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

NCT ID: NCT05318937

Document Date: Protocol Version 3.0: 21 September 2022

STUDY TITLE

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

SHORT TITLE

A Study to Evaluate the Effects of SAGE-718 in Participants with Parkinson's Disease Cognitive Impairment

PROTOCOL NUMBER: 718-CNP-202

IND NUMBER: 134217

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] Cambridge, MA 02142 Phone: [redacted]
Date of Original Protocol (Version 1)	22 November 2021
Date of Amendment 1 (Version 2)	10 February 2022
Date of Amendment 2 (Version 3)	09 August 2022

Confidentiality Statement

SPONSOR APPROVAL

Protocol Number:	718-CNP-202
Study Title:	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effects of SAGE-718 in Parkinson's Disease Cognitive Impairment
Protocol Version and Date:	Version 03, 09 August 2022

{See appended electronic signature page}

[redacted]

Date (DD MMM YYYY)

{See appended electronic signature page}

[redacted], MD

Date (DD MMM YYYY)

{See appended electronic signature page}

[redacted], PhD

Date (DD MMM YYYY)

{See appended electronic signature page}

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[redacted], MS
[redacted]

Date (DD MMM YYYY)

{See appended electronic signature page}

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[redacted]
[redacted]

Date (DD MMM YYYY)

{See appended electronic signature page}

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[redacted], MD, PhD
[redacted]

Date (DD MMM YYYY)

INVESTIGATOR'S AGREEMENT

I have read the 718-CNP-202 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

CONTACT INFORMATION

Table 1: Contact Information

Sage Study Physician and 24-hour emergency contact	[redacted], MD	215 First Street Cambridge, MA 02142 Phone: [redacted]
Serious Adverse Event (SAE) Reporting Contact	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 e-mail: Sage.Safety@iqvia.com Fax: 1-855-638-1674 SAE Hotline: 1-855-564-2229
	[redacted], MD	[redacted]
	[redacted], PhD	[redacted]
	[redacted], MD	[redacted]
Product Complaints	Sage Therapeutics	e-mail: productcomplaints@sagerx.com Phone: 1-833-554-7243

1. SYNOPSIS

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

Name of Investigational Product:
SAGE-718 oral softgel lipid capsule

Name of Active Ingredient:
SAGE-718

Protocol Number: 718-CNP-202

IND Number: 134217

EudraCT Number: not assigned

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

Short Title: A Study to Evaluate the Effects of SAGE-718 in Participants with Parkinson's Disease Cognitive Impairment

Number of Sites and Study Location: Approximately 30 sites in the United States

Phase of Development: 2

Planned Duration for each Study Participant:

The duration of participation (from Screening through the final Follow-up visit) for each participant is estimated to be up to 14 weeks, including 3-week Screening Period, 1-week Baseline Period, 6-week Treatment Period, and 4-week Follow-up Period.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of SAGE-718 on cognitive performance in participants with Parkinson's Disease (PD)–Mild Cognitive Impairment (MCI).	• Change from Baseline to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test.
Secondary	
• To evaluate the safety and tolerability of SAGE-718 in participants with PD-MCI.	• Proportion of participants experiencing treatment -emergent adverse events (TEAEs) and severity of TEAEs. • Number of participants who withdraw due to adverse events (AEs).
[redacted]	
• To evaluate the safety and tolerability of SAGE-718 on other safety parameters.	• Change from Baseline in vital signs, clinical laboratory parameters, electrocardiograms (ECGs), and [redacted]

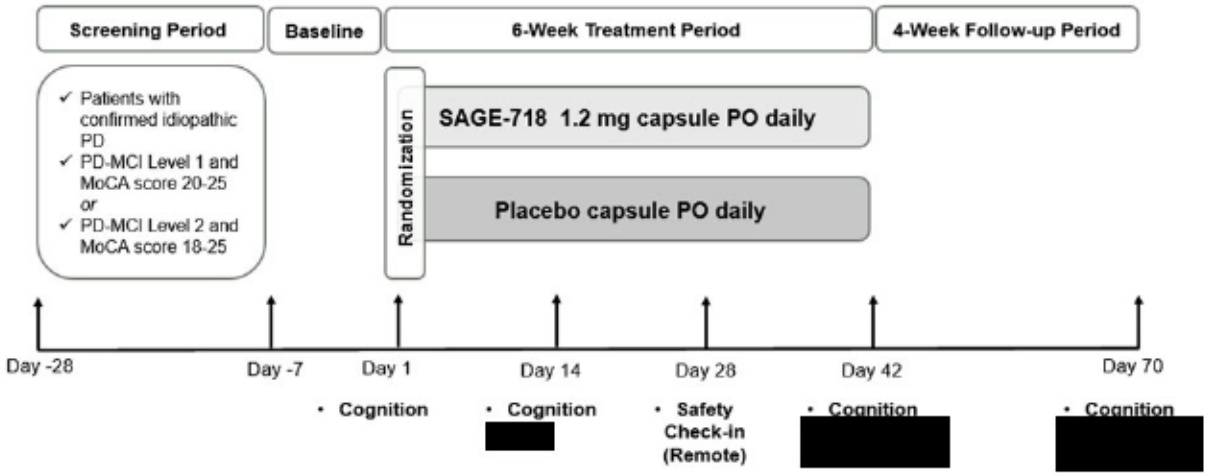
[redacted]

Study Description:

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

Eligible participants with a confirmed diagnosis of idiopathic PD by 2015 Movement Disorder Society (MDS) criteria at Screening and who meet MDS Task Force Criteria for MCI in PD (excluding requirement for United Kingdom (UK) PD Brain Bank diagnostic criteria) will receive a 1.2 mg dose of SAGE-718 or placebo daily for 6 weeks.

Assessments will be performed as outlined in the Schedule of Assessments (Table 2) and the Schedule of [redacted], Biochemical and Genetic Sampling (Table 3). The scales are to be administered after the daily dose of investigational product (IP) during the Treatment Period, and at approximately the same time of day (±2 hours) throughout the study. For participants receiving medication for PD symptoms, assessments are to be administered in the "on" state (defined as the period in which motor symptoms are mitigated due to the effects of PD medication).



Abbreviations: Cognition = Cognitive assessments (includes Wechsler Adult Intelligence Scale-IV [WAIS-IV] Coding test; [redacted], and Montreal Cognitive Assessment [MoCA]. [redacted]; PD-MCI = Parkinson's Disease Mild Cognitive Impairment; [redacted]; PO = orally.

See Table 2 for specific schedule of each test.

Screening Period

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

Baseline Period

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

Treatment Period

Eligible participants will be randomized 1:1 to receive 1.2 mg of SAGE-718, or matching placebo for 42 days. Beginning on Day 1 and continuing through Day 42, participants will self-administer blinded investigational product (IP) once per day in the morning. No dosing will be permitted beyond Day 42.

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

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

Follow-up Period

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

Number of Participants (planned): Up to 76 participants will be dosed to obtain up to 30 evaluable participants per treatment arm.

Eligibility Criteria

Inclusion Criteria:

Each eligible participant must:

1. be capable of providing informed consent;
2. have signed an informed consent form (ICF) prior to any study-specific procedures being performed;
3. be willing and, in the opinion of the investigator, able to comply with study procedures;
4. be between the ages of 50 and 75 years, inclusive, at Screening;
5. meet the following criteria for PD-MCI:
    a. have a confirmed diagnosis of idiopathic PD according to 2015 MDS clinical diagnostic criteria, and
    b. meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria).
6. meet the following criteria for MoCA:
    a. for participants meeting Level 1 PD-MCI criteria, have a MoCA score of 20 to 25 (inclusive) at Screening;
    b. for participants meeting Level 2 PD-MCI criteria (within the past year), have a MoCA score of 18 to 25 (inclusive) at Screening;
7. be able to complete the Color Trails Test 1 (including the ability to follow rater redirection and correct errors), and, based on participant's performance and investigator's opinion, is expected to be capable of engaging in prolonged cognitive testing for the duration of the study.
8. meet criteria for modified Hoehn and Yahr Stage I to III (mild to moderate motor severity) at Screening;
9. have stable motor symptoms for at least 4 weeks prior to Screening, in the opinion of the investigator;
10. have stable concomitant medication dose and frequency for at least 4 weeks prior to the first IP administration, and which is expected to remain stable for the duration of the study;
11. agree, if female, to use an acceptable highly effective method of contraception during participation in the study and for 30 days following the last dose of IP (refer to Section 8.2.4 for acceptable forms of contraception), unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating

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

12. agree, if male, to use an acceptable method of highly effective contraception during the Treatment Period and for 30 days after receiving the last dose of IP, unless the participant does not engage in sexual relations that carry a risk of pregnancy (refer to Section 8.2.4 for acceptable forms of contraception);
13. agree, if male, to abstain from sperm donation during the Treatment Period and for 30 days after receiving the last dose of IP and
14. agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.

Exclusion Criteria

Each eligible participant must not:

1. have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer), unless the participant participated solely in the placebo arm of the study.
2. have clinically significant comorbid medical conditions, a chronic condition that is unstable, or are taking concomitant medications that, in the opinion of the investigator, may make the participant unsuitable for inclusion or have the potential to compromise safety and/or compliance with study requirements;
3. have a diagnosis of dementia of any etiology, including but not limited to: Dementia with Lewy Bodies, Alzheimer's Dementia, and Vascular Dementia;
4. have any parkinsonism other than PD, including secondary parkinsonism or atypical parkinsonism;
5. be experiencing motor symptoms or fluctuations in motor symptoms associated with PD that will interfere with completing study procedures, including assessments administered by touch-screen devices, in the opinion of the investigator;
6. have an ongoing central nervous system condition other than PD that in the opinion of the investigator could influence the outcome of the study (including active neurologic and/or nonremitted psychiatric disorders);
7. have experienced significant psychotic symptoms, including hallucinations or delusions, within the past 3 months, in the opinion of the investigator;
8. have a history of brain surgery, deep brain stimulation, or any history of hospitalization due to a brain injury;
9. have a history, presence, and/or current evidence of clinically relevant intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion);
10. be receiving any of the following prohibited medications:
    a. medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine[a], amantadine, ketamine, or related compounds.
    b. medications that inhibit cholesterol absorption (eg, ezetimibe).
    c. bile acid sequestrants (eg, colesevelam, cholestyramine).
    d. other medications given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance.

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

[a]Memantine is prohibited within 30 days of screening and during the entire course of the study.

11. have an alcohol or drug use disorder within the past 12 months as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria;
12. have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood;

[redacted]

14. have any of the following clinically significant medical conditions:
    a. any clinically significant finding on 12-lead ECG during Screening or Baseline
    b. any clinically significant supine vital signs (heart rate, systolic and diastolic blood pressure) during Screening or Baseline (note: vital sign measurements may be repeated once).
15. have significant hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease;
16. have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1 or HIV-2, and/or has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) or positive HCV viral load at Screening;
17. have a positive pregnancy test, be pregnant, be lactating, or intend to breastfeed during the study;
18. be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted); or
19. is known to be allergic to any SAGE-718 excipients, including soy lecithin.

Investigational Product Dosage and Mode of Administration:

SAGE-718 1.2 mg or matching placebo will be self-administered as oral softgel lipid capsule(s) once daily in the morning.

Duration of Treatment: IP will be administered once daily for 42 days (6 weeks).

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

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

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

The Full Analysis Set will include all participants in the Safety Set who have baseline and at least 1 postbaseline efficacy evaluation.

[redacted]

Safety Analysis

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher. A TEAE is defined as an AE with onset after the first dose of IP. The proportion of participants experiencing TEAEs will be displayed by treatment group and 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. Vital signs, laboratory parameters, ECGs, [redacted] data will be summarized by treatment group. Additional analyses will be detailed in the SAP.

Efficacy Analysis

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

[redacted]

Sample Size Calculation

Assuming a placebo-adjusted treatment effect size of 0.75 (Burdick 2014) in the WAIS-IV Coding test, a total sample size of 60 evaluable participants (30 per arm) will provide 80% power at a two-sided significance level α=0.05.

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

Table 2: Schedule of Assessments

Assessments[a]	Screening Period	Baseline	Treatment Period				Follow-Up Period
	Days -28 to -8	Day -7 (±2 days)	Day 1[b]	Day 14 (±2 days)	Day 28[c] (±2 days) Phone Call	Day 42[d] (-2 days)	Day 70 (±4 days) or ET
Informed consent[e]	X						
Inclusion/exclusion criteria	X	X	X				
Randomization			X				
Medical history and demographics[f]	X						
Participant training[g]	X	X					
Body weight	X		X			X	X
Body height	X						
Vital signs (including orthostatics)[h]	X		X	X		X	X
Physical examination[i]	X		X	X		X	X
FSH test[j]	X						
Serology test[k]	X						
12-lead ECG[l]	X			X		X	X
Clinical laboratory assessments[m]	X		X	X		X	X
Urine drug test	X		X	X		X	X
Alcohol breath test	X		X	X		X	X
Pregnancy test[n]	X		X				X
[redacted]							
Optional biochemical research sample[o]	X			X		X	
Optional genetic research sample[o]	X						

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

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

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

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

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

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

[d] Dosing ends on Day 42.

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

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

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

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

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

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

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

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

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

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

[o] Refer to Table 3 for details.

[redacted]

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

[redacted]

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

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

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

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

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

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

Table 3: Schedule of [redacted], Biochemical, and Genetic Sampling

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

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

[redacted]

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

2. TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
24SHC	24(S)-hydroxycholesterol
AE	adverse event
BMI	body mass index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	Coronavirus Disease 2019
C_{max}	maximum concentration
CS	clinically significant
[redacted]	[redacted]
[redacted]	[redacted]
DSST	Digit Symbol Substitution Test
ECG	electrocardiogram
eCRF	electronic case report form
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
[redacted]	[redacted]
GMP	Good Manufacturing Practice
IADL	instrumental activities of daily living
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board

Abbreviation	Definition
IRT	interactive response technology
KI	knowledgeable informant
LC-MS/MS	liquid chromatography with tandem mass spectrometry
MCI	mild cognitive impairment
MedDRA	Medical Dictionary of Regulatory Activities
MDS	Movement Disorder Society
[redacted]	[redacted]
MoCA	Montreal Cognitive Assessment
NCS	not clinically significant
[redacted]	[redacted]
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
PAM	positive allosteric modulator
PD	Parkinson's Disease
[redacted]	[redacted]
PDAQ-15 KI	Penn Parkinson's Daily Activities Questionnaire-15 Knowledgeable Informant
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic
PVT	Psychomotor Vigilance Test
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
UP	unanticipated problem
US	United States
USM	urgent safety measure

Abbreviation	Definition
WAIS-IV	Wechsler Adult Intelligence Scale-IV

4. INTRODUCTION

The estimated prevalence for Parkinson's Disease (PD) in the United States (US) is nearly 1 million, with a projected increase to 1.2 million by 2030 (Parkinson's Foundation 2021; Marras 2018). Mild cognitive impairment (MCI) is common in patients who have PD with diagnosis rates approaching 60% (Cholerton 2013). Parkinson's Disease Mild Cognitive Impairment (PD-MCI) is associated with decreased quality of life and impaired functioning. Moreover, patients with PD-MCI are at a high risk for developing dementia (Litvan 2011). Despite the high frequency of occurrence and debilitating impact of PD-MCI, there is a lack of therapeutic options for mitigation or delay of cognitive impairment in PD (Martinez-Horta 2019).

Preclinical data indicate that patients who have PD have reduced plasma levels of a specific oxysterol, 24(S)-hydroxycholesterol (24SHC; Di Natale 2018). This molecule acts as an endogenous positive allosteric modulator (PAM) of the N-methyl-D-aspartate (NMDA) receptor (Paul 2013) and has been correlated with performance on cognitive tasks. NMDA receptors are a subtype of glutamate receptors with a fundamental and well-documented role in regulating synaptic strength, health, and plasticity.

SAGE-718 is a novel oxysterol-based NMDA receptor PAM that acts at the 24SHC binding site and modulates the response of the receptor to endogenous glutamate. SAGE-718 only affects receptor function in the presence of endogenous glutamate – it does not directly activate the receptor and is not expected to cause NMDA receptor-associated glutamatergic excitotoxicity. Positive modulation of NMDA receptors is hypothesized to produce beneficial effects in conditions associated with reduced NMDA receptor function, activity, or expression. Preclinical studies have shown promise for improving cognitive deficits in conditions with decreased plasma levels of the endogenous NMDA receptor PAM 24SHC (Collingridge 2013).

4.1. Dose Justification

SAGE-718 has been well tolerated in healthy participants, a small cohort of Huntington's disease participants, and in ongoing clinical studies in participants with Parkinson's and Alzheimer's Disease. However, based on nonclinical findings, the US Food and Drug Administration imposed a median maximum concentration (C_{max}) cap of 45 ng/mL. To date, clinical studies have used doses that resulted in exposures within this cap; neither SAEs nor AEs leading to discontinuation have been reported. For additional information on exposure caps, see the SAGE-718 Investigator's Brochure.

A daily dose of 1.2 mg of SAGE-718 in a lipid based, softgel formulation, or corresponding blinded placebo, will be given to participants in the trial each morning. The dose is selected to provide pharmacokinetic (PK) exposures that are similar to those achieved in prior studies that have shown evidence of target engagement (consistent with the NMDA hypothesis for pro-cognitive effects). [redacted]

Effect of SAGE-718 on cognitive function in participants with PD will be evaluated in this randomized, placebo-controlled, double-blind study. Additional data on the effects of SAGE-718 in participants with PD will be collected throughout, including assessments of [redacted].

5. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of SAGE-718 on cognitive performance in participants with PD-MCI.	• Change from Baseline to Day 42 in the Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding test.
Secondary	
• To evaluate the safety and tolerability of SAGE-718 oral capsule in participants with PD-MCI.	• Proportion of participants experiencing treatment-emergent adverse events (TEAEs) and severity of TEAEs. • Number of participants who withdraw due to adverse events (AEs).
[redacted]	
• To evaluate the safety and tolerability of SAGE-718 oral capsule on other safety parameters.	• Change from Baseline in vital signs, clinical laboratory parameters, electrocardiograms (ECGs), and [redacted].

[redacted]

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

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

Eligible participants with a confirmed diagnosis of idiopathic PD by 2015 Movement Disorder Society (MDS) criteria at Screening and who meet MDS Task Force Criteria for MCI in PD (excluding requirement for United Kingdom (UK) PD Brain Bank diagnostic criteria) will receive a 1.2 mg dose of SAGE-718 or placebo daily for 6 weeks (42 days).

Assessments will be performed as outlined in the Schedule of Assessments (Table 2) and the Schedule of [redacted] and Biochemical and Genetic Sampling (Table 3). The study schematic is displayed in Figure 1.

For participants receiving medication for PD symptoms, the scales are to be administered in the "on" state (defined as the period in which motor symptoms are mitigated due to the effects of PD medication). For clinician administered scales, the same individual should administer the scale whenever possible.

6.1.1. Screening Period

The Screening Period begins with the informed consent process for prospective participants, including optional caregivers. Subsequent screening assessments will be performed between Day -28 and Day -8 to determine eligibility, including assessments of cognitive and motor function.

An adult caregiver is optional but highly recommended for each participant to support completion of study activities and to answer questions about the participant's condition.

6.1.2. Baseline Period

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

6.1.3. Treatment Period

Eligible participants will be randomized 1:1 to receive 1.2 mg of SAGE-718 or placebo for 42 days. Beginning on Day 1 and continuing through Day 42, participants will self-administer blinded investigational product (IP) once per day in the morning. No dosing will be permitted beyond Day 42.

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

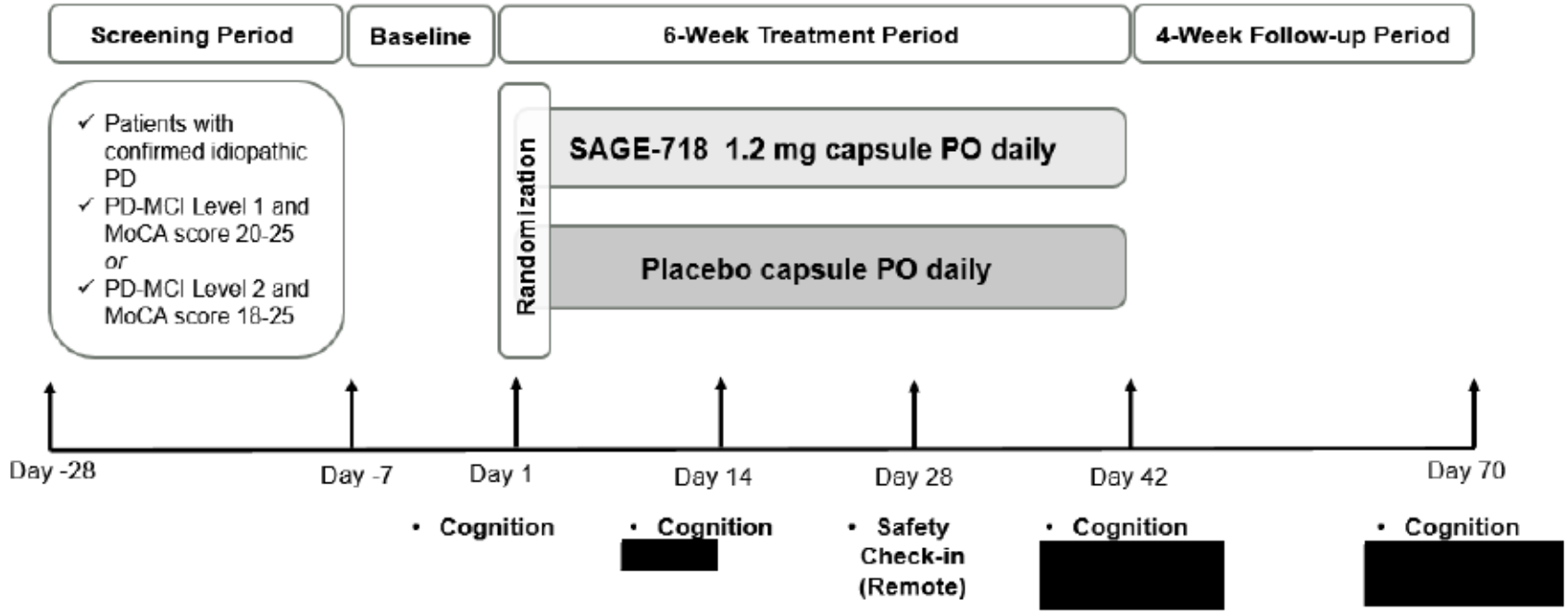
The scales are to be administered after the daily dose of blinded IP during the Treatment Period, and at approximately the same time of day (±2 hours) throughout the study.

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

6.1.4. Follow-up Period

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

Figure 1: Study Schematic



Abbreviations: Cognition = Cognitive assessments (includes Wechsler Adult Intelligence Scale-IV [WAIS-IV] Coding test; [redacted], and Montreal Cognitive Assessment [MoCA]. [redacted] PD-MCI = Parkinson's Disease Mild Cognitive Impairment; [redacted]; PO = orally.
See Table 2 for specific schedule of each test.

6.2. Number of Participants

Up to 76 participants will be dosed to obtain up to 30 evaluable participants per treatment arm. Additional participants may be randomized if the early discontinuation rate is higher than expected.

6.3. Treatment Assignment

SAGE-718 1.2 mg or placebo will be self-administered as oral softgel lipid capsule(s) once daily in the morning

6.4. Dose Adjustment Criteria

6.4.1. Stopping Criteria

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

6.4.2. Dose Evaluation Committee

A Dose Evaluation Committee (DEC) will be convened as needed [redacted]. The initial DEC meeting will be convened at a reasonable time after the first 5 nonplacebo participants have completed the active dosing portion of the study [redacted]

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

6.4.3. 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 participants.

6.5. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Inclusion Criteria

Each eligible participant must:

1. be capable of providing informed consent;
2. have signed an informed consent form (ICF) prior to any study-specific procedures being performed;
3. be willing and, in the opinion of the investigator, able to comply with study procedures;
4. be between the ages of 50 and 75 years, inclusive, at Screening;
5. meet the following criteria for PD-MCI:
    a. have a confirmed diagnosis of idiopathic PD according to 2015 MDS clinical diagnostic criteria, and
    b. meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria).
6. meet the following criteria for MoCA:
    a. for participants meeting Level 1 PD-MCI criteria, have a MoCA score of 20 to 25 (inclusive) at Screening;
    b. for participants meeting Level 2 PD-MCI criteria (within the past year), have a MoCA score of 18 to 25 (inclusive) at Screening;
7. be able to complete the Color Trails Test 1 (including the ability to follow rater redirection and correct errors), and, based on participant's performance and investigator's opinion, is expected to be capable of engaging in prolonged cognitive testing for the duration of the study.
8. meet criteria for modified Hoehn and Yahr Stage I to III (mild to moderate motor severity) at Screening;
9. have stable motor symptoms for at least 4 weeks prior to Screening, in the opinion of the investigator;
10. have stable concomitant medication dose and frequency for at least 4 weeks prior to the first IP administration, and which is expected to remain stable for the duration of the study;
11. agree, if female, to use an acceptable highly effective method of contraception during participation in the study and for 30 days following the last dose of IP (refer to Section 8.2.4 for acceptable forms of contraception), unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [FSH] >40 mIU/mL), surgically sterile (hysterectomy or bilateral oophorectomy or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does not include abstinence);
12. agree, if male, to use an acceptable method of highly effective contraception during the Treatment Period and for 30 days after receiving the last dose of IP, unless the participant does not engage in sexual relations that carry a risk of pregnancy (refer to Section 8.2.4 for acceptable forms of contraception);

13. agree, if male, to abstain from sperm donation during the Treatment Period and for 30 days after receiving the last dose of IP; and
14. agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.

7.2. Exclusion Criteria

Each eligible participant must not:

1. have participated in a previous clinical study of SAGE-718, have participated in a previous gene therapy study, or have received study treatment in any other drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer), unless the participant participated solely in the placebo arm of the study.
2. have clinically significant comorbid medical conditions, a chronic condition that is unstable, or are taking concomitant medications that, in the opinion of the investigator, may make the participant unsuitable for inclusion or have the potential to compromise safety and/or compliance with study requirements;
3. have a diagnosis of dementia of any etiology, including but not limited to: Dementia with Lewy Bodies, Alzheimer's Dementia, and Vascular Dementia;
4. have any parkinsonism other than PD, including secondary parkinsonism or atypical parkinsonism;
5. be experiencing motor symptoms or fluctuations in motor symptoms associated with PD that will interfere with completing study procedures, including assessments administered by touch-screen devices, in the opinion of the investigator;
6. have an ongoing central nervous system condition other than PD that in the opinion of the investigator could influence the outcome of the study (including active neurologic and/or nonremitted psychiatric disorders);
7. have experienced significant psychotic symptoms, including hallucinations or delusions, within the past 3 months, in the opinion of the investigator;
8. have a history of brain surgery, deep brain stimulation, or any history of hospitalization due to a brain injury;
9. have a history, presence, and/or current evidence of clinically relevant intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion);
10. be receiving any of the following prohibited medications:
    a. medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine[a], amantadine, ketamine, or related compounds.
    b. medications that inhibit cholesterol absorption (eg, ezetimibe).
    c. bile acid sequestrants (eg, colesevelam, cholestyramine).
    d. other medications given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance.
    e. cannabis or other tetrahydrocannabinol (THC)-containing substances (any route of administration), regardless of whether or not they are prescribed.

    [a]Memantine is prohibited within 30 days of screening and during the entire course of the study.

11. have an alcohol or drug use disorder within the past 12 months as per Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria;
12. have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood;

[redacted]

14. have any of the following clinically significant medical conditions:
    a. any clinically significant finding on 12-lead ECG during Screening or Baseline
    b. any clinically significant supine vital signs (heart rate, systolic and diastolic blood pressure) during Screening or Baseline (note: vital sign measurements may be repeated once).
15. have significant hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease;
16. have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1or HIV-2, and/or has detectable hepatitis B surface antigen, anti-hepatitis C virus (HCV) or positive HCV viral load at Screening;
17. have a positive pregnancy test, be pregnant, be lactating, or intend to breastfeed during the study;
18. be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted); or
19. is known to be allergic to any of SAGE-718 excipients, including soy lecithin).

7.3. 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 AEs or-serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, with the approval of the medical monitor.

7.4. Investigational Product Discontinuation and Early Termination from the Study

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

7.4.1. Investigational Product Discontinuation

When a participant is discontinued from IP, the participant should continue, if willing, to participate in the remainder of the study by attending all scheduled visits per the SOA.

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's source documentation 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 discontinues IP and/or stops participation in the study for any reason.

7.4.2. Early Termination from the Study

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

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

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

7.4.3. Lost to Follow-up

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

7.4.4. 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.

8. TREATMENT OF PARTICIPANTS

8.1. Description of Investigational Product

SAGE-718 softgel lipid capsules are opaque, white to off-white, oval capsules containing either 0.3, 0.6, 0.9, or 1.2 mg of SAGE-718 drug substance. Placebo is matching in appearance.

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

8.2.1. Prior and Concomitant Medications and/or Supplements

All medications and supplements taken within 60 days prior to Screening, all medications used to treat PD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent [redacted], and cognitive manifestations of PD are to be recorded. Information regarding diagnosis, isolation, and/or hospitalization due to coronavirus disease 2019 (COVID-19) will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at screening and throughout the study

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

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

8.2.2. Prohibited Medications

Participation in a previous SAGE-718 study or gene therapy study is prohibited. 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 that inhibit cholesterol absorption (eg, ezetimibe),
- Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine),

- Any psychotropic medications, including antidepressants and anxiolytics, unless the dose and frequency have been stable for at least 4 weeks prior to the first IP administration and are expected to remain stable for the duration of the study,
- Medications with potent effects at the NMDA receptor, including memantine[a], amantadine, cycloserine, ketamine, or related compounds,
- Other medications given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance,
- Cannabis or other THC-containing substances (any route of administration), regardless of whether or not they are prescribed.

[a]Memantine is prohibited within 30 days of screening and during the entire course of the study.

8.2.3. Other Restrictions

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

8.2.4. 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). (Note: vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the participants of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)

Acceptable forms of contraception for male participants include:

- History of successful 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).

8.3. Intervention after the End of the Study

Not applicable.

8.4. Treatment Adherence

Beginning on Day 1 and continuing through Day 42, participants will self-administer blinded IP once per day in the morning. At clinic visits, participants will self-administer the IP under staff supervision, followed by assessments of cognitive function, [redacted]. Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by examination of the used packaging, and counting any returned capsules. This information will be documented in the source files and interactive response technology (IRT), along with any deviations from the prescribed dosage regimen. Details about IP accountability are included in Section 9.6.1.

8.5. Randomization and Blinding

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

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

8.5.1. Emergency Unblinding

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

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Investigational Product

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

Table 4: Investigational Product

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

[a] US only
[b] SAGE-718 1.2 mg dose will be administered in this study.

9.2. Investigational Product Packaging and Labeling

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

The composition and pharmaceutical quality of the oral softgel lipid capsule 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.

9.3. Investigational Product Storage

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

The IP must be carefully stored at the temperature specified in the investigator's brochure and (where applicable) in the pharmacy manual, securely and separately from other drugs. The IP may not be used for any purpose other than the present study. After the study is completed, all

unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s) in accordance with study-specific Pharmacy Manual.

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

9.4. Investigational Product Preparation

SAGE-718 1.2 mg or placebo will be provided as an oral capsule for self-administration once daily in the morning through Day 42 visit.

9.5. Investigational Product Administration

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

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

9.6. Investigational Product Accountability, Handling, and Disposal

9.6.1. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the Investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the investigator's brochure and the study-specific Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

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

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

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

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

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

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

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

More detailed information can be found in the SAGE-718 investigator's brochure and study-specific Pharmacy Manual.

9.6.2. Product Complaints

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

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

10. SCREENING, EFFICACY AND CLINICAL PHARMACOLOGY ASSESSMENTS

A variety of measures will be employed in this study to evaluate cognitive function, [redacted]. All assessments are to be completed according to the Schedule of Assessments (Table 2) and the Schedule of [redacted], Biochemical and Genetic Sampling (Table 3).

During the Screening and Baseline Period, participants will be trained by study staff on the use of all software applications and devices necessary for the conduct of the study.

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

In-clinic visits will entail cognitive assessment administered by computer-based and paper/pen forms, self-report questionnaires, and interview measures.

Participants will complete daily assessments each morning during the Treatment Period. Participants will also be issued a mobile device that will be used to complete daily assessments. At scheduled clinic visits, the task will be performed in the clinic under observation by study staff, otherwise the participant will perform this task remotely (at home).

An adult caregiver is optional but highly recommended for each participant to support completion of study activities and to answer questions about the participant's condition.

10.1. Screening Assessments

10.1.1. Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a clinician-administered measure designed specifically to detect MCI and is widely used in clinical settings. This assessment is expected to take approximately 10 minutes to complete. The test is scored from zero to 30, with scores 26 or higher indicating normal cognition (Nasreddine 2005).

Note: In addition to Screening, [redacted] as outlined in Table 2.

[redacted]

[redacted]

[redacted]

[redacted]

10.2.2. Wechsler Adult Intelligence Scale-IV Coding Test

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

[redacted]

[redacted]

[redacted]

10.3. Daily (Mobile Phone-Based) Assessments

10.3.1. Psychomotor Vigilance Task

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

10.3.2. Digit Symbol Substitution Test

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

10.3.3. National Sleep Foundation Sleep Diary

Once daily in the morning, participants will briefly answer 5 questions about sleep length, sleep latency, night awakenings, and sleep quality. These questions have been modified from version 6 of the National Sleep Foundation Sleep Diary (Suni 2021). This diary will be completed each morning during the Treatment Period using a mobile device. At scheduled clinic visits, the task

will be performed in the clinic under observation by study staff, otherwise the participant will perform this task remotely (at home).

[redacted]

[redacted]

[redacted]

10.4.2. Modified Hoehn and Yahr Staging Scale

Modified Hoehn and Yahr Staging Scale (Goetz 2004) is a scale used by clinicians to categorize the degree of progression of PD in an individual.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.6.2. Penn Parkinson's Daily Activities Questionnaire-15 Knowledgeable Informant (PDAQ-15 KI)

The Penn Parkinson's Daily Activities Questionnaire-15 Knowledgeable Informant (KI) (PDAQ-15 KI) is a caregiver-reported outcome that measures the cognitive IADL in PD. The instrument is completed by a person knowledgeable of the participant, the KI. The PDAQ-15 KI was created as an abbreviated version of the PDAQ-50 consisting of 15 of the original 50 items and demonstrates strong psychometric properties across the spectrum of cognitive impairment. The items are scored for difficulty in performing each IADL on a 'none' (4), 'a little' (3), 'somewhat'

(2), 'a lot' (1) and 'cannot do' (0) with the total score ranging from 0 to 60 (higher scores indicating better IADL function).

[redacted]

10.7.2. Pharmacodynamic Assessments

Blood samples will be collected, stored, and analyzed to identify biochemical and/or genetic markers associated with SAGE-718 pharmacodynamic characteristics. The samples and the results of the analyses may be used to help design future clinical studies, develop compounds, or

develop assays and diagnostic or other tests. The sponsor will store the de-identified samples in a secure storage space with adequate measures to protect participant confidentiality. Only the sponsor and those persons or entities working with the sponsor will have access to the samples and associated data.

10.7.3. Optional Biochemical Research

When participant consent is provided, plasma samples for exploratory biochemical analysis will be collected at the time points indicated in Table 2 and Table 3, and may be stored for future research. The purpose of this research is to identify biochemical pathways related to disease susceptibility and to assess factors involved in the metabolism or response to SAGE-718. Additional biochemical analyses may be conducted if it is hypothesized that the analyses may help advance understanding of the clinical data.

10.7.4. Optional Genetic Research

When participant consent is provided, a whole blood sample for genetic testing will be collected at the time points indicated in Table 2 and Table 3. The objective of this genetic testing is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variations may influence an individual's response (ie, distribution, safety, tolerability, and efficacy) to SAGE-718. Specific genetic variations of interest include but are not limited to: classes of genes encoding enzymes involved in the metabolism of SAGE-718, genes associated with the expression and function of NMDA receptors, and genes associated with the production and degradation of glycine and glutamate.

Future research may suggest other genes or gene categories as potential candidates for influencing not only response to SAGE-718, but also susceptibility to disorders for which SAGE-718 is being developed. Thus, this genetic research may involve the study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

11. SAFETY ASSESSMENTS

11.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2) and Schedules of [redacted], Biochemical, and Genetic Sampling (Table 3).

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

11.1.1. Demography and Medical History

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

11.1.2. Weight and Height

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

11.1.3. Physical Examination

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

A full physical examination will be conducted during Screening and at Day 42 (End of Treatment). At other visits (Table 2), an abbreviated physical examination will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical assessment as determined by the investigator. Unscheduled, symptom directed examinations may be conducted at any time at the discretion of the investigator.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal, NCS, or abnormal, CS, in source documents.

11.1.4. COVID-19 Questions

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

11.1.5. 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.

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

11.1.6. Electrocardiogram (ECG)

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

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

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

11.1.7. Laboratory Assessments

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

Table 5: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, total protein, lactate dehydrogenase, gamma glutamyl transferase *Other*: triglycerides, total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], creatine phosphokinase, thyroid stimulating hormone [TSH] and reflex to free triiodothyronine (T3)/thyroxine (T4) if TSH is abnormal.
Hematology	Red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]).
Urinalysis	Protein, glucose, pH, blood, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrites
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio
Serology (screening only)	Hepatitis B and C screening tests, human immunodeficiency virus (HIV)-1 and -2 antibody

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

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

11.1.7.1. Drugs of Abuse, Alcohol

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

11.1.7.2. Pregnancy Testing

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

[redacted]

11.1.9. COVID-19 Questions

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

11.2. Adverse and Serious Adverse Events

11.2.1. Adverse Event Definition

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

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 CS. Any abnormalities that meet the criteria for a SAE should be reported in an expedited manner. Laboratory abnormalities and changes from baseline in vital signs and ECGs that are

clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

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

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

11.2.2. Serious Adverse Event (SAE) Definition

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

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

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

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

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

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

Investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

11.2.3. Definition of Urgent Safety Measure (USM) and Unanticipated Problem (UP)

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

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

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

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

Any UP must be reported within 24 hours of awareness via email to Sage and designee due to the urgent reporting requirements to regulators and IRB(s)/IECs(s).

11.2.4. Relationship to Investigational Product

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

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

	plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE.

11.2.5. Recording Adverse Events

AEs spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), 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 under Section 11.2.2. An AE of severe intensity may not necessarily be considered serious.

11.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage Therapeutics and designee within 24 hours of the study site staff becoming aware of the SAE(s) (see Table 1 for contact information). 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 Therapeutics or designee.

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

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

Sage Therapeutics, 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.

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

11.3. Pregnancy

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

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

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

11.4. 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.

12. STATISTICS

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.

12.1. Data Analysis Sets

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

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

The Full Analysis Set will include all participants in the Safety Set who have baseline and at least 1 postbaseline efficacy evaluation.

[redacted]

12.2. 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.

12.3. General Considerations

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

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

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

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

Continuous data will be summarized in terms of the number of participants, mean, standard deviation, minimum value, Q1, median, Q3, and maximum value. Categorical data will be summarized using frequency counts and percentages.

12.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, years of education, employment history, current employment status, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized using the Safety Set.

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

Medical history will be summarized and listed by participant.

12.5. Efficacy Analysis

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

Additional analyses will be detailed in the SAP.

12.5.1. Multiplicity Adjustment

Not applicable.

12.5.2. Sensitivity Analyses

Not applicable.

12.6. Safety Analyses

Safety and tolerability of SAGE-718 will be evaluated by the frequency of TEAEs and change from baseline in vital signs, clinical laboratory analytes, ECGs, and [redacted]. Safety data will be listed by participant and summarized by treatment group, maximum severity, and relationship to IP. Vital signs, laboratory parameters, ECGs, and [redacted] data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set.

Additional analyses will be detailed in the SAP.

12.6.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher. A TEAE is defined as an AE with onset after the first dose of IP. The proportion of participants experiencing TEAEs will be displayed by treatment group and 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.

12.6.2. Clinical Laboratory Evaluations

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

12.6.3. Physical Examinations

A full physical examination is to be conducted during Screening and at Day 42. At other visits, physical examinations will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems and followed by a targeted physical assessment as needed. A symptom-directed examination may be conducted at any time at the discretion of the investigator. The occurrence of a physical examination (yes/no) and the date performed will be listed by participant.

12.6.4. Vital Signs

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

12.6.5. 12-Lead Electrocardiogram

ECG will be measured after the participant has been in the supine position for at least 5 minutes. The following ECG parameters will be listed for each 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 CS values of QTcF will be summarized by treatment. ECG findings will be listed by participant and visit

12.6.6. 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.

All medications and supplements taken within 60 days prior to Screening through the duration of the study will be recorded, as well as all medications used to treat PD regardless of timing. 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.

[redacted]

12.6.8. Other Safety Analysis

Not applicable.

12.7. Clinical Pharmacology Analyses

[redacted]

12.8. Sample Size and Power

Assuming a placebo-adjusted treatment effect size of 0.75 (Burdick 2014) in the WAIS-IV Coding test, a total sample size of 60 evaluable participants (30 per arm) will provide 80% power at a two-sided significance level α=0.05.

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

12.8.1. Interim and Data Monitoring Committee Analysis

Not applicable.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

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

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

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRF, 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, medical records, source documents, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

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

13.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an IEC or an IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP/GCP and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) 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.

13.3. Institutional Review Board or Independent Ethics Committee

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

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 13.2 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, ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Protocol deviations that harm or increase the possibility of harm to the rights and welfare of a participant, or a deviation made without prior IRB/IEC approval to eliminate an immediate hazard to the participant should be reported to the IRB/IEC per the IRB/IEC's written procedures.

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

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

15. ETHICS

15.1. Ethics Review

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

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

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

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

15.2. 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.

15.3. 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 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 ICF. A copy of the signed ICF must be given to the participant.

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.

15.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data (including but not limited to, retained biological samples, images and/or recordings) will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Sage Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct visits at the investigation site and supporting 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 medical records 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).

16.2. Retention of Records

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

17. 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.

18. LIST OF REFERENCES

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