening, abbreviated examinations thereafter (see Section 12.1.3).

f EEG to be performed for all participants during Screening. If indicated, an unscheduled 1-hour EEG will be performed for that participant (see Section 12.1.6).

g ECG will be measured after the participant has been in the supine position for at least 5 minutes.

h "Baseline/Screening" C-SSRS form at Screening and "Since Last Visit" C-SSRS form thereafter.

i Samples for clinical laboratory assessments, detailed in Table 4, to be collected ≤2 hours prior to dosing during the Treatment Period, and any time of day at other time points. Participants are to be in a fasted state for screening assessments only.

j Alcohol testing will be performed in the clinic, either by urine dipstick or breathalyzer.

k To confirm self-reported postmenopausal status in women only.

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

m To include testing for hepatitis B and C, HIV-1, and HIV-2

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

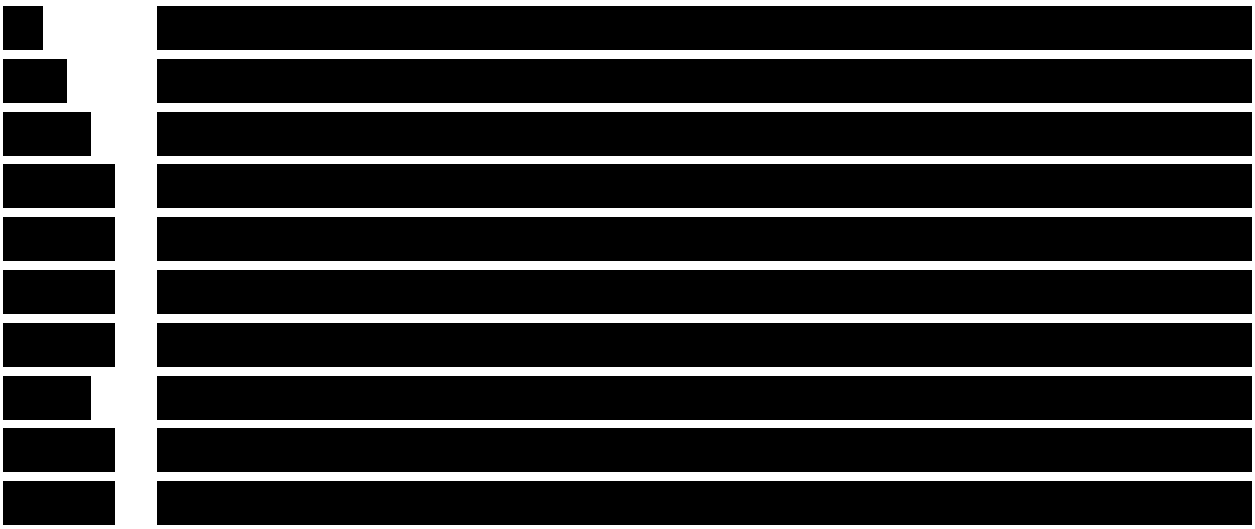
q Participants and study partners will be trained to use all study-related software and devices. Additional guidance will be provided on choosing a meal with approximately 30 g of fat.
r Includes select tests of the [redacted] (see Section 11.1). [redacted] tests are to be performed postdose during the Treatment Period and at approximately the same time of day (±2 hours) throughout the study.
s Includes [redacted]
t Measures directed to study partners may be administered by telephone or in person.
[redacted]
v Daily reminders will be sent to participants to complete assessments of [redacted] within 1 hour following IP administration, either remotely (at home) or in the clinic during the Treatment Period (with observation by study staff during scheduled clinic visits).
w On visit days during the Treatment Period, participants will self-administer IP in the clinic under the supervision of study staff after the predose assessments and consumption of a morning meal.
x Study staff will dispense sufficient IP for daily dosing at home until the next scheduled visit (see Section 9.4).
y On Days 7 and 14, participants will return used IP packaging and any unused IP for site staff to document.
z At Screening, include all psychotropic medications used within 12 weeks of informed consent, any other medications and supplements taken within 60 days of informed consent, and all medication used to treat AD, regardless of timing. After Screening, all changes to any medication or supplements should be captured.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]			
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]				[redacted]

[redacted]

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES



[redacted]

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
DEC	Dose Evaluation Committee
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
PET	positron emission tomography
[redacted]	[redacted]
QTcF	QT interval corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

5. INTRODUCTION

Diminished ability to learn and remember new information is the clinical hallmark of Alzheimer's disease (AD) and is associated with decreased quality of life and impaired functioning. Primary memory impairment tends to be followed by functional decline in networks that promote language, attention, executive functions, and visuospatial abilities (Weintraub 2012). SAGE-718 is hypothesized to correct disruptions in these large-scale neuroanatomical networks through positive allosteric activity at N-Methyl-D-aspartate (NMDA) receptors.

A subtype of glutamate receptors, NMDA receptors have a fundamental and well-documented role in regulating synaptic strength, health, and plasticity. The NMDA receptor antagonist memantine is approved as a treatment for AD, targeting glutamate excitotoxicity in later stages of the disease. However, blockade of NMDA receptor signaling can result in impaired neuroplasticity and cognitive deficits (Molinuevo 2005). Administration of a short-term NMDA partial agonist (D-cycloserine) in a small study of AD patients improved their scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale, suggesting that NMDA-enhancing agents can benefit cognition in AD (Tsai 1999).

SAGE-718 is a novel, oxysterol-based, positive allosteric modulator of NMDA receptors that modulates the response to endogenous glutamate (Paul 2013). SAGE-718 only affects receptor function in the presence of endogenous glutamate, thus it does not directly activate the receptor and is not expected to cause glutamatergic excitotoxicity. SAGE-718 has been well tolerated in both healthy participants and a small cohort of Huntington's disease participants in previous clinical studies. However, based on nonclinical findings, the US Food and Drug Administration imposed a maximum median concentration (C_{max}) cap of 45 ng/mL. To date, clinical studies have used doses that resulted in exposures within this cap; neither serious adverse events (SAEs) nor AEs leading to discontinuation have been reported. A once-daily 3-mg dose of SAGE-718 is not predicted to exceed a median C_{max} of 45 ng/mL. For additional information on exposure caps, see the SAGE-718 Investigator's Brochure.

A direct correlation between SAGE-718 Oral Tablet exposure and fat intake has been observed in healthy adults, with significantly lower exposure in fasting participants than in the same participants after moderate and high fat-containing meals. Additionally, as fat levels increased, exposure variability decreased, allowing for more predictable C_{max} levels. Thus, in this study SAGE-718 will be administered after consumption of a morning meal containing approximately 30 g of fat. Based on the data from healthy participants, this regimen is projected to produce a median C_{max} of approximately 35 to 40 ng/mL at steady state.

The safety, tolerability, and [redacted] of SAGE-718 Oral Tablet will be evaluated in this open-label study in individuals meeting diagnostic criteria for mild cognitive impairment (MCI) or mild dementia due to AD with otherwise stable neuropsychiatric symptoms. Additional data on the effects of SAGE-718 will be collected throughout, including assessments of [redacted].

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

6.1.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of orally administered SAGE-718 in participants with MCI or mild dementia due to AD

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)

6.2.2. Secondary Endpoint

- Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms (ECGs), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS)

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label study evaluating the safety and tolerability of SAGE-718 and its effects [redacted] in participants with MCI or mild dementia due to AD. Eligible participants will have a confirmed diagnosis of MCI or mild dementia due to AD, according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines, which will be confirmed via the Clinical Dementia Rating Dementia Staging Instrument® (CDR). Participants will self-administer 3.0 mg of SAGE-718 once daily in the morning for 14 days within 1 hour after initiating a meal containing approximately 30 g of fat. Dosing and morning food intake will be tracked in a participant diary. Assessments will be performed as outlined in the Schedule of Assessments (Table 2) [redacted].

At any time during the study, Sage may elect to form a Dose Evaluation Committee (DEC). If convened, this DEC will review the available data and provide recommendations for adjusting

the dose, administration schedule, and/or food intake and make adjustments for subsequent participants, if appropriate (see Section 7.4.2).

In the setting of public health advisories related to COVID-19, assessments scheduled to be conducted at the study site may be performed via telephone/video if feasible. For assessments that cannot be conducted by phone or video, an in-home visit may be conducted.

7.1.1. Screening Period

The Screening Period will begin with the informed consent process for prospective participants, including study partners. Subsequent screening assessments will be performed between Day -21 and Day -8 to determine eligibility, including but not limited to: assessments of [redacted], vital signs, clinical laboratory tests, electrocardiogram (ECG), magnetic resonance imaging (MRI) of the brain, and C-SSRS. An electroencephalogram (EEG) will also be performed for all participants during Screening.

7.1.2. Baseline Period

The Baseline Period will occur from Day -7 through Day -1. During this period, each participant will receive dietary counseling to aid in choosing a morning meal containing approximately 30 g of fat to consume prior to dosing. On Day -7 (±1 day), participants will visit the clinic for confirmation of continued eligibility and collection of baseline [redacted] safety data. Additionally, participants will be trained on the use of a mobile data capture device [redacted] Participants will continue to complete these assessments daily during the Baseline Period, using the mobile device remotely (at home), with the support of a study partner. On Day -1, participants will return to the study site for confirmation of continued eligibility and collection of further baseline [redacted] safety data.

7.1.3. Treatment Period

Beginning on Day 1 and continuing through Day 14, participants will self-administer 3.0 mg of SAGE 718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after initiating a meal containing approximately 30 g of fat, in accordance with the guidelines provided in a nutritional information brochure. During this period, participants will continue to complete daily assessments [redacted] via mobile device either remotely (at home) or in the clinic (at scheduled clinic visits) and will track investigative product (IP) dosing and predose food intake in a participant diary.

On Day 1, Day 7 (±1 day), and Day 14, participants will arrive at the clinic in the morning prior to IP dosing and completion of daily mobile device tasks. Following predose procedures (ie, body weight, vital signs, ECG, followed by blood and urine collection for clinical laboratory analyses, [redacted] participants will eat a morning meal, then take the IP and complete the mobile device tasks under staff supervision.

At scheduled clinic visits during the Treatment Period, study staff will dispense a sufficient amount of SAGE-718 for daily administration until the next scheduled study visit. In addition to the clinic visits, study staff will contact participants by telephone on Day 4 to document any TEAEs and/or changes in concomitant medications.

7.1.4. Follow-up Period

Study staff will contact participants by telephone on Day 21 (±1 day) to document any TEAEs and/or changes in concomitant medications. Participants will return to the clinic on Day 28 (±2 days) for a follow-up visit.

7.2. Number of Participants

Up to 22 participants are planned to be dosed to obtain up to 20 participants that complete 14 days of dosing in this study. Additional participants may be dosed if the early discontinuation rate is greater than 10%.

7.3. Treatment Assignment

In this open-label study, all participants will receive 3.0 mg of SAGE-718 once daily for 14 days.

7.4. Dose Adjustment Criteria

Dosing may be interrupted in an individual participant due to an AE considered by the investigator to be related to IP, however, no individual dose reductions will be permitted.

7.4.1. Stopping Criteria

If clinical events suspicious for seizure occur after Screening, an unscheduled EEG will be performed for review by an independent epileptologist to identify evidence of seizure activity (see Section 12.1.6). Should the independent epileptologist identify evidence for a subclinical or clinical seizure, dosing with SAGE-718 will be stopped for that participant.

7.4.2. Dose Evaluation Committee

At any time during this study, Sage may elect to form a DEC (preferably after at least 5 participants have completed 14 days of dosing). If convened, this DEC will be responsible for reviewing the available data and providing recommendations for adjusting the dose, administration schedule, or food intake recommendations for subsequent participants. The DEC will include, at a minimum, the Sage program medical lead, a Sage Drug Safety and Pharmacovigilance physician, and a clinical operations representative and will be supported by a Sage biostatistician.

7.5. Criteria for Study Termination

Sage Therapeutics 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 participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

To be eligible to enroll in this study, participants must:

1. Be capable of providing informed consent
2. Have signed an informed consent form 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 his/her study partner
    b. A 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 magnetic resonance imaging (MRI) report, obtained within the 2 years preceding the Baseline Period, that is consistent with the diagnosis of AD-MCI with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment
6. Have a score of 15 to 24 (inclusive) on the Montreal Cognitive Assessment at Screening
7. Have an estimated premorbid IQ ≥85 (as assessed by the Test of Premorbid Functioning, performed at Screening)
8. Have a study partner who is reliable, competent, at least 18 years of age, willing to be available to the study center by phone, support study-specific activities, and accompany the participant to study visits as needed
9. Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded), able to travel to the study center, and in the opinion of the investigator likely to be able to continue to travel to the study center to complete study visits for the duration of the study
10. Have stable concomitant medication usage per the following criteria:
    a. For psychotropic medications, including acetylcholinesterase inhibitors and other medications that are likely to have an effect on cognitive performance, the dose and frequency must remain stable for at least 12 weeks prior to the first IP administration and be expected to remain stable for the duration of the study
    b. For all other concomitant medications, the dose and frequency must remain stable for at least 4 weeks prior to the first IP administration and be expected to remain stable for the duration of the study
11. Agree, if female, to use an acceptable highly effective method of contraception (as defined in Section 9.2.4) 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 >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 (as defined in Section 9.2.4) during the 14-day Treatment Period and for 2 weeks 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 14-day Treatment Period and for 2 weeks after receiving the last dose of IP
14. Agree to refrain from drugs of abuse and alcohol for the duration of the study

8.2. Participant Exclusion Criteria

To be eligible to enroll in this study, participants must not:

1. Have participated previously in a clinical study of SAGE-718, or have used any other investigational drug, biologic, or device or have participated in a clinical drug, biologic, or device study within 30 days or 5 half-lives (whichever is longer) prior to Screening
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, a chronic condition that is unstable or requires more than 2 medications to be controlled, or be 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 of brain surgery, deep brain stimulation, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury
6. Have a history, presence, and/or current evidence of a clinically significant 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
7. Have a history of possible or probable cerebral amyloid angiopathy, according to the Boston Criteria (Greenberg 1995)
8. Have a history of treatment with an anti-amyloid therapy (including biologics) without subsequent MRI demonstrating the absence of amyloid-related imaging abnormalities
9. Be receiving any of the following prohibited medications:
    a. Medications with potent effects at the NMDA receptor, including amantadine, ketamine, cycloserine, or related compounds
    b. Memantine within the 4 weeks prior to IP administration

c. Medications that inhibit cholesterol absorption (eg, ezetimibe)

d. Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)

e. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as described in the 2019 American Geriatrics Society Updated Beers® Criteria for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019)

f. Prescribed cannabis or other THC-containing substances

10. Have an alcohol or drug use disorder within the past 12 months, as per DSM-5 criteria
11. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood
12. Have current or recent suicidality, defined as follows:
    a. Suicidal ideation within the past month, as evidenced by a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) on the C-SSRS during Screening or Baseline
    b. Suicidal behavior within the past year, as evidenced by a "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) on the C-SSRS during Screening or Baseline
    c. Participant presents a serious risk of suicide in the opinion of the investigator
13. Have any of the following clinically significant medical conditions:
    a. Any clinically significant finding on 12-lead ECG during Screening or Baseline
    b. Supine vital signs outside of the following ranges during Screening or Baseline; vital sign measurements may be repeated once for initial values outside these ranges:
        – Heart rate <50 or >100 bpm
        – Systolic blood pressure <100 or >160 mmHg
        – Diastolic blood pressure <60 or >100 mmHg
14. Have a history, presence, and/or current evidence of serologic positive results for HIV-1 or HIV-2
15. Have a positive pregnancy test or be lactating at Screening or Day -1
16. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted)

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 or are not entered in the study. A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAEs.

8.4. Investigational Product Discontinuation and Early Termination from the Study

8.4.1. Investigational Product Discontinuation

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 recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops participation in the study for any reason.

Participants who discontinue IP will be invited by the investigator to complete all of the scheduled study visits and assessments (except IP administration) through the end of the Treatment Period (Day 14). Those who decline continued participation through Day 14 will be asked to complete an Early Termination Visit.

8.4.2. Early Termination from the Study

For participants who are terminated from the study early, if possible, an Early Termination Visit should be conducted as described in Table 2. 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. Loss to Follow Up

A participant will be deemed lost to follow up after 3 attempts at contacting the participant have been unsuccessful.

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 Oral Tablets are immediate release, white to off-white, round tablets containing 0.5 mg of SAGE-718 Drug Substance.

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

9.2.1. Prior and Concomitant Medications and/or Supplements

To be eligible to participate in this study, any concomitant medications must have been taken at a stable dose and frequency for at least 4 weeks before the first IP administration and be expected to continue at that stable dose until the final study visit is complete. For psychotropic medications, including acetylcholinesterase inhibitors and other medications that are likely to have an effect on cognitive performance, the dose and frequency must have been stable for at least 12 weeks prior to the first IP administration and be expected to remain stable for the duration of the study.

The start and end dates, route, dose/units, frequency, and indication for all relevant medications and/or supplements will be recorded at Screening. Medications to be recorded include all psychotropic medications used within 12 weeks of informed consent, any other medications and supplements taken within 60 days of informed consent, and all medication used to treat AD, regardless of timing. After Screening, all changes to any medication or supplements 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 on the eCRF.

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 to determine participant eligibility and throughout the study.

9.2.2. Prohibited Medications

Treatment with an investigational drug 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 NMDA receptor, including memantine, amantadine, ketamine, cycloserine, or related compounds
- Medications that inhibit cholesterol absorption (eg, ezetimibe)
- Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)
- Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as described in the 2019 American

Geriatrics Society Updated Beers® Criteria for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019)

- Prescribed cannabis or other THC-containing substances

9.2.3. Other Restrictions

Participants must agree not to consume alcohol or any drugs of abuse (including marijuana) during the study.

9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- 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)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- 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

The investigator(s) or designated staff will observe the participant taking the first dose of IP to identify any potential risks to adherence (such as difficulty opening the packaging or swallowing the tablets). The time and dose of IP administration will be noted in the source documents. The clinician will provide instructions for self-administration of the IP and train the participant to track adherence to the IP regimen and food intake in a participant diary. At the Day 1, and Day 7 visits, a supply of IP will be dispensed for participants to take at home once daily until the next scheduled visit. Participants will be required to bring all components of the IP packaging,

including empty bottles and unused medication, and the participant diary to the clinic at every visit.

Adherence to the dosing regimen will be assessed at each in-clinic visit. Adherence will be assessed by reviewing the participant diary, examining the used packaging, and counting any tablets returned by the participant. This information will be documented in the source files and eCRF, along with any deviations from the prescribed dosage regimen. Details about IP accountability are included in Section 10.6.

9.5. Randomization and Blinding

This is an open-label study, in which all participants will received unblinded IP.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

SAGE-718 Oral Tablets are immediate release, white to off-white, round tablets containing 0.5 mg of SAGE-718 Drug Substance. The tablets are composed of SAGE-718 Drug Substance, mannitol, microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate.

10.2. Investigational Product Packaging and Labeling

SAGE-718 Oral Tablets are packaged in high density polyethylene bottles with desiccant, induction seal, and child-resistant closures.

The composition and pharmaceutical quality of the oral tablet 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. The site pharmacist or designee will prepare labels for individual doses.

10.3. Investigational Product Storage

SAGE-718 Oral Tablets should be stored in the supplied bottles with 1 g desiccant, capped with a child-resistant closure and induction seal, and stored at room temperature. Refer to the shipping documentation for product expiry information.

10.4. Investigational Product Preparation

The IP will be provided to the site in tablet form. It will be administered orally as described below.

10.5. Investigational Product Administration

Each 3.0-mg dose of IP will be self-administered as 6 tablets containing 0.5 mg of SAGE-718, once daily in the morning within 1 hour after initiating a meal containing approximately 30 g of

fat. Participants are to swallow the tablets 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

Upon receipt of IP, the pharmacist will inspect the IP and complete and follow the instructions regarding receipt and storage in the SAGE-718 Investigator's Brochure and in the pharmacy manual. A copy of the shipping documentation will be kept in the study files. The IP provided is for use only as directed in this protocol.

The investigator or designee must keep a record of all IP received, used, and returned/discarded. If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

Designated site staff will dispense the IP to participants at weekly clinic visits as outlined in the Schedule of Assessments (Table 2).

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Sage Therapeutics or designee will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation. At the end of the study, any unused IP will be returned to Sage Therapeutics for destruction or destroyed locally per standard operating procedures at the site; disposition of IP will be documented.

More detailed information can be found in the SAGE-718 Investigator's Brochure and in the pharmacy manual.

10.7. 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).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

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

Abnormalities in physical examinations, vital signs, electrocardiograms (ECGs), MRI, and out of range values in laboratory test results will be interpreted by an investigator as clinically significant or not clinically significant 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) and a full medical history will be documented. Premorbid IQ will be estimated by administration of the Test of Premorbid Functioning, which uses a word-reading scale to estimate premorbid cognitive and memory function in individuals with dementia (Wechsler 2009).

Medical history must include a confirmed diagnosis of MCI or mild dementia due to AD according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines. This diagnosis will be confirmed via the administration of the CDR. The CDR is a clinician-administered 5-point scale to characterize a patient's level of impairment due to dementia in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Morris 1993). In addition to full medical history, all nonpharmacological methods [redacted] used to treat or prevent [redacted] AD are to be recorded.

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index will be calculated and documented.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. A full physical examination will be performed at Screening, to include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) [redacted]. Thereafter, physical examinations will include brief assessments of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion.

12.1.4. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Systolic and diastolic blood pressure are to be measured after the participant has been supine for at least 5 minutes prior to the measurement. Orthostatic 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.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed at the time points described in Table 2. At each time point, the ECGs will be recorded in triplicate at 1-minute intervals. The standard intervals (heart rate, PR, QRS, QT, and 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).

12.1.6. Electroencephalogram

During Screening, EEG monitoring using the 10 to 20 international system for EEG electrode placement will occur for a duration of 1 hour. The assessment may be performed on any single day during the Screening Period, at any time of day, but preferably not while the participant is in a fasted state.

If clinical events suspicious for seizure occur after Screening (eg, episodes of altered consciousness and/or involuntary motor behaviors), an unscheduled 1-hour EEG will be performed for safety. An additional 1-hour EEG may be performed at the discretion of the investigator to follow up on results from any unscheduled EEG. The EEG recording will be reviewed by an independent epileptologist to identify evidence of seizure risk (eg, spikes or spike and wave discharges), subclinical seizure (eg, synchronous sharp waves and/or synchronous spike and wave discharges), seizure corresponding to a clinical event, or changes consistent with a postseizure state (eg, focal slowing and/or diffuse slowing). Should the independent epileptologist identify evidence for a subclinical or clinical seizure, dosing with SAGE-718 will be stopped for that participant. All EEG abnormalities suggestive of seizure risk or postseizure state will be reviewed by the study medical monitor.

12.1.7. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. will be collected for hematology, biochemistry, coagulation, urinalysis, and serology at the time points detailed in Table 2 and Table 3.

During Screening only, samples for clinical laboratory assessments will be collected from participants when they are in a fasted state.

Analytes to be evaluated are summarized in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	Renal Panel: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate Hepatic Panel: albumin, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase Other: triglycerides, cholesterol (LDL, HDL), creatine phosphokinase, thyroid stimulating hormone

Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if RBC indices are abnormal, reflex RBC morphology is indicated
Urinalysis	protein, glucose, pH, blood, leukocytes, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite
Serology (screening only)	hepatitis B surface antigen, hepatitis C IgM antibody, HIV-1 antibody, HIV-2 antibody

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal.

12.1.7.1. Pregnancy Testing

Serum pregnancy (human chorionic gonadotropin) tests will be conducted for all female participants during Screening; urine pregnancy tests will be conducted for all female participants that are not postmenopausal or surgically sterile at other scheduled time points. A urine pregnancy test will also be performed as part of the early termination assessments for participants who discontinue the study early.

12.1.7.2. Drugs of Abuse and Alcohol

Testing for selected drugs of abuse will be performed via urine dipstick at the study site (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, THC, and opiates). Alcohol use will be tested by either urine dipstick or breathalyzer at the study site.

12.1.8. Columbia–Suicide Severity Rating Scale

Suicidality will be monitored during the study using the C-SSRS (Posner 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the participant with suicidal ideation and behavior, and a postbaseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes ‘yes’ or ‘no’ responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The “Baseline/Screening” C-SSRS form will be completed at Screening (lifetime history and past 24 months). The “Since Last Visit” C-SSRS form will be completed at all subsequent time points outlined in Table 2.

12.1.9. 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 standard operating procedures 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.

12.2. 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 study treatment has been administered.

A TEAE is defined as an adverse event with onset after the start of IP, or any worsening of a preexisting medical condition/adverse event 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 study treatment, require therapeutic medical intervention, meet protocol-specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an 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.

Subjects 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 clinically significant. 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event Definition

A serious adverse event 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 informed consent form (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. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each adverse event (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.

12.2.4. Recording Adverse Events

Adverse events 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), resolution (date and time), 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 in Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.5. 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 or designee 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 or 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 or designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage, or designee, is 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. 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.

Sage, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law and investigators.

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, preeclampsia) 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.

12.4. Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the dose described in protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

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 Safety Set will include all participants who were administered IP and will be used to describe the safety data.

[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.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in participant data listings.

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to the first dose of IP.

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, maximum, Q1, and Q3. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, sex, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index, will be summarized using the Safety Set.

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

Medical history, MRI results, and amyloid-PET results will be listed by participant.

[redacted]

[redacted]

13.6. Safety Analyses

Safety and tolerability of SAGE-718 will be evaluated by TEAEs and change from baseline in vital signs, clinical laboratory analytes, ECGs, and responses on the C-SSRS. Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set.

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities version 22.0 or higher. 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 clinically significant 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 clinically significant values will be summarized by treatment. Vital sign results will be listed by participant and timing of collection.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. The derived mean of each parameter will also be listed. Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram 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 September 2015, or later.

At Screening, all psychotropic medications used by the participant within 12 weeks before informed consent, any other medications and supplements within 60 days before informed consent, and all medications used to treat AD, regardless of timing, will be recorded. After Screening, all changes to any medication or supplements should be captured. 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. Columbia–Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS at Baseline and by visit during the Treatment Period will be listed and summarized for all participants. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

[redacted]

13.8. Sample Size and Power

No formal sample size calculation was made for this study. Twenty participants completing 14 days of dosing are considered sufficient to assess preliminary safety and tolerability and for signal-finding [redacted] after 14 days of repeated dosing with of SAGE-718. Assuming a 10% dropout rate, approximately 22 total participants will be required to obtain 20 completers. Additional participants may be dosed if the early discontinuation rate is >10%.

13.8.1. Interim and Data Monitoring Committee Analysis

Not applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage standard operating procedures to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or its representatives. This will be documented in a Clinical Trial Agreement between Sage Therapeutics and the investigator.

During the study, a monitor from Sage Therapeutics 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms 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, 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 Independent Ethics Committee or an Institutional Review Board 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 and/or International Conference on Harmonisation (ICH) GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/IEC about an inspection.

14.3. Institutional Review Board or 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 Good Clinical Practice 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. Significant protocol deviations 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 Informed Consent Form, 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 investigational product. 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. 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 Informed Consent Form. A copy of the signed Informed Consent Form 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 investigational product. 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

American Geriatrics Society Beers Criteria Update Expert Panel. J Am Geriatr Soc. 2019 Apr;67(4):674-694. doi: 10.1111/jgs.15767. Epub 2019 Jan 29

Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgemont). 2007;4(7):28-37. Adapted from: Kay SR. Positive and negative symptoms in schizophrenia: Assessment and research (Monograph). Clinical and Experimental Psychiatry. 1991;5. Modified from Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration. 1976;218-22.

[redacted]

Greenberg SM, Rebeck GW, Vonsattel JP, et al. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann. Neurol. 1995;38 (2):254-9.

Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration. 1976.

Jutten RJ, Peeters CF, Leijdesdorff SM, et al. Detecting functional decline from normal aging to dementia: Development and validation of a short version of the Amsterdam IADL Questionnaire. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2017;8:26-35.

Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12:233-239.

Molinuevo J, et al. Memantine: Targeting glutamate excitotoxicity in AD and other dementias. Am Journal of AD & Other Dementias. 2005;77-85.

Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993;43:2412-2414

Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. J Am Ger Soc. 2005 Mar;53(4):695-699.

[redacted]

Paul SM, Doherty JJ, Robichaud AJ, et al. The major brain cholesterol metabolite 24(S)-hydroxycholesterol is a potent allosteric modulator of N-methyl-D-aspartate receptors. J Neurosci. 2013;33:17290-17300.

Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-77.

Tsai GE, et al. Improved cognition in Alzheimer's disease with short-term D-cycloserine treatment. Am J Psychiatry. 1999 Mar;156(3):467-9.

Wechsler D. Test of premorbid functioning. San Antonio, TX: The Psychological Corporation. 2009.

Weintraub S, et al. The neuropsychological profile of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(4):a006171.

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psych Res. 1983;17:37-49.

Protocol 718-CNA-201, Amendment 1

Date of Amendment: 23 September 2020

AN OPEN-LABEL EVALUATION OF THE SAFETY AND TOLERABILITY 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 revise the scheduled procedures and eligibility criteria to include more prospective participants. Changes to clarify the study design are outlined below:

- Revised the eligibility criteria requiring magnetic resonance imaging (MRI) results prior to screening, adding MRI to the procedures scheduled during screening for participants who do not have prior MRI results obtained within 2 years
- Added an eligibility criterion to exclude participants without acceptable previous MRI results who may have a condition that precludes undergoing an MRI
- Removed the eligibility requirement for documented evidence of a molecular marker of Alzheimer's Disease (AD) at screening
- [redacted]
- Clarified the exclusion criterion for intracranial abnormality to specify conditions likely to call into question a primary diagnosis of AD
- Included an explanation that some procedures/visits in the protocol may be performed virtually or via home visit, if necessary to respond to local COVID-19 risks, and that information related to participant COVID-19 status will be collected as medical history and collection of AEs and prior/concomitant medications
- [redacted] Minor textual changes have been made throughout the protocol to increase clarity on the procedures of the study.
- Minor corrections to typographical errors, punctuation, grammar, abbreviations, and formatting have been made

Sage Therapeutics™

o (617) 949.4256 f (617) 299.8379
215 First Street, Cambridge, MA 02142
www.sagerx.com

May 19, 2021

718-CNA-201 Protocol Administrative Letter #1

Study Title: An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

718-CNA-201 Clinical Sites:

This memo is to inform you of a clarification to the 718-CNA-201 Protocol Version 2.0 (Amendment 1), dated 23 September 2020. The clarification will be incorporated into the next protocol amendment and questions may be directed to the Sage or PRA study team. See clarification below in **bold**:

Section 12.1.6 Electroencephalogram:

- During screening, EEG monitoring using the 10 to 20 international system for EEG electrode placement will occur for a duration of **up to** 1 hour

Rationale: The missing detail was inadvertently omitted in the protocol. EEGs are intended to follow the standard clinical practice at the site and flexibility in duration is required.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 19-May-2021 | 11:30 EDT
[redacted]

[redacted], MD

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 19-May-2021 | 11:11 EDT
[redacted]

[redacted]

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I am the author of this document
Signing Time: 19-May-2021 | 10:18 EDT
[redacted]

[redacted] MS

AN OPEN-LABEL EVALUATION OF THE SAFETY AND TOLERABILITY OF SAGE-718 IN PARTICIPANTS WITH MILD COGNITIVE IMPAIRMENT OR MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE

PROTOCOL NUMBER: 718-CNA-201

Investigational Product	SAGE-718
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact and Medical Monitor	[redacted], MD [redacted] Phone: [redacted]
Date of Original Protocol	11 May 2020

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.

SPONSOR APPROVAL

Protocol Number: 718-CNA-201

Study Title: An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

Protocol Version and Date: Version 1, 11 May 2020

DocuSigned by:
[redacted]
5/11/2020
[redacted]
Date (DD MMM YYYY)
[redacted]

DocuSigned by:
[redacted]
5/11/2020
[redacted], MD
Date (DD MMM YYYY)
[redacted]

DocuSigned by:
[redacted]
5/11/2020
[redacted], MS
Date (DD MMM YYYY)
[redacted]

DocuSigned by:
[redacted]
5/12/2020
[redacted], MLA
Date (DD MMM YYYY)
[redacted]

DocuSigned by:
[redacted]
5/11/2020
[redacted]
Date (DD MMM YYYY)
[redacted]

DocuSigned by:
[redacted]
5/19/2020
[redacted], MD
Date (DD MMM YYYY)
[redacted]

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-718. I have read the 718-CNA-201 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

Role in Study	Name	Contact Details
Sage Study Physician	[redacted]	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142 Phone: [redacted]
SAE Reporting	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 e-mail: [redacted] Fax: [redacted] SAE Hotline: [redacted]
Product Complaints Sage Therapeutics	Product Complaints Sage Therapeutics	e-mail: [redacted] Phone: [redacted]

2. SYNOPSIS

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

Name of Investigational Product:
SAGE-718 Oral Tablet

Name of Active Ingredient:
SAGE-718

Title of Study:
An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease

Number of Sites and Study Location: Approximately 5 sites in the US

Phase of Development: 2

Planned Duration for each Study Participant: Each participant's involvement will be approximately 7 weeks, including a maximum 2-week Screening Period, a 1-week Baseline Period, a 2-week Treatment Period, and a 2-week Follow-up Period.

Objectives:

Primary Objective

- To evaluate the safety and tolerability of orally administered SAGE-718 in participants with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD)

[redacted]

Endpoints:

Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)

Secondary Endpoint

- Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms (ECGs), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS)

[redacted]

[redacted]

Study Description:

This is an open-label study evaluating the safety and tolerability of SAGE-718 and its effects [redacted] in participants with MCI or mild dementia due to AD. Eligible participants will have a confirmed diagnosis of MCI or mild dementia due to AD, according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines, which will be confirmed via the CDR® Dementia Staging Instrument. Participants will self-administer 3.0 mg of SAGE-718 once daily in the morning for 14 days within 1 hour after initiating a meal containing approximately 30 g of fat. Dosing and morning food intake will be tracked in a participant diary. 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, including study partners. Subsequent screening assessments will be performed between Day -21 and Day -8 to determine eligibility, including but not limited to: assessments of [redacted], vital signs, clinical laboratory tests, electrocardiogram (ECG),and C-SSRS.

An electroencephalogram (EEG) will also be performed for all participants during Screening, preferably not in a fasted state.

Baseline Period

The Baseline Period will occur from Day -7 through Day -1. During this period, each participant will

receive dietary counseling to aid in choosing a morning meal containing approximately 30 g of fat to consume prior to dosing. On Day -7 (±1 day), participants will visit the clinic for confirmation of continued eligibility and collection of baseline [redacted] safety data. Additionally, participants will be trained on the use of a mobile data capture device [redacted] Participants will continue to complete these assessments daily during the Baseline Period, using the mobile device remotely (at home), with the support of a study partner. On Day -1, participants will return to the study site for confirmation of continued eligibility and collection of further baseline [redacted] safety data.

Treatment Period

Beginning on Day 1 and continuing through Day 14, participants will self-administer 3.0 mg of SAGE-718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after initiating a meal containing approximately 30 g of fat, in accordance with the guidelines provided in a nutritional information brochure. During this period, participants will continue to complete daily assessments [redacted] via mobile device either remotely (at home) or in the clinic (at scheduled in-clinic visits) and will track investigational product (IP) dosing and predose food intake in a participant diary.

On Day 1, Day 7 (±1 day), and Day 14, participants will arrive at the clinic in the morning prior to IP dosing and completion of daily mobile device tasks. Following predose procedures (ie, body weight, vital signs, ECG, followed by blood and urine collection for clinical laboratory analyses, [redacted] participants will eat a morning meal, then take the IP and complete the mobile device tasks under staff supervision.

At scheduled clinic visits during the Treatment Period, study staff will dispense a sufficient amount of SAGE-718 for daily administration until the next scheduled study visit. In addition to the clinic visits, study staff will contact participants by telephone on Day 4 to document any TEAEs and/or changes in concomitant medications.

Follow-up Period

Study staff will contact participants by telephone on Day 21 (±1 day) to document any TEAEs and/or changes in concomitant medications. Participants will return to the clinic on Day 28 (±2 days) for a follow-up visit.

Dose Evaluation Committee

At any time during the study, Sage may elect to form a Dose Evaluation Committee (DEC). If convened, this DEC will review the available data and provide recommendations for adjusting the dose, administration schedule, and/or food intake and make adjustments for subsequent participants, if appropriate (see Section 7.4.2).

Number of Participants (planned): Up to 22 participants will be dosed to obtain up to 20 participants that complete 14 days of dosing in this study. Additional participants may be dosed if the early discontinuation rate is >10%.

Eligibility Criteria:

Inclusion criteria

Each eligible participant must:

1. Be capable of providing informed consent
2. Have signed an informed consent form 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 his/her study partner
   b. A 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. Documented evidence of a positive molecular marker for AD (either a positive amyloid positron emission tomography scan or β-amyloid and tau levels in cerebrospinal fluid that are consistent with underlying AD pathology)
   e. Documented magnetic resonance imaging (MRI) report consistent with the diagnosis of AD-MCI with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment
6. Have a score of 15 to 24 (inclusive) on the Montreal Cognitive Assessment at Screening
7. Have an estimated premorbid IQ ≥85 (as assessed by the Test of Premorbid Functioning, performed at Screening)
8. Have a study partner who is reliable, competent, at least 18 years of age, willing to be available to the study center by phone, support study-specific activities, and accompany the participant to study visits as needed
9. Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded), able to travel to the study center, and in the opinion of the investigator likely to be able to continue to travel to the study center to complete study visits for the duration of the study
10. Have stable concomitant medication usage per the following criteria:
    a. For psychotropic medications, including acetylcholinesterase inhibitors and other medications that are likely to have an effect on cognitive performance, the dose and frequency must remain stable for at least 12 weeks prior to the first IP administration and be expected to remain stable for the duration of the study
    b. For all other concomitant medications, the dose and frequency must remain stable for at least 4 weeks prior to the first IP administration and be expected to remain stable for the duration of the study
11. Agree, if female, to use an acceptable highly effective method of contraception (as defined in Section 9.2.4)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 >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 (as defined in Section 9.2.4) during the 14-day Treatment Period and for 2 weeks 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 14-day Treatment Period and for 2 weeks after receiving the last dose of IP
14. Agree to refrain from drugs of abuse and alcohol for the duration of the study

Exclusion Criteria

Each eligible participant must not:

1. Have participated previously in a clinical study of SAGE-718, or have used any other investigational drug, biologic, or device or have participated in a clinical drug, biologic, or

device study within 30 days or 5 half-lives (whichever is longer) prior to Screening

2. Have clinically significant comorbid medical conditions, a chronic condition that is unstable or requires more than 2 medications to be controlled, or be 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
3. Have any medical or neurological condition (other than AD) that might be contributing to the participant's cognitive impairment or history of cognitive decline
4. Have a history of brain surgery, deep brain stimulation, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury
5. Have a history, presence, and/or current evidence of an intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion)
6. Have a history of possible or probable cerebral amyloid angiopathy, according to the Boston Criteria (Greenberg 1995)
7. Have a history of treatment with an anti-amyloid therapy (including biologics) without subsequent MRI demonstrating the absence of amyloid-related imaging abnormalities
8. Be receiving any of the following prohibited medications:
    a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including amantadine, ketamine, cycloserine, or related compounds
    b. Memantine within the 4 weeks prior to IP administration
    c. Medications that inhibit cholesterol absorption (eg, ezetimibe)
    d. Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)
    e. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as described in the 2019 American Geriatrics Society Updated Beers® Criteria for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019)
    f. Prescribed cannabis or other THC-containing substances
9. Have an alcohol or drug use disorder within the past 12 months, as per DSM-5 criteria
10. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood
11. Have current or recent suicidality, defined as follows:
    a. Suicidal ideation within the past month, as evidenced by a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) on the C-SSRS during Screening or Baseline
    b. Suicidal behavior within the past year, as evidenced by a "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) on the C-SSRS during Screening or Baseline
    c. Participant presents a serious risk of suicide in the opinion of the investigator
12. Have any of the following clinically significant medical conditions:
    a. Any clinically significant finding on 12-lead ECG during Screening or Baseline
    b. Supine vital signs outside of the following ranges during Screening or Baseline; vital sign measurements may be repeated once for initial values outside these ranges:
        – Heart rate <50 or >100 bpm
        – Systolic blood pressure <100 or >160 mmHg
        – Diastolic blood pressure <60 or >100 mmHg

13. Have a history, presence, and/or current evidence of serologic positive results for HIV-1 or HIV-2
14. Have a positive pregnancy test or be lactating at Screening or Day -1
15. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted)

Investigational Product Dosage and Mode of Administration: SAGE-718 3.0 mg will be self-administered as six 0.5-mg oral tablets, once daily in the morning within 1 hour after initiating a meal containing approximately 30 g of fat.

Duration of Treatment: 14 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 and 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

Safety Set will include all participants who were administered IP and will be used to describe the safety data.

Full Analysis Set will include all participants who initiate IP and have baseline and at least 1 postbaseline [redacted] evaluation.

[redacted]

Safety Analysis

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities with the overall incidence of AEs displayed by System Organ Class and preferred term. Incidence of TEAEs will also be presented by maximum severity, and relationship to IP. Data from vital signs, clinical laboratory analytes, ECGs, and C-SSRS will be summarized using descriptive statistics.

[redacted]

Table 2: Schedule of Assessments

Study Period	Screening	Baseline		Treatment				Follow Up	
Study Day	D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 [a]	D 7 (±1 d)	D 14 or ET	D 21 [a] (±1 d)	D 28 (±2 d)
Informed consent [b]	X								
Inclusion/exclusion criteria	X	X	X						
Medical history and demographics [c]	X								
Body weight	X			X		X	X		X
Body height	X								
CDR®	X								
[redacted]									
Test of Premorbid Functioning	X								
Vital signs [d]	X	X	X	X		X	X		X
Physical examination [e]	X	X	X				X		
EEG [f]	X								
12-lead ECG [g]	X		X	X		X	X		X
C-SSRS [h]	X	X	X	X		X	X		X
Clinical laboratory tests [i]	X		X			X	X		X
Alcohol test [j]	X	X							
Urine drug test	X	X	X	X		X	X		
FSH test [k]	X								
Pregnancy test [l]	X		X				X		X
Serology test [m]	X								
[redacted]									
Participant training [o]		X	X						
[redacted]									

Study Period	Screening	Baseline		Treatment				Follow Up	
Study Day	D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 [a]	D 7 (±1 d)	D 14 or ET	D 21 [a] (±1 d)	D 28 (±2 d)
Remote assessments [t]		X							
IP self-administration [u]				X (once daily)					
IP dispensation [v]				X		X			
IP accountability [w]				X					
Safety telephone call					X			X	
TEAEs/SAEs	X								
Concomitant medications [x]	X								

Abbreviations: CDR = Clinical Dementia Rating Dementia Staging Instrument; C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; ECG = electrocardiogram; EEG = electroencephalogram; ET = early termination; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; IP = investigational product; [redacted]; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Notes: In the event of ET, efforts should be made to collect the Day 14 visit assessments.

When scheduled for the same time point, procedures should be performed in the following order: vital signs, ECG, blood draws, morning meal, IP dosing, then any scheduled postdose and/or [redacted].

In the setting of public health advisories or similar risks to patient safety, assessments scheduled to be conducted at the study site may be performed via telephone/video if feasible. For assessments that cannot be conducted by phone or video, an in-home visit may be conducted.

a Day 4 and Day 21 visits will occur via scheduled telephone calls.

b Both study partners and participants are to be consented during the Screening Period.

c In addition to full medical history, all nonpharmacological methods (eg, [redacted]) used to treat or prevent [redacted] of AD are to be recorded.

d Vital signs to include temperature, respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position and standing position at all scheduled time points (see Section 12.1.4).

e Full physical examination to be conducted at Screening, abbreviated examinations thereafter (see Section 12.1.3).

f EEG to be performed for all participants during Screening, preferably not in a fasted state. If indicated, an unscheduled 1-hour EEG will be performed for that participant (see Section 12.1.6).

g ECG will be measured after the participant has been in the supine position for at least 5 minutes.

h "Baseline/Screening" C-SSRS form at Screening and "Since Last Visit" C-SSRS form thereafter.

i Samples for clinical laboratory assessments, detailed in Table 4, to be collected ≤2 hours prior to dosing during the Treatment Period, and any time of day at other time points. Participants are to be in a fasted state for screening assessments only.

j Alcohol testing will be performed in the clinic, either by urine dipstick or breathalyzer.

k To confirm self-reported postmenopausal status in women only.

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

m To include testing for hepatitis B and C, HIV-1, and HIV-2

[redacted]

o Participants and study partners will be trained to use all study-related software and devices. Additional guidance will be provided on choosing a meal with approximately 30 g of fat.

[redacted]

[redacted]

t Daily reminders will be sent to participants to complete assessments [redacted] within 1 hour following IP administration, either remotely (at home) or in the clinic during the Treatment Period (with observation by study staff during scheduled clinic visits).
u On visit days during the Treatment Period, participants will self-administer IP in the clinic under the supervision of study staff after the predose assessments and consumption of a morning meal.
v Study staff will dispense sufficient IP for daily dosing at home until the next scheduled visit (see Section 9.4).
w On Days 7 and 14, participants will return used IP packaging and any unused IP for site staff to document.
x At Screening, include all psychotropic medications used within 12 weeks of informed consent, any other medications and supplements taken within 60 days of informed consent, and all medication used to treat AD, regardless of timing. After Screening, all changes to any medication or supplements should be captured.

[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]			[redacted]	[redacted]
[redacted]	[redacted]			
[redacted]				
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]				[redacted]

[redacted]

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

[redacted]

[redacted]

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
AD	Alzheimer's disease
AE	adverse event
[redacted]	[redacted]
DEC	Dose Evaluation Committee
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
QTcF	QT interval corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event

5. INTRODUCTION

Diminished ability to learn and remember new information is the clinical hallmark of Alzheimer's disease (AD) and is associated with decreased quality of life and impaired functioning. Primary memory impairment tends to be followed by functional decline in networks that promote language, attention, executive functions, and visuospatial abilities (Weintraub 2012). SAGE-718 is hypothesized to correct disruptions in these large-scale neuroanatomical networks through positive allosteric activity at N-Methyl-D-aspartate (NMDA) receptors.

A subtype of glutamate receptors, NMDA receptors have a fundamental and well-documented role in regulating synaptic strength, health, and plasticity. The NMDA receptor antagonist memantine is approved as a treatment for AD, targeting glutamate excitotoxicity in later stages of the disease. However, blockade of NMDA receptor signaling can result in impaired neuroplasticity and cognitive deficits (Molinuevo 2005). Administration of a short-term NMDA partial agonist (D-cycloserine) in a small study of AD patients improved their scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale, suggesting that NMDA-enhancing agents can benefit cognition in AD (Tsai 1999).

SAGE-718 is a novel, oxysterol-based, positive allosteric modulator of NMDA receptors that modulates the response to endogenous glutamate (Paul 2013). SAGE-718 only affects receptor function in the presence of endogenous glutamate, thus it does not directly activate the receptor and is not expected to cause glutamatergic excitotoxicity. SAGE-718 has been well tolerated in both healthy participants and a small cohort of Huntington's disease participants in previous clinical studies. However, based on nonclinical findings, the US Food and Drug Administration imposed a maximum median concentration (C_{max}) cap of 45 ng/mL. To date, clinical studies have used doses that resulted in exposures within this cap; neither serious adverse events (SAEs) nor AEs leading to discontinuation have been reported. A once-daily 3-mg dose of SAGE-718 is not predicted to exceed a median C_{max} of 45 ng/mL. For additional information on exposure caps, see the SAGE-718 Investigator's Brochure.

A direct correlation between SAGE-718 Oral Tablet exposure and fat intake has been observed in healthy adults, with significantly lower exposure in fasting participants than in the same participants after moderate and high fat-containing meals. Additionally, as fat levels increased, exposure variability decreased, allowing for more predictable C_{max} levels. Thus, in this study SAGE-718 will be administered after consumption of a morning meal containing approximately 30 g of fat. Based on the data from healthy participants, this regimen is projected to produce a median C_{max} of approximately 35 to 40 ng/mL at steady state.

The safety, tolerability, [redacted] of SAGE-718 Oral Tablet will be evaluated in this open-label study in individuals meeting diagnostic criteria for mild cognitive impairment (MCI) or mild dementia due to AD with otherwise stable neuropsychiatric symptoms. Additional data on the effects of SAGE-718 will be collected throughout, [redacted]

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

6.1.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of orally administered SAGE-718 in participants with MCI or mild dementia due to AD

[redacted]

6.2. Endpoints

6.2.1. Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)

6.2.2. Secondary Endpoint

- Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms (ECGs), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS)

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label study evaluating the safety and tolerability of SAGE-718 and its effects [redacted] in participants with MCI or mild dementia due to AD. Eligible participants will have a confirmed diagnosis of MCI or mild dementia due to AD, according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines, which will be confirmed via the CDR® Dementia Staging Instrument. Participants will self-administer 3.0 mg of SAGE-718 once daily in the morning for 14 days within 1 hour after initiating a meal containing approximately 30 g of fat. Dosing and morning food intake will be tracked in a participant diary. Assessments will be performed as outlined in the Schedule of Assessments (Table 2) [redacted]

At any time during the study, Sage may elect to form a Dose Evaluation Committee (DEC). If convened, this DEC will review the available data and provide recommendations for adjusting

the dose, administration schedule, and/or food intake and make adjustments for subsequent participants, if appropriate (see Section 7.4.2).

7.1.1. Screening Period

The Screening Period will begin with the informed consent process for prospective participants, including study partners. Subsequent screening assessments will be performed between Day -21 and Day -8 to determine eligibility, including but not limited to: assessments of cognitive function, vital signs, clinical laboratory tests, electrocardiogram (ECG),and C-SSRS.

An electroencephalogram (EEG) will also be performed for all participants during Screening, preferably not in a fasted state.

7.1.2. Baseline Period

The Baseline Period will occur from Day -7 through Day -1. During this period, each participant will receive dietary counseling to aid in choosing a morning meal containing approximately 30 g of fat to consume prior to dosing. On Day -7 (±1 day), participants will visit the clinic for confirmation of continued eligibility and collection of baseline [redacted] safety data. Additionally, participants will be trained on the use of a mobile data capture device [redacted] Participants will continue to complete these assessments daily during the Baseline Period, using the mobile device remotely (at home), with the support of a study partner. On Day -1, participants will return to the study site for confirmation of continued eligibility and collection of further baseline [redacted] safety data.

7.1.3. Treatment Period

Beginning on Day 1 and continuing through Day 14, participants will self-administer 3.0 mg of SAGE 718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after initiating a meal containing approximately 30 g of fat, in accordance with the guidelines provided in a nutritional information brochure. During this period, participants will continue to complete daily assessments [redacted] via mobile device either remotely (at home) or in the clinic (at scheduled clinic visits) and will track investigative product (IP) dosing and predose food intake in a participant diary.

On Day 1, Day 7 (±1 day), and Day 14, participants will arrive at the clinic in the morning prior to IP dosing and completion of daily mobile device tasks. Following predose procedures (ie, body weight, vital signs, ECG, followed by blood and urine collection for clinical laboratory analyses, [redacted] participants will eat a morning meal, then take the IP and complete the mobile device tasks under staff supervision.

At scheduled clinic visits during the Treatment Period, study staff will dispense a sufficient amount of SAGE-718 for daily administration until the next scheduled study visit. In addition to the clinic visits, study staff will contact participants by telephone on Day 4 to document any TEAEs and/or changes in concomitant medications.

7.1.4. Follow-up Period

Study staff will contact participants by telephone on Day 21 (±1 day) to document any TEAEs and/or changes in concomitant medications. Participants will return to the clinic on Day 28 (±2 days) for a follow-up visit.

7.2. Number of Participants

Up to 22 participants are planned to be dosed to obtain up to 20 participants that complete 14 days of dosing in this study. Additional participants may be dosed if the early discontinuation rate is greater than 10%.

7.3. Treatment Assignment

In this open-label study, all participants will receive 3.0 mg of SAGE-718 once daily for 14 days.

7.4. Dose Adjustment Criteria

Dosing may be interrupted in an individual participant due to an AE considered by the investigator to be related to IP, however, no individual dose reductions will be permitted.

7.4.1. Stopping Criteria

If clinical events suspicious for seizure occur after Screening, an unscheduled EEG will be performed for review by an independent epileptologist to identify evidence of seizure activity (see Section 12.1.6). Should the independent epileptologist identify evidence for a subclinical or clinical seizure, dosing with SAGE-718 will be stopped for that participant.

7.4.2. Dose Evaluation Committee

At any time during this study, Sage may elect to form a DEC (preferably after at least 5 participants have completed 14 days of dosing). If convened, this DEC will be responsible for reviewing the available data and providing recommendations for adjusting the dose, administration schedule, or food intake recommendations for subsequent participants. The DEC will include, at a minimum, the Sage program medical lead, a Sage Drug Safety and Pharmacovigilance physician, and a clinical operations representative and will be supported by a Sage biostatistician.

7.5. Criteria for Study Termination

Sage Therapeutics 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 participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

To be eligible to enroll in this study, participants must:

1. Be capable of providing informed consent
2. Have signed an informed consent form 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 his/her study partner
    b. A 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. Documented evidence of a positive molecular marker for AD (either a positive amyloid positron emission tomography scan or β-amyloid and tau levels in cerebrospinal fluid that are consistent with underlying AD pathology)
    e. Documented magnetic resonance imaging (MRI) report consistent with the diagnosis of AD-MCI with no clinically significant findings of non-AD pathology that could account for the observed cognitive impairment
6. Have a score of 15 to 24 (inclusive) on the Montreal Cognitive Assessment at Screening
7. Have an estimated premorbid IQ ≥85 (as assessed by the Test of Premorbid Functioning, performed at Screening)
8. Have a study partner who is reliable, competent, at least 18 years of age, willing to be available to the study center by phone, support study-specific activities, and accompany the participant to study visits as needed
9. Be ambulatory (use of assistance devices such as a walker or cane is acceptable; individuals requiring a wheelchair are excluded), able to travel to the study center, and in the opinion of the investigator likely to be able to continue to travel to the study center to complete study visits for the duration of the study
10. Have stable concomitant medication usage per the following criteria:
    a. For psychotropic medications, including acetylcholinesterase inhibitors and other medications that are likely to have an effect on cognitive performance, the dose and frequency must remain stable for at least 12 weeks prior to the first IP administration and be expected to remain stable for the duration of the study
    b. For all other concomitant medications, the dose and frequency must remain stable for at least 4 weeks prior to the first IP administration and be expected to remain stable for the duration of the study

11. Agree, if female, to use an acceptable highly effective method of contraception (as defined in Section 9.2.4) 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 >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 (as defined in Section 9.2.4) during the 14-day Treatment Period and for 2 weeks 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 14-day Treatment Period and for 2 weeks after receiving the last dose of IP
14. Agree to refrain from drugs of abuse and alcohol for the duration of the study

8.2. Participant Exclusion Criteria

To be eligible to enroll in this study, participants must not:

1. Have participated previously in a clinical study of SAGE-718, or have used any other investigational drug, biologic, or device or have participated in a clinical drug, biologic, or device study within 30 days or 5 half-lives (whichever is longer) prior to Screening
2. Have clinically significant comorbid medical conditions, a chronic condition that is unstable or requires more than 2 medications to be controlled, or be 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
3. Have any medical or neurological condition (other than AD) that might be contributing to the participant's cognitive impairment or history of cognitive decline
4. Have a history of brain surgery, deep brain stimulation, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury
5. Have a history, presence, and/or current evidence of an intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion)
6. Have a history of possible or probable cerebral amyloid angiopathy, according to the Boston Criteria (Greenberg 1995)
7. Have a history of treatment with an anti-amyloid therapy (including biologics) without subsequent MRI demonstrating the absence of amyloid-related imaging abnormalities
8. Be receiving any of the following prohibited medications:
    a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including amantadine, ketamine, cycloserine, or related compounds
    b. Memantine within the 4 weeks prior to IP administration
    c. Medications that inhibit cholesterol absorption (eg, ezetimibe)

d. Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)

e. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as described in the 2019 American Geriatrics Society Updated Beers® Criteria for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019)

f. Prescribed cannabis or other THC-containing substances

9. Have an alcohol or drug use disorder within the past 12 months, as per DSM-5 criteria
10. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood
11. Have current or recent suicidality, defined as follows:

    a. Suicidal ideation within the past month, as evidenced by a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) on the C-SSRS during Screening or Baseline

    b. Suicidal behavior within the past year, as evidenced by a "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) on the C-SSRS during Screening or Baseline

    c. Participant presents a serious risk of suicide in the opinion of the investigator

12. Have any of the following clinically significant medical conditions:

    a. Any clinically significant finding on 12-lead ECG during Screening or Baseline

    b. Supine vital signs outside of the following ranges during Screening or Baseline; vital sign measurements may be repeated once for initial values outside these ranges:

        – Heart rate <50 or >100 bpm

        – Systolic blood pressure <100 or >160 mmHg

        – Diastolic blood pressure <60 or >100 mmHg

13. Have a history, presence, and/or current evidence of serologic positive results for HIV-1 or HIV-2
14. Have a positive pregnancy test or be lactating at Screening or Day -1
15. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted)

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 or are not entered in the study. A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAEs.

8.4. Investigational Product Discontinuation and Early Termination from the Study

8.4.1. Investigational Product Discontinuation

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 recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops participation in the study for any reason.

Participants who discontinue IP will be invited by the investigator to complete all of the scheduled study visits and assessments (except IP administration) through the end of the Treatment Period (Day 14). Those who decline continued participation through Day 14 will be asked to complete an Early Termination Visit.

8.4.2. Early Termination from the Study

For participants who are terminated from the study early, if possible, an Early Termination Visit should be conducted as described in Table 2. 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. Loss to Follow Up

A participant will be deemed lost to follow up after 3 attempts at contacting the participant have been unsuccessful.

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 Oral Tablets are immediate release, white to off-white, round tablets containing 0.5 mg of SAGE-718 Drug Substance.

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

9.2.1. Prior and Concomitant Medications and/or Supplements

To be eligible to participate in this study, any concomitant medications must have been taken at a stable dose and frequency for at least 4 weeks before the first IP administration and be expected to continue at that stable dose until the final study visit is complete. For psychotropic medications, including acetylcholinesterase inhibitors and other medications that are likely to have an effect on cognitive performance, the dose and frequency must have been stable for at least 12 weeks prior to the first IP administration and be expected to remain stable for the duration of the study.

The start and end dates, route, dose/units, frequency, and indication for all relevant medications and/or supplements will be recorded at Screening. Medications to be recorded include all psychotropic medications used within 12 weeks of informed consent, any other medications and supplements taken within 60 days of informed consent, and all medication used to treat AD, regardless of timing. After Screening, all changes to any medication or supplements 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 on the eCRF.

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

9.2.2. Prohibited Medications

Treatment with an investigational drug 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 [redacted] performance [redacted] 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 NMDA receptor, including memantine, amantadine, ketamine, cycloserine, or related compounds
- Medications that inhibit cholesterol absorption (eg, ezetimibe)
- Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine)
- Other medications given at doses or in combinations that are likely to have a deleterious effect on [redacted] performance, as described in the 2019 American

Geriatrics Society Updated Beers® Criteria for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019)

- Prescribed cannabis or other THC-containing substances

9.2.3. Other Restrictions

Participants must agree not to consume alcohol or any drugs of abuse (including marijuana) during the study.

9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- 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)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- 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

The investigator(s) or designated staff will observe the participant taking the first dose of IP to identify any potential risks to adherence (such as difficulty opening the packaging or swallowing the tablets). The time and dose of IP administration will be noted in the source documents. The clinician will provide instructions for self-administration of the IP and train the participant to track adherence to the IP regimen and food intake in a participant diary. At the Day 1, and Day 7 visits, a supply of IP will be dispensed for participants to take at home once daily until the next scheduled visit. Participants will be required to bring all components of the IP packaging,

including empty bottles and unused medication, and the participant diary to the clinic at every visit.

Adherence to the dosing regimen will be assessed at each in-clinic visit. Adherence will be assessed by reviewing the participant diary, examining the used packaging, and counting any tablets returned by the participant. This information will be documented in the source files and eCRF, along with any deviations from the prescribed dosage regimen. Details about IP accountability are included in Section 10.6.

9.5. Randomization and Blinding

This is an open-label study, in which all participants will received unblinded IP.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

SAGE-718 Oral Tablets are immediate release, white to off-white, round tablets containing 0.5 mg of SAGE-718 Drug Substance. The tablets are composed of SAGE-718 Drug Substance, mannitol, microcrystalline cellulose, sodium starch glycolate, and sodium stearyl fumarate.

10.2. Investigational Product Packaging and Labeling

SAGE-718 Oral Tablets are packaged in high density polyethylene bottles with desiccant, induction seal, and child-resistant closures.

The composition and pharmaceutical quality of the oral tablet 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. The site pharmacist or designee will prepare labels for individual doses.

10.3. Investigational Product Storage

SAGE-718 Oral Tablets should be stored in the supplied bottles with 1 g desiccant, capped with a child-resistant closure and induction seal, and stored at room temperature. Refer to the shipping documentation for product expiry information.

10.4. Investigational Product Preparation

The IP will be provided to the site in tablet form. The pharmacist will dispense the tablets into unit doses to be administered orally as described below.

10.5. Investigational Product Administration

Each 3.0-mg dose of IP will be self-administered as 6 tablets containing 0.5 mg of SAGE-718, once daily in the morning within 1 hour after initiating a meal containing approximately 30 g of

fat. Participants are to swallow the tablets 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

Upon receipt of IP, the pharmacist will inspect the IP and complete and follow the instructions regarding receipt and storage in the SAGE-718 Investigator's Brochure and in the pharmacy manual. A copy of the shipping documentation will be kept in the study files. The IP provided is for use only as directed in this protocol.

The investigator or designee must keep a record of all IP received, used, and returned/discarded. If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

Designated site staff will dispense the IP to participants at weekly clinic visits as outlined in the Schedule of Assessments (Table 2).

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Sage Therapeutics or designee will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation. At the end of the study, any unused IP will be returned to Sage Therapeutics for destruction or destroyed locally per standard operating procedures at the site; disposition of IP will be documented.

More detailed information can be found in the SAGE-718 Investigator's Brochure and in the pharmacy manual.

10.7. 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).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

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

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

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented. Premorbid IQ will be estimated by administration of the Test of Premorbid Functioning (Wechsler 2009).

Medical history must include a confirmed diagnosis of MCI or mild dementia due to AD according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines. This diagnosis will be confirmed via the administration of the CDR. The CDR is a clinician-administered 5-point scale to characterize a patient's level of impairment due to dementia in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Morris 1993). The Test of Premorbid Functioning uses a word-reading scale to estimate premorbid [redacted] function in individuals with dementia (Wechsler 2009). In addition to full medical history, all nonpharmacological methods [redacted] used to treat or prevent [redacted] AD are to be recorded.

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index will be calculated and documented.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. A full physical examination will be performed at Screening, to include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) [redacted]. Thereafter, physical examinations will include brief assessments of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion.

12.1.4. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Systolic and diastolic blood pressure are to be measured after the participant has been supine for at least 5 minutes prior to the measurement. Orthostatic 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.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed at the time points described in Table 2. At each time point, the ECGs will be recorded in triplicate at 1-minute intervals. The standard intervals (heart rate, PR, QRS, QT, and 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).

12.1.6. Electroencephalogram

During Screening, EEG monitoring using the 10 to 20 international system for EEG electrode placement will occur for a duration of 1 hour. The assessment may be performed on any single day during the Screening Period, at any time of day, but preferably not while the participant is in a fasted state.

If clinical events suspicious for seizure occur after Screening (eg, episodes of altered consciousness and/or involuntary motor behaviors), an unscheduled 1-hour EEG will be performed for safety. An additional 1-hour EEG may be performed at the discretion of the investigator to follow up on results from any unscheduled EEG. The EEG recording will be reviewed by an independent epileptologist to identify evidence of seizure risk (eg, spikes or spike and wave discharges), subclinical seizure (eg, synchronous sharp waves and/or synchronous spike and wave discharges), seizure corresponding to a clinical event, or changes consistent with a postseizure state (eg, focal slowing and/or diffuse slowing). Should the independent epileptologist identify evidence for a subclinical or clinical seizure, dosing with SAGE-718 will be stopped for that participant. All EEG abnormalities suggestive of seizure risk or postseizure state will be reviewed by the study medical monitor.

12.1.7. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. will be collected for hematology, biochemistry, coagulation, urinalysis, and serology at the time points detailed in Table 2 and Table 3.

During Screening only, samples for clinical laboratory assessments will be collected from participants when they are in a fasted state.

Analytes to be evaluated are summarized in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	Renal Panel: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate Hepatic Panel: albumin, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase Other: triglycerides, cholesterol (LDL, HDL), creatine phosphokinase, thyroid stimulating hormone
Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if RBC indices are abnormal, reflex RBC morphology is indicated
Urinalysis	protein, glucose, pH, blood, leukocytes, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite
Serology (screening only)	hepatitis B surface antigen, hepatitis C IgM antibody, HIV-1 antibody, HIV-2 antibody

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal.

12.1.7.1. Pregnancy Testing

Serum pregnancy (human chorionic gonadotropin) tests will be conducted for all female participants during Screening; urine pregnancy tests will be conducted for all female participants that are not postmenopausal or surgically sterile at other scheduled time points. A urine pregnancy test will also be performed as part of the early termination assessments for participants who discontinue the study early.

12.1.7.2. Drugs of Abuse and Alcohol

Testing for selected drugs of abuse will be performed via urine dipstick at the study site (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, THC, and opiates). Alcohol use will be tested by either urine dipstick or breathalyzer at the study site.

12.1.8. Columbia–Suicide Severity Rating Scale

Suicidality will be monitored during the study using the C-SSRS (Posner 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the participant with suicidal ideation and behavior, and a postbaseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The "Baseline/Screening" C-SSRS form will be completed at Screening (lifetime history and past 24 months). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points outlined in Table 2.

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 study treatment has been administered.

A TEAE is defined as an adverse event with onset after the start of IP, or any worsening of a preexisting medical condition/adverse event 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 study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an 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.

Subjects 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 clinically significant. 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event Definition

A serious adverse event 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 informed consent form (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. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each adverse event (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.

12.2.4. Recording Adverse Events

Adverse events 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), resolution (date and time), 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 in Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.5. 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 or designee 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 or 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 or designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage, or designee, is 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. 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.

Sage, or designee, will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law and investigators.

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, preeclampsia) 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.

12.4. Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds the dose described in protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

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 Safety Set will include all participants who were administered IP and will be used to describe the safety data.

[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.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in participant data listings.

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to the first dose of IP.

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, maximum, Q1, and Q3. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, sex, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index, will be summarized using the Safety Set.

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

Medical history will be listed by participant.

[redacted]

13.6. Safety Analyses

Safety and tolerability of SAGE-718 will be evaluated by TEAEs and change from baseline in vital signs, clinical laboratory analytes, ECGs, and responses on the C-SSRS. Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set.

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities version 22.0 or higher. 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 clinically significant 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 clinically significant values will be summarized by treatment. Vital sign results will be listed by participant and timing of collection.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each of the triplicate ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. The derived mean of each parameter will also be listed. Mean ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. Electrocardiogram 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 September 2015, or later.

At Screening, all psychotropic medications used by the participant within 12 weeks before informed consent, any other medications and supplements within 60 days before informed consent, and all medications used to treat AD, regardless of timing, will be recorded. After Screening, all changes to any medication or supplements should be captured. 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. Columbia–Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS at Baseline and by visit during the Treatment Period will be listed and summarized for all participants. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

[redacted]

13.8. Sample Size and Power

No formal sample size calculation was made for this study. Twenty participants completing 14 days of dosing are considered sufficient to assess preliminary safety and tolerability and for signal-finding [redacted] after 14 days of repeated dosing with of SAGE-718. Assuming a 10% dropout rate, approximately 22 total participants will be required to obtain 20 completers. Additional participants may be dosed if the early discontinuation rate is >10%.

13.8.1. Interim and Data Monitoring Committee Analysis

Not applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage standard operating procedures to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or its representatives. This will be documented in a Clinical Trial Agreement between Sage Therapeutics and the investigator.

During the study, a monitor from Sage Therapeutics 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms 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, 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 Independent Ethics Committee or an Institutional Review Board 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 and/or International Conference on Harmonisation (ICH) GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/IEC about an inspection.

14.3. Institutional Review Board or 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 Good Clinical Practice 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. Significant protocol deviations 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 Informed Consent Form, 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 investigational product. 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. 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 Informed Consent Form. A copy of the signed Informed Consent Form 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 investigational product. 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

American Geriatrics Society Beers Criteria Update Expert Panel. J Am Geriatr Soc. 2019 Apr;67(4):674-694. doi: 10.1111/jgs.15767. Epub 2019 Jan 29

Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgemont). 2007;4(7):28-37. Adapted from: Kay SR. Positive and negative symptoms in schizophrenia: Assessment and research (Monograph). Clinical and Experimental Psychiatry. 1991;5. Modified from Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration. 1976;218-22.

[redacted]

Greenberg SM, Rebeck GW, Vonsattel JP, et al. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Ann. Neurol. 1995;38 (2):254-9.

Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration. 1976.

Jutten RJ, Peeters CF, Leijdesdorff SM, et al. Detecting functional decline from normal aging to dementia: Development and validation of a short version of the Amsterdam IADL Questionnaire. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2017;8:26-35.

Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12:233-239.

Molinuevo J, et al. Memantine: Targeting glutamate excitotoxicity in AD and other dementias. Am Journal of AD & Other Dementias. 2005;77-85.

Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993;43:2412-2414

Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. J Am Ger Soc. 2005 Mar;53(4):695-699.

[redacted]

Paul SM, Doherty JJ, Robichaud AJ, et al. The major brain cholesterol metabolite 24(S)-hydroxycholesterol is a potent allosteric modulator of N-methyl-D-aspartate receptors. J Neurosci. 2013;33:17290-17300.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-77.

Tsai GE, et al. Improved cognition in Alzheimer's disease with short-term D-cycloserine treatment. Am J Psychiatry. 1999 Mar;156(3):467-9.

Wechsler D. Test of premorbid functioning. San Antonio, TX: The Psychological Corporation. 2009.

Weintraub S, et al. The neuropsychological profile of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(4):a006171.

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psych Res. 1983;17:37-49.