

Official Title: An Open-Label Evaluation of the Safety and Tolerability of SAGE-718
in Participants with Parkinson's Disease Mild Cognitive Impairment

NCT Number: NCT04476017

Document Dates: Protocol Version 5.0: 29-April-2021



**An Open-Label Evaluation of the Safety and Tolerability of
SAGE-718 in Participants with Parkinson’s Disease Mild
Cognitive Impairment**

PROTOCOL NUMBER: 718-CNP-201

Investigational Product	SAGE-718
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact and Medical Monitor	[REDACTED] MD [REDACTED] Cambridge, MA 02142 Phone: [REDACTED]
Date of Original Protocol	04 March 2020
Date of Amendment 1	16 April 2020
Date of Amendment 2	27 May 2020
Date of Amendment 3	25 January 2021
Date of Amendment 4	28 April 2021

Confidentiality Statement

The confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Sage Therapeutics, Inc.

Clinical Protocol
718-CNP-201, Version 5

Sage Therapeutics, Inc.
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SPONSOR APPROVAL

Protocol Number: 718-CNP-201

Study Title: An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Parkinson’s Disease Mild Cognitive Impairment

Protocol Version and Date: Version 5, 28 April 2021

DocuSigned by:
[Redacted]

Signer Name: [Redacted] 28-Apr-2021 | 13:01 EDT
 Signing Reason: I approve this document
 Signing Time: 28-Apr-2021 | 13:01 EDT

[Redacted] Date (DD MMM YYYY)

DocuSigned by:
[Redacted]

Signer Name: [Redacted] 28-Apr-2021 | 11:38 EDT
 Signing Reason: I am the author of this document
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DocuSigned by:
[Redacted]

Signer Name: [Redacted] 28-Apr-2021 | 13:16 EDT
 Signing Reason: I approve this document
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Signer Name: [Redacted] 29-Apr-2021 | 08:26 EDT
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MLA

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718-CNP-201, Version 5

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[Redacted]



Signer Name: [Redacted]
Signing Reason: I approve this document
Signing Time: 28-Apr-2021 | 11:36 EDT

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DocuSigned by:

[Redacted]



Signer Name: [Redacted]
Signing Reason: I have reviewed this document
Signing Time: 28-Apr-2021 | 12:11 EDT

28-Apr-2021 | 12:11 EDT

[Redacted]

[Redacted] MD, PhD

Date (DD MMM YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-718. I have read the 718-CNP-201 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date (DD/MMM/YYYY)

CONTACT INFORMATION

Table 1: Contact Information

Sage Study Physician and 24-hour emergency contact	██████████ MD	215 First Street Cambridge, MA 02142 Phone: ██████████
SAE Reporting	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 e-mail: Sage.Safety@iqvia.com Fax: 1-855-638-1674 SAE Hotline: 1-855-564-2229
Product Complaints	Sage Therapeutics	e-mail: ██████████ Phone: ██████████

2. SYNOPSIS

Name of Sponsor/Company: Sage Therapeutics, referred to herein as “Sage”
Name of Investigational Product: SAGE-718 Oral Tablet
Name of Active Ingredient: SAGE-718
Title of Study: An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Parkinson’s Disease Mild Cognitive Impairment
Number of Sites and Study Location: Approximately 10 sites in the US
Phase of Development: 2
Planned Duration for each Study Participant: Each participant’s involvement will last approximately 7 weeks in Part A and 9 weeks in Part B, including a maximum 2-week Screening Period, a 1-week Baseline Period, a 2-week Treatment Period in Part A or 4-week Treatment Period in Part B, and a 2-week Follow-up Period.
Objectives: <u>Primary Objective</u> <ul style="list-style-type: none">To evaluate the safety and tolerability of orally administered SAGE-718 in participants with Parkinson’s disease mild cognitive impairment (PD-MCI) <p>[REDACTED]</p>
Endpoints: <u>Primary Endpoint</u> <ul style="list-style-type: none">Incidence of treatment-emergent adverse events (TEAEs) <u>Secondary Endpoint</u> <ul style="list-style-type: none">Change from baseline in vital signs, clinical laboratory analytes, electrocardiograms (ECGs), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS) <p>[REDACTED]</p>

[REDACTED]

Study Description:

This is an open-label study evaluating the safety and tolerability of SAGE-718 and its effects on [REDACTED] in participants with PD-MCI. Eligible participants with a confirmed diagnosis of idiopathic PD by 2015 Movement Disorder Society (MDS) criteria (Berardelli 2013) at Screening and who meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria) will receive a 3.0 mg dose of SAGE-718 daily for 14 days (Part A) or for 28 days (Part B). Participants will be instructed to take the daily dose of investigational product (IP) in the morning within 1 hour of initiating a meal containing approximately 30 g of fat. Assessments will be performed as outlined in the Schedules of Assessments (Table 2 and Table 4) and the [REDACTED]

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

Screening Period

The Screening Period begins with the informed consent process for prospective participants, including study partners. Subsequent screening assessments will be performed between Day -21 and

Day -8 to determine eligibility, including assessments of [REDACTED].

Baseline Period

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

Treatment Period

Beginning on Day 1 and continuing through Day 14 in Part A and Day 28 in Part B, participants will self-administer 3.0 mg SAGE-718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after initiating a meal containing approximately 30 g of fat, in accordance with the guidelines provided in a nutritional information brochure. Participants will continue to complete daily assessments of [REDACTED] via mobile device either remotely (at home), or in the clinic at scheduled visits and will track IP dosing and predose food intake in a participant diary.

At scheduled visits during the Treatment Period, participants will arrive at the clinic in the morning prior to IP dosing and completion of daily mobile device tasks. Following predose procedures, participants will eat a morning meal, then take the IP and complete the mobile device tasks under staff supervision.

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

Follow-up Period

In Part A, study staff will contact participants by telephone on Day 21 to document any AEs and/or changes in concomitant medications. Participants will return to the clinic on Day 28 (± 2 days) for a follow-up visit.

In Part B, participants will return to the clinic for follow-up visits on Day 35 and Day 42.

Number of participants (planned): Up to 33 participants (11 in Part A and 22 in Part B) will be dosed to obtain up to 30 participants who complete dosing in this study. Additional participants may be dosed if the early discontinuation rate is $>10\%$.

Eligibility criteria:

Inclusion criteria

Each eligible participant must:

1. Be capable of providing informed consent
2. Have signed an informed consent form prior to any study-specific procedures being performed
3. Be willing and, in the opinion of the investigator, able to comply with study procedures
4. Be between the ages of 50 and 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

- b. Meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria)
6. Have a score of 20 to 25 (inclusive) on the MoCA at Screening
7. Meet criteria for Hoehn and Yahr Stage I to III (mild to moderate motor severity) at Screening
8. Have an estimated premorbid IQ ≥ 85 (as assessed by the Test of Premorbid Functioning [TOPF], performed at Screening)
9. Be willing to invite a study partner who is reliable, competent, and at least 18 years of age to participate in the study
10. Be ambulatory, able to travel to the study center, and in the opinion of the investigator likely to be able to continue to travel to the study center to complete study visits for the duration of the study
11. Have stable concomitant medication dose and frequency for at least 4 weeks prior to the first IP administration that is expected to remain stable for the duration of the study
12. Have stable motor symptoms for at least 4 weeks prior to screening, in the opinion of the investigator
13. Agree, if female, to use an acceptable highly effective method of contraception (as defined in Section 9.2.4) during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [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
14. Agree, if male, to use an acceptable method of highly effective contraception (as defined in Section 9.2.4) during the Treatment Period and for 2 weeks after receiving the last dose of IP, unless the participant does not engage in sexual relations that carry a risk of pregnancy
15. Agree, if male, to abstain from sperm donation during the Treatment Period and for 2 weeks after receiving the last dose of IP
16. Agree to refrain from drugs of abuse and alcohol for the duration of the study

Exclusion Criteria

Each eligible participant must not:

1. Have participated previously in a clinical study of SAGE-718, or have used any other investigational drug, biologic, or device or have participated in a clinical drug, biologic, or device study within 30 days or 5 half-lives (whichever is longer) prior to Screening
2. Have clinically significant comorbid medical conditions, a chronic condition that is unstable or requires more than 2 medications to be controlled, or be taking concomitant medications that, in the opinion of the investigator, may make the participant unsuitable for inclusion or have the potential to compromise safety and/or compliance with study requirements
3. Have a diagnosis of dementia of any etiology, including but not limited to: Dementia associated with PD (probable or possible), Dementia with Lewy Bodies, Alzheimer's Dementia, and Vascular Dementia
4. Have any indication of parkinsonism other than idiopathic PD, including secondary parkinsonism or atypical parkinsonism
5. In the opinion of the investigator, be experiencing unpredictable fluctuations in motor and/or

- nonmotor symptoms associated with PD
6. Have an ongoing central nervous system condition other than idiopathic PD, including active neurologic and/or nonremitted psychiatric disorders, in the opinion of the investigator
 7. Have a history of brain surgery, deep brain stimulation, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury
 8. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion)
 9. Have experienced significant psychotic symptoms within the past 3 months, including those associated with PD medications, as determined by the investigator
 10. Have a history of possible or probable cerebral amyloid angiopathy according to the Boston Criteria ([Greenberg 1995](#))
 11. Be receiving any of the following prohibited medications:
 - a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine, amantadine, ketamine, or related compounds
 - b. Medications that inhibit cholesterol absorption (eg, ezetimibe)
 - c. Bile acid sequestrants (eg, colestevlam, 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, as based on the 2019 American Geriatrics Society Updated Beers[®] Criteria for Potentially Inappropriate Medication Use in Older Adults ([American Geriatrics Society 2019](#))
 - e. Prescribed cannabis or other THC-containing substances
 12. Have an alcohol or drug use disorder within the past 12 months as per DSM-5 criteria
 13. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood
 14. Have current or recent suicidality, defined as follows:
 - a. Suicidal ideation within the past month, as evidenced by a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) on the screening or baseline Columbia–Suicide Severity Rating Scale (C-SSRS)
 - b. Suicidal behavior within the past year, as evidenced by a "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) on the C-SSRS during Screening or Baseline
 - c. Present a serious risk of suicide in the opinion of the investigator
 15. Have any of the following clinically significant medical conditions:
 - a. Any clinically significant finding on 12-lead ECG during Screening or Baseline
 - b. Supine vital signs outside of the following ranges during Screening or Baseline; vital sign measurements may be repeated once if initial values exceed these ranges:
 - Heart rate <50 or >100 bpm
 - Systolic blood pressure <100 or >160 mmHg
 - Diastolic blood pressure <60 or >100 mmHg
 16. Have significant hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease
 17. Have a history, presence, and/or current evidence of serologic positive results for HIV-1 or HIV-2

<p>18. Have a positive pregnancy test or be lactating at Screening or Day -1</p> <p>19. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted)</p>
<p>Investigational Product, Dosage and Mode of Administration: SAGE-718 3.0 mg will be self-administered as six 0.5 mg oral tablets, once daily in the morning within 1 hour after initiating a meal containing approximately 30 g of fat.</p>
<p>Duration of Treatment: 14 days in Part A or 28 days in Part B</p>
<p>Statistical Methods:</p> <p>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.</p> <p>General Considerations</p> <p>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.</p> <p>Analysis Sets</p> <p><u>Safety Set</u> will include all participants who were administered IP and will be used to describe the safety data.</p> <p><u>Full Analysis Set</u> will include all participants who initiate IP and have baseline and at least 1 postbaseline efficacy evaluation.</p>
<p>Safety Analysis</p> <p>AEs will be coded using Medical Dictionary for Regulatory Activities with the overall incidence of AEs displayed by System Organ Class and preferred term. Incidence of treatment-emergent AEs will also be presented by maximum severity and relationship to IP. Data from vital signs, clinical laboratory measures, ECGs, and C-SSRS will be summarized using descriptive statistics.</p> <p>Efficacy Analysis</p> <p>The endpoints for each of the [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 baseline [REDACTED], and assessment time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) at each time point will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, a Toeplitz or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. Line plots of change from baseline scores will be plotted with standard error bars. Other continuous efficacy endpoints, including [REDACTED] will be summarized using similar methods.</p>
<p>Sample Size Calculation:</p> <p>No formal sample size calculation was made for this study. Up to 10 participants completing 14 days of dosing in Part A and 20 participants completing 28 days of dosing in Part B are considered</p>

sufficient to assess preliminary safety and tolerability and for signal-finding of [REDACTED] after repeated daily dosing with SAGE-718.

Assuming a 10% dropout rate, approximately 33 total participants will be required to obtain 30 completers. Additional participants may be dosed if the early discontinuation rate is >10%.

Table 2: Schedule of Assessments (Part A)

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

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

Abbreviations: C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; ECG = electrocardiogram; EEG = electroencephalogram; ET = early termination; FSH = follicle stimulating hormone; IP = investigational product; [REDACTED] SAE = serious adverse event; TEAE = treatment-emergent adverse events; [REDACTED]

- Note: In the event of early termination, efforts should be made to collect the Day 14 visit assessments. When scheduled for the same time point, procedures should be performed in the following order: vital signs, ECG, blood draws, morning meal, IP dosing, then any scheduled postdose and/or [REDACTED]. In the setting of public health advisories or similar risks to patient safety, assessments scheduled to be conducted at the study site may be performed via telephone/video if feasible. For assessments that cannot be conducted by phone or video, an in-home visit may be conducted.
- a Day 4 and Day 21 visits will occur via scheduled telephone calls.
 - b Both participants and study partners are to be consented during the Screening Period.
 - c In addition to full medical history, all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of PD are to be recorded.
 - d Vital signs to include temperature, respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position and standing position at all scheduled time points.
 - e A full physical examination is to be conducted during Screening. Thereafter, 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.
 - f An EEG will be performed for all participants at any time of day during Screening, preferably in a fed state. Subsequently, if the investigator or study staff become aware of events suspicious for seizure, an unscheduled 1-hour EEG will be performed for that participant. A second, follow-up, 1-hour EEG may be performed at the discretion of the investigator.
 - g ECG will be measured after the participant has been in the supine position for at least 5 minutes.
 - h “Baseline/Screening” C-SSRS form at Screening and “Since Last Visit” C-SSRS form thereafter.
 - i Samples for clinical laboratory assessments, detailed in Table 6, are to be collected ≤2 hours prior to dosing during the Treatment Period, and any time of day at other time points. Participants are to be in a fasted state for screening assessments only.
 - j Alcohol testing will be performed in the clinic, either by urine dipstick or breathalyzer.
 - k To confirm self-reported postmenopausal status in women only.
 - l Serum pregnancy tests for all female participants at Screening; urine pregnancy tests will be conducted for all female participants who are not postmenopausal or surgically sterile at other scheduled time points.
 - m To include testing for hepatitis B and C, HIV 1, and HIV 2

[REDACTED]

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

[REDACTED]

t Daily reminders will be sent to participants via a mobile device to complete assessments of [REDACTED] (see Section 11.1) within 1 hour following IP administration either remotely (at home) or in the clinic under observation by the study staff.

[REDACTED]

- v On visit days during the Treatment Period, participants will self-administer IP in the clinic under the supervision of study staff after the predose assessments and consumption of a morning meal.
- w Study staff will dispense sufficient IP for daily dosing at home until the next scheduled visit.
- y At clinic visits during the Treatment Period, participants will return used IP packaging and any unused IP for site staff to document.
- x At Screening, to include all medications and supplements taken within 60 days and all medications used to treat PD regardless of timing. At visits subsequent to Screening, all changes to any medication should be captured.

[REDACTED]

Note: The start day of IP administration is Day 1 and all sampling times are relative to this time.

[REDACTED]

Table 4: Schedule of Assessments (Part B)

Study Period	Screening	Baseline		Treatment						Follow Up	
		D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 ^a	D 7 (±1 d)	D 14 (±1 d)	D 21 ^a (±1 d)	D 28 or ET	D 35 (±1 d)
Informed consent ^b	X										
Inclusion/exclusion criteria	X	X	X								
Medical history and demographics ^c	X										
Body weight	X			X		X	X	X	X	X	X
Body height	X										
Hoehn and Yahr staging	X										
Montreal Cognitive Assessment	X										
Test of Premorbid Functioning	X										
Vital signs ^d	X	X	X	X		X	X	X	X	X	X
Physical examination ^e	X	X	X						X		
EEG ^f	X										
12-lead ECG ^g	X		X				X		X		X
C-SSRS ^h	X	X	X	X		X	X	X	X	X	X
Clinical laboratory tests ⁱ	X		X				X		X		X
Alcohol test ^j	X	X									
Urine drug test	X	X	X	X		X	X	X	X		
FSH test ^k	X										
Pregnancy test ^l	X		X				X		X		X
Serology test ^m	X										
Participant training ^o		X	X								

Study Period	Screening	Baseline		Treatment						Follow Up	
		D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 ^a	D 7 (±1 d)	D 14 (±1 d)	D 21 ^a (±1 d)	D 28 or ET	D 35 (±1 d)
[REDACTED]											
Remote assessments ^t		X	X	X	X	X	X	X	X	X	X
[REDACTED]											
IP self-administration ^u				X	X	X	X	X	X		
IP dispensation ^v				X		X	X	X			
IP accountability ^w						X	X	X	X		
Safety telephone call					X						
TEAEs/SAEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications ^x	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; ECG = electrocardiogram; EEG = electroencephalogram; ET = early termination; FSH = follicle stimulating hormone; IP = investigational product; [REDACTED] SAE = serious adverse event; TEAE = treatment-emergent adverse events; [REDACTED]

- Note: In the event of early termination, efforts should be made to collect the Day 14 visit assessments. When scheduled for the same time point, procedures should be performed in the following order: vital signs, ECG, blood draws, morning meal, IP dosing, then any scheduled postdose and/or [REDACTED].
- In the setting of public health advisories due to COVID-19 or similar risks to patient safety, assessments scheduled to be conducted at the study site may be performed via telephone/video if feasible. For assessments that cannot be conducted by phone or video, an in-home visit may be conducted.
- a Day 4 visit will occur via scheduled telephone call.
 - b Both participants and study partners are to be consented during the Screening Period.
 - c In addition to full medical history, all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of PD are to be recorded.
 - d Vital signs to include temperature, respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position and standing position at all scheduled time points.
 - e A full physical examination is to be conducted during Screening. Thereafter, 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.
 - f An EEG will be performed for all participants at any time of day during Screening, preferably in a fed state. Subsequently, if the investigator or study staff become aware of events suspicious for seizure, an unscheduled 1-hour EEG will be performed for that participant. A second, follow-up, 1-hour EEG may be performed at the discretion of the investigator.
 - g ECG will be measured after the participant has been in the supine position for at least 5 minutes.
 - h “Baseline/Screening” C-SSRS form at Screening and “Since Last Visit” C-SSRS form thereafter.
 - i Samples for clinical laboratory assessments, detailed in Table 6, are to be collected ≤2 hours prior to dosing during the Treatment Period, and any time of day at other time points. Participants are to be in a fasted state for screening assessments only.
 - j Alcohol testing will be performed in the clinic, either by urine dipstick or breathalyzer.
 - k To confirm self-reported postmenopausal status in women only.

- l Serum pregnancy tests for all female participants at Screening; urine pregnancy tests will be conducted for all female participants who are not postmenopausal or surgically sterile at other scheduled time points.
- m To include testing for hepatitis B and C, HIV-1, and HIV-2

[REDACTED]

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

[REDACTED]

- t Daily reminders will be sent to participants via a mobile device to complete assessments of [REDACTED] (see Section 11.1) within 1 hour following IP administration either remotely (at home) or in the clinic under observation by the study staff.

[REDACTED]

- v On visit days during the Treatment Period, participants will self-administer IP in the clinic under the supervision of study staff after the predose assessments and consumption of a morning meal.
- w Study staff will dispense sufficient IP for daily dosing at home until the next scheduled visit.
- y At clinic visits during the Treatment Period, participants will return used IP packaging and any unused IP for site staff to document.
- x At Screening, to include all medications and supplements taken within 60 days and all medications used to treat PD regardless of timing. At visits subsequent to Screening, all changes to any medication should be captured.

[REDACTED]

[REDACTED]

Note: The start day of IP administration is Day 1, and all sampling times are relative to this time.

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	43
[REDACTED]	[REDACTED]	43
[REDACTED]	[REDACTED]	43
[REDACTED]	[REDACTED]	43
[REDACTED]	[REDACTED]	44
[REDACTED]	[REDACTED]	44
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[REDACTED]	[REDACTED]	44
[REDACTED]	[REDACTED]	45
[REDACTED]	[REDACTED]	45
[REDACTED]	[REDACTED]	45
[REDACTED]	[REDACTED]	45
[REDACTED]	[REDACTED]	45
[REDACTED]	[REDACTED]	45
[REDACTED]	[REDACTED]	45
[REDACTED]	[REDACTED]	45
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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation	Definition
AE	adverse event
ECG	electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
MDS	Movement Disorder Society
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
PAM	positive allosteric modulator
PD-MCI	Parkinson's disease mild cognitive impairment
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	Suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

Mild cognitive impairment is common in patients who have Parkinson's disease, and is associated with decreased quality of life and impaired functioning. Moreover, patients with PD mild cognitive impairment (PD-MCI) are at a high risk for developing dementia (Litvan 2011). 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 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).

SAGE-718 has been well tolerated in both healthy participants and a small cohort of Huntington's disease participants in previous clinical studies. However, based on nonclinical findings, the US Food and Drug Administration imposed a 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. A once-daily 3-mg dose of SAGE-718 is not predicted to exceed a median C_{max} of 45 ng/mL. For additional information on exposure caps, see the SAGE-718 Investigator's Brochure.

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

The safety, tolerability, and [REDACTED] of SAGE-718 Oral Tablet will be evaluated in this open-label study in participants with a diagnosis of PD-MCI. Additional data on the effects of SAGE-718 in participants with PD-MCI will be collected throughout, including assessments of [REDACTED]

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

6.1.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of orally administered SAGE-718 in participants with PD-MCI.

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

6.2. Endpoints

6.2.1. Primary Endpoint

The primary endpoint of this study is the incidence of treatment-emergent adverse events (TEAEs).

6.2.2. Secondary Endpoint

The secondary endpoint of this study will be assessed as the change from baseline in vital signs, clinical laboratory analytes, electrocardiograms (ECGs), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS).

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label study evaluating the safety and tolerability of SAGE-718 and its effects on [REDACTED] in participants with PD-MCI. Eligible participants with a confirmed diagnosis of idiopathic PD by 2015 Movement Disorder Society (MDS) criteria (Berardelli 2013) at Screening and who meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria) will receive a 3.0 mg dose of SAGE-718 daily for 14 days (Part A) or for 28 days (Part B). Participants will be instructed to take the daily dose of investigational product (IP) in the morning within 1 hour of initiating a meal containing approximately 30 g of fat. Assessments will be performed as outlined in the Schedules of Assessments (Table 2 and Table 4) and the [REDACTED].

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

7.1.1. Screening Period

The Screening Period begins with the informed consent process for prospective participants, including study partners. Subsequent screening assessments will be performed between Day -21 and Day -8 to determine eligibility, including assessments of [REDACTED].

7.1.2. Baseline Period

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

7.1.3. Treatment Period

Beginning on Day 1 and continuing through Day 14 in Part A and Day 28 in Part B, participants will self-administer 3.0 mg SAGE-718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after initiating a meal containing approximately 30 g of fat, in accordance with the guidelines provided in a nutritional information brochure. Participants will continue to complete daily assessments of [REDACTED] via mobile device either remotely (at home), or in the clinic at scheduled visits and will track IP dosing and predose food intake in a participant diary.

At scheduled visits during the Treatment Period, participants will arrive at the clinic in the morning prior to IP dosing and completion of daily mobile device tasks. Following predose

procedures, participants will eat a morning meal, then take the IP and complete the mobile device tasks under staff supervision

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

7.1.4. Follow-up Period

In Part A, study staff will contact participants by telephone on Day 21 to document any AEs and/or changes in concomitant medications. Participants will return to the clinic on Day 28 (± 2 days) for a follow-up visit.

In Part B, participants will return to the clinic for 2 follow-up visits on Day 35 and Day 42.

7.2. Number of Participants

Up to 33 participants (11 in Part A and 22 in Part B) are planned to be dosed to obtain up to 30 participants who complete dosing in this study. Additional participants may be dosed if the early discontinuation rate is greater than 10%.

7.3. Treatment Assignment

In this open-label study, all participants will receive 3.0 mg of SAGE-718 once daily for 14 days in Part A and for 28 days in Part B.

7.4. Dose Adjustment Criteria

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

7.4.1. Stopping Criteria

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

7.4.2. Dose Evaluation Committee

A Dose Evaluation Committee may be convened to review [REDACTED] and safety data when at least 5 participants have completed 14 days of dosing to consider adjusting the dose, administration schedule, or food intake recommendations for subsequent participants. The Dose Evaluation Committee will include, at a minimum, the Sage program medical lead, a Sage Drug Safety and Pharmacovigilance physician, and a clinical operations representative and will be supported by a Sage biostatistician.

7.5. Criteria for Study Termination

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

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

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

1. Be capable of providing informed consent
2. Have signed an informed consent form prior to any study-specific procedures being performed
3. Be willing and, in the opinion of the investigator, able to comply with study procedures
4. Be between the ages of 50 and 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
 - b. Meet MDS Task Force Criteria for MCI in PD (excluding requirement for UK PD Brain Bank diagnostic criteria)
6. Have a score of 20 to 25 (inclusive) on the MoCA at Screening
7. Meet criteria for Hoehn and Yahr Stage I to III (mild to moderate motor severity) at Screening
8. Have an estimated premorbid IQ ≥ 85 (as assessed by the Test of Premorbid Functioning [TOPF], performed at Screening)
9. Be willing to invite a study partner who is reliable, competent, and at least 18 years of age to participate in the study
10. Be ambulatory, able to travel to the study center, and in the opinion of the investigator likely to be able to continue to travel to the study center to complete study visits for the duration of the study
11. Have stable concomitant medication dose and frequency for at least 4 weeks prior to the first IP administration that is expected to remain stable for the duration of the study
12. Have stable motor symptoms for at least 4 weeks prior to screening, in the opinion of the investigator
13. Agree, if female, to use an acceptable highly effective method of contraception (as defined in Section 9.2.4) during participation in the study and for 30 days following the last dose of IP, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle stimulating hormone [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
14. Agree, if male, to use an acceptable method of highly effective contraception (as defined in Section 9.2.4) during the Treatment Period and for 2 weeks after receiving the last dose of IP, unless the participant does not engage in sexual relations that carry a risk of pregnancy

15. Agree, if male, to abstain from sperm donation during the Treatment Period and for 2 weeks after receiving the last dose of IP
16. Agree to refrain from drugs of abuse and alcohol for the duration of the study

8.2. Participant Exclusion Criteria

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

1. Have participated previously in a clinical study of SAGE-718, or have used any other investigational drug, biologic, or device or have participated in a clinical drug, biologic, or device study within 30 days or 5 half-lives (whichever is longer) prior to Screening
2. Have clinically significant comorbid medical conditions, a chronic condition that is unstable or requires more than 2 medications to be controlled, or be taking concomitant medications that, in the opinion of the investigator, may make the participant unsuitable for inclusion or have the potential to compromise safety and/or compliance with study requirements
3. Have a diagnosis of dementia of any etiology, including but not limited to: Dementia associated with PD (probable or possible), Dementia with Lewy Bodies, Alzheimer's Dementia, and Vascular Dementia
4. Have any indication of parkinsonism other than idiopathic PD, including secondary parkinsonism or atypical parkinsonism
5. In the opinion of the investigator, be experiencing unpredictable fluctuations in motor and/or nonmotor symptoms associated with PD
6. Have an ongoing central nervous system condition other than idiopathic PD, including active neurologic and/or nonremitted psychiatric disorders, in the opinion of the investigator
7. Have a history of brain surgery, deep brain stimulation, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury
8. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion)
9. Have experienced significant psychotic symptoms within the past 3 months, including those associated with PD medications, as determined by the investigator
10. Have a history of possible or probable cerebral amyloid angiopathy according to the Boston Criteria ([Greenberg 1995](#))
11. Be receiving any of the following prohibited medications:
 - a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine, amantadine, ketamine, or related compounds
 - b. Medications that inhibit cholesterol absorption (eg, ezetimibe)
 - c. Bile acid sequestrants (eg, colestevlam, 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, based on the 2019 American Geriatrics Society Updated Beers[®] Criteria for

Potentially Inappropriate Medication Use in Older Adults ([American Geriatrics Society 2019](#))

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

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention or are not entered in the study. A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAEs.

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. Rescreened participants will be assigned a new participant number.

8.4. Investigational Product Discontinuation and Early Termination from the Study

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

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

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

8.4.1. Investigational Product Discontinuation

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

8.4.2. Early Termination from the Study

For participants who are terminated from the study early, if possible, an Early Termination Visit should be conducted as described in [Table 2](#) or [Table 4](#). The participant will be permanently discontinued both from the IP and from the study at that time.

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

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

8.4.3. Loss to Follow Up

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

8.4.4. Replacement of Participants

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

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

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

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

9.2.1. Prior and Concomitant Medications and/or Supplements

To be eligible to participate in this study, any concomitant medications must have been taken at a stable dose and frequency for at least 4 weeks before the first IP administration and be expected to continue at that stable dose until the final study visit is complete.

The start and end dates, route, dose/units, frequency, and indication for all relevant medications and/or supplements will be recorded at Screening, to include all medications and supplements taken within 60 days and all medications used to treat PD regardless of timing. 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 eCRF.

Because this study aims to measure effects on [REDACTED], 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 [REDACTED] [REDACTED] at Screening to determine participant eligibility and throughout the study.

9.2.2. Prohibited Medications

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

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

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

- Medications with potent effects at the NMDA receptor, including memantine, amantadine, ketamine, or related compounds
- Medications that inhibit cholesterol absorption (eg, ezetimibe)
- Bile acid sequestrants (eg, colestevlam, cholestyramine)
- 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, based on the 2019 American Geriatrics Society Updated Beers[®] Criteria for

Potentially Inappropriate Medication Use in Older Adults ([American Geriatrics Society 2019](#))

- Prescribed cannabis or other THC-containing substances

9.2.3. Other Restrictions

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

9.2.4. Acceptable Forms of Contraception

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

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening)
- Vasectomized partner (performed at least 3 months prior to Screening)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to Screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

Not applicable.

9.4. Treatment Adherence

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

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

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

9.5. Randomization and Blinding

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

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

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

10.2. Investigational Product Packaging and Labeling

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

The composition and pharmaceutical quality of the oral tablet will be maintained according to current Good Manufacturing Practice (GMP). Labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/Good Clinical Practice (GCP) guidelines and all other applicable regulations will be prepared by Sage Therapeutics. The site pharmacist or designee will prepare labels for individual doses.

10.3. Investigational Product Storage

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

10.4. Investigational Product Preparation

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

10.5. Investigational Product Administration

Each 3.0-mg dose of IP will be self-administered as 6 tablets containing 0.5 mg of SAGE-718, once daily in the morning within 1 hour after initiating a meal containing approximately 30 g of fat. Participants are to swallow the tablets whole with approximately 240 mL (8 fluid ounces) of water. For doses taken in the clinic, site staff will watch the participant self-administer the IP.

10.6. Investigational Product Accountability, Handling, and Disposal

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

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

Designated site staff will dispense the IP to participants at weekly clinic visits as outlined in the Schedules of Assessments ([Table 2](#) and [Table 4](#)).

In Part B, site staff will access the interactive response technology (IRT) at the Screening Visit to obtain a participant identification number for each participant. On Day 1, site staff will access the IRT to enroll the eligible participant. During IP-dispensing clinic visits, site staff will access the IRT to obtain the medication identification number for the IP to be dispensed to that participant. The medication ID number and the number of tablets dispensed must be recorded. After Day 1, the participant will return all empty packaging and unused IP to the site at each clinic visit during the dosing period, and the number of tablets returned by the participant must be recorded.

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

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

10.7. Product Complaints

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

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

[REDACTED]

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11.1.9. Daily Remote Assessments

Participants will complete daily assessments using a mobile device each morning during the Treatment Period within 1 hour after IP administration. 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). Daily reminders will be provided to complete these assessments ([REDACTED]).

11.2. Clinical Pharmacology Assessments

[REDACTED]

11.2.1.1. Blood Sample Collection

Plasma samples for [REDACTED] will be collected according to the sampling collection times specified in Table 2, [REDACTED] Table 4, and [REDACTED]. The start day of IP administration is Day 1, and all postdose sampling times are relative to this time.

An additional [REDACTED] may be collected at any time if clinically indicated and at the discretion of the investigator (eg, for unusual or severe AEs).

Each sample will be marked with unique identifiers with at least the study number, participant number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the case report form. Samples will be shipped according to the instructions in the laboratory manual.

[REDACTED]
[REDACTED]

11.2.2. Pharmacodynamic Assessments

Blood samples will be collected, stored, and analyzed to identify [REDACTED] [REDACTED] 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 deidentified 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.

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]



12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedules of Assessments (Table 2 and Table 4) and the [REDACTED]

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

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 throughout the study. Questions to be asked are as follows:

- Were you diagnosed with COVID-19 by a healthcare professional?
 - If the answer is “no”, no further questions.
 - If the answer is “yes”, the following questions are asked:
 - Did you have a test? If yes, was the result positive, negative or inconclusive?
 - Were you isolated? If yes, what were the dates of isolation?
 - Were you hospitalized? If yes, what were the dates of hospitalization?

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented.

12.1.1.1. Screening Assessments

The following assessments will be performed only at Screening to confirm participant eligibility:

- Hoehn and Yahr Staging Scale (Goetz 2004): a scale used by clinicians to categorize the degree of progression of PD in an individual
- Test of Premorbid Functioning (Wechsler 2009): a language-based neuropsychological tool administered to participants in order to determine their level of intellectual function prior to the onset of cognitive impairment

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. A full physical examination will be performed at Screening, to include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as [REDACTED]. Thereafter, abbreviated physical examinations will

include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion.

12.1.4. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Systolic and diastolic blood pressure are to be measured after the participant has been supine for at least 5 minutes prior to the measurement. Orthostatic blood pressure and heart rate will also be measured after the participant has been in the supine position for at least 5 minutes and then repeated approximately 1 and 3 minutes after standing.

12.1.5. Electrocardiogram

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

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

12.1.6. Electroencephalogram

During Screening, EEG monitoring using the 10 to 20 international system for EEG electrode placement will occur for a duration of 1 hour. The assessment may be performed on any single day during the Screening Period, at any time of day, but preferably while the participant is in a fed state. If clinical events suspicious for seizure occur after Screening (eg, episodes of altered consciousness and/or involuntary motor behaviors), an unscheduled 1-hour EEG will be performed for safety. An additional 1-hour EEG may be performed at the discretion of the investigator to follow up on results from any unscheduled EEG. The EEG recording will be reviewed by an independent epileptologist to identify evidence of seizure risk (eg, spikes or spike and wave discharges), subclinical seizure (eg, synchronous sharp waves and/or synchronous spike and wave discharges), seizure corresponding to a clinical event, or changes consistent with a postseizure state (eg, focal slowing and/or diffuse slowing). Should the independent epileptologist identify evidence for a subclinical or clinical seizure, dosing with SAGE-718 will be stopped for that participant. All EEG abnormalities suggestive of seizure risk or postseizure state will be reviewed by the study medical monitor.

12.1.7. Laboratory Assessments

Blood and urine samples will be collected for hematology, biochemistry, coagulation, urinalysis, and serology at the time points detailed in [Table 2](#) and [Table 4](#). During Screening only, samples for clinical laboratory assessments will be collected from participants when they are in a fasted state.

Analytes to be evaluated are summarized below:

Table 6: Summary of Clinical Laboratory Analytes

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

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

12.1.7.1. Pregnancy Testing

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

12.1.7.2. Drugs of Abuse and Alcohol

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

12.1.7.3. Columbia–Suicide Severity Rating Scale

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

The “Baseline/Screening” C-SSRS form will be completed at Screening (lifetime history and past 24 months). The “Since Last Visit” C-SSRS form will be completed at all subsequent time points outlined in [Table 2](#) and [Table 4](#).

12.2. Adverse Events and Serious Adverse Events

12.2.1. Adverse Event Definition

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

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

Laboratory abnormalities and changes from baseline in vital signs, and ECGs are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for 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 form (ICF) 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 clinically significant. Any AEs that are unresolved at the participant’s last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event Definition

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

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

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

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

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

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

12.2.3. Relationship to Investigational Product

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

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

12.2.4. 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 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.5. Reporting Serious Adverse Events

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

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

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

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

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

12.3. Pregnancy

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

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

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

12.4. Overdose

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

13. STATISTICS

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

13.1. Data Analysis Sets

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

The Full Analysis Set will include all participants in the Safety Set with baseline and at least 1 postbaseline efficacy evaluations.

13.2. Handling of Missing Data

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

13.3. General Considerations

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

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

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

13.4. Demographics and Baseline Characteristics

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

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

Medical history will be listed by participant.

13.5. Efficacy Analysis

The endpoints for each of the [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 baseline [REDACTED]

and assessment time point. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p values) at each time point will be reported where applicable. An unstructured covariance structure will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, a Toeplitz or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. Line plots of change from baseline scores will be plotted with standard error bars. Other continuous efficacy endpoints, including [REDACTED] will be summarized using similar methods.

Additional analyses will be detailed in the SAP.

13.5.1. Multiplicity Adjustment

Not applicable.

13.5.2. Sensitivity Analyses

Not applicable.

13.6. Safety Analyses

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

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities version 22.0 or higher. A TEAE is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

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

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

13.6.2. Clinical Laboratory Evaluations

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

13.6.3. Physical Examinations

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

13.6.4. Vital Signs

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

13.6.5. 12-Lead Electrocardiogram

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

13.6.6. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary (WHO-DD) September 2015, or later.

All medications and supplements taken within 60 days prior to informed consent 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.

13.6.7. Columbia–Suicide Severity Rating Scale

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

[REDACTED]

13.8. Sample Size and Power

No formal sample size calculation was made for this study. Ten participants completing 14 days of dosing in Part A and 20 completing 28 days of dosing in Part B are considered sufficient to assess preliminary safety and tolerability and for signal-finding of [REDACTED] after repeated dosing with of SAGE-718. Assuming a 10% dropout rate, approximately 33 total participants

will be required to obtain 30 completers. Additional participants may be dosed if the early discontinuation rate is >10%.

13.8.1. Interim and Data Monitoring Committee Analysis

Not applicable.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

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

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

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

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

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

14.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an 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/International Conference on Harmonisation (ICH) GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/IEC about an inspection.

14.3. Institutional Review Board or Independent Ethics Committee

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

The investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Significant protocol deviations should be reported to the IRB/IEC per the IRB/IEC's written procedures.

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

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

Throughout the study participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be documented in the participant's source records, and when applicable, an updated ICF will be provided.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

19. LIST OF REFERENCES

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[REDACTED]

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[REDACTED]

Protocol 718-CNP-201, Amendment 4

Date of Amendment: 28 April 2021

An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Parkinson's Disease Mild Cognitive Impairment

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to add a Part B to explore the safety and efficacy of longer duration dosing (28 versus 14 days). Associated changes to the planned number of participants, planned study duration and duration of treatment, schedule of assessments, and sample size and power based on the addition of Part B have been incorporated.

Other changes incorporated with this amendment include the following:

- Included a provision that participants who screen fail may be rescreened once, with the approval of the medical monitor. Rescreened participants will be assigned a new participant number.
- Corrected text in Section 9.2.1 Prior and Concomitant Medications and/or Supplements to align with inclusion criterion #11 to state that concomitant medications must have been taken at a stable dose and frequency for at least 4 weeks before the first IP administration.
- Added text to describe IP accountability, handling, and disposal due to the addition of Part B.
- Added COVID-19 questions to be asked to document information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 as part of medical history, AE collection, and prior/concomitant medication/procedure collection throughout the study.
- Minor textual changes have been made throughout the protocol to increase clarity on the procedures of the study.

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

718-CNP-201, Amendment 3

Date of Amendment: 25 January 2021

An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Parkinson's Disease Mild Cognitive Impairment

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to broaden range of eligible participants by revising the participant eligibility criteria. Several additional changes are being implemented as outlined below:

- Inclusion criterion 9 has been updated to allow entry to otherwise eligible participants who do not have an eligible study partner.
- Inclusion criterion 10 has been revised to allow entry to participants who require the use of a walker or wheelchair.
- Inclusion criterion 11 has been revised to allow entry to participants who have been taking any concomitant medications at stable dose and frequency for at least 4 weeks prior to IP administration.
- Inclusion criterion 12 has been revised to allow entry to participants whose motor symptoms have been stable for at least 4 weeks prior to screening.
- Exclusion criterion 6 has been updated to allow the investigator to determine the presence of ongoing central nervous system conditions, whether or not they have been diagnosed prior to Screening.
- Exclusion criterion 9 has been revised to exclude participants who have experienced significant psychotic symptoms, as determined by the investigator.
- Exclusion criterion 11d has been clarified to allow the investigator to assess whether a prospective participant's medications could have a deleterious effect on cognitive performance.
- Signatories have been updated to reflect sponsor staff changes.
- Minor textual changes have been made throughout the protocol to increase clarity on the procedures of the study, and corrections to typographical errors, punctuation, grammar, abbreviations, and formatting have been made.

718-CNP-201Amendment 2

Date of Amendment: 27 May 2020

An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Parkinson's Disease Mild Cognitive Impairment

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to clarify the procedures to be followed in the study. These and other changes are being implemented as outlined below:

- To decrease burden on sites and patients, tests for drugs of abuse will now be performed via urine tests at the site at all time points, instead of serum testing at a central laboratory.
- The description of [REDACTED] has been updated to reflect the use of [REDACTED].
- Minor revisions have been added throughout to improve clarity and readability, including in-line citations and internal cross-references.

A detailed summary of changes is provided in [Table 1](#). Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 2 Detailed Summary of Changes

The primary section of the protocol affected by the changes in Protocol Amendment 2 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: *To decrease burden on sites and patients, tests for drugs of abuse will now be performed via urine tests at the site at all time points, instead of serum testing at a central laboratory.*

The primary change occurs in Section 12.1.7.2, Drugs of Abuse and Alcohol.

Revised text:

~~During Screening and Baseline, urine will be tested at the study site. Testing~~ for selected drugs of abuse **will be performed via urine dipstick at the study site** (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, THC, and opiates). ~~Thereafter, drug testing will be performed at a central laboratory using the blood samples collected for clinical laboratory assessments.~~ Alcohol use will be tested ~~via~~ **by either** urine dipstick or breathalyzer at the study site.

Sections also affected by this change:

Table 2, Schedule of Assessments

Purpose: *Text revisions have been added to improve clarity and readability.*

The primary change occurs in Section 7.1, Overall Study Design.

Revised text:

7.1.1. Screening Period

The Screening Period begins with the informed consent process for prospective participants, including study partners. Subsequent screening assessments will be performed between Day -21 and Day -8 to determine eligibility, ~~including assessments of~~ [REDACTED]

7.1.2. Baseline Period

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

7.1.3. Treatment Period

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

On Day 1, Day 7 (± 1 day), and Day 14, participants will arrive at the clinic in the morning prior to IP dosing and completion of daily mobile device tasks. Following predose procedures,

participants will eat a morning meal, then take the IP **and complete the mobile device tasks** under staff supervision.

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

7.1.4 Follow-up Period

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

Sections also affected by this change:

Synopsis

Purpose: *Duplicative text has been removed from the description of statistical methods.*

The primary change occurs in: Section 2, Synopsis.

Deleted text: Safety Analysis

AEs will be coded using Medical Dictionary for Regulatory Activities with the overall incidence of AEs displayed by System Organ Class and preferred term. Incidence of treatment-emergent AEs will also be presented by maximum severity and relationship to IP. Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics. ~~Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum, and maximum. 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.~~

Purpose: *Duplicative text has been removed from the description of restricted participant activities.*

The primary change occurs in: Section 9.2.3, Other Restrictions.

Revised text: ~~Participants must be willing to comply with all study procedures and restrictions, including the following for the time frames specified:~~

~~Consumption of **agree not to use** alcohol or any drugs of abuse (including marijuana) during the study~~

Purpose: *Clarification has been added to ensure [REDACTED] are performed after IP dosing.*

The primary change occurs in: Section 11.1, Efficacy Assessments.

Revised text: ~~At~~**During the 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 SAGE-718 during the Treatment Period, and at approximately the same time of day (±2 hours) throughout the study. Additionally, participants should be in a fed state during [REDACTED].

Purpose: *Text has been deleted to provide an accurate description of the version of the instrument that will be used in this study.*

The primary change occurs in: [REDACTED].

Revised text:Based on a screening question in each subdomain, the study partner only answers

Purpose: *Text has been added to clarify that assessments performed via mobile device will occur in the clinic on scheduled visit days.*

The primary change occurs in Section 11.1.9., Daily Remote Assessments.

Revised text:Participants will ~~receive~~**complete daily assessments using a mobile device each morning during the Treatment Period within 1 hour after IP administration. 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). Daily reminders will be provided to complete** ~~these assessments (~~ **these assessments (** ~~within 1 hour after IP administration. On clinic visit days, participants will complete these tasks with the supervision of study staff, and~~ **within 1 hour after IP administration. On clinic visit days, participants will complete these tasks with the supervision of study staff, and** ~~).~~

Sections also affected by this change:

Purpose: *Descriptions of eligibility assessments have been added.*

The primary change occurs in: Section 12.1.1, Demography and Medical History.

Added text:12.1.1.1. Eligibility Assessments

The following assessments will be performed only at Screening to confirm participant eligibility: Hoehn &Yahr Staging Scale (Goetz 2004): a scale used by clinicians to categorize the degree of progression of PD in an individual

Test of Premorbid Functioning (Wechsler 2009): a language-based neuropsychological tool administered to participants in order to determine their level of intellectual function prior to the onset of cognitive impairment

Purpose: *Clarification was added that alcohol test results will be listed in the statistical analyses.*

The primary change occurs in the Section 13.4, Demographics and Baseline Characteristics.

Revised text:

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

Purpose: *Revised the description of the planned to align study procedures across the program.*

The primary change occurs in Section 13.7.

Revised text:

[REDACTED]

[REDACTED]

Purpose: *Duplicative text was removed from Table 2 and replaced with cross-references.*

The primary change occurs in Table 2, Schedule of Assessments, footnotes.

Revised text:

~~en~~ [REDACTED]

[REDACTED]

[REDACTED]

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

[REDACTED]

to be performed **postdose during the Treatment Period and** at approximately the same time of day (± 2 hours) throughout the study ~~and postdose during the Treatment Period.~~

[REDACTED]

~~fr~~ Measures directed to study partners may be administered by telephone or in person.

[REDACTED]

~~wt~~ Daily reminders will be sent to participants via a mobile device to complete ~~measures~~**assessments** of [REDACTED]

~~On~~ within 1 hour following IP administration. ~~On~~ ~~scheduled visit days, participants will perform these tasks~~ **either remotely (at home) or** in the clinic under observation by the study staff.

~~xu~~ On visit days during the Treatment Period, participants will self-administer IP in the clinic under the supervision of study staff after the predose assessments **and consumption of a morning meal.**

~~yv~~ Study staff will dispense sufficient IP ~~for the participant to self-administer~~ daily **dosing** at home until the next scheduled visit.

Purpose: *Unnecessary duplicative text was removed from the planned statistical methods.*

The primary change occurs in the Section 13.3, General Considerations.

Revised text:

All participant data, including those that are derived, that support the tables and figures will be presented in participant data listings. ~~Some data may be presented only in participant data listings and some may be presented with a corresponding table or figure; these will be indicated in relevant sections below.~~

Purpose: *Correct typographical errors, punctuation, grammar, abbreviations, and formatting.*

These changes are not listed individually.

718-CNP-210 Amendment 1

Date of Amendment: 16 April 2020

An Open-Label Evaluation Of The Safety And Tolerability Of Sage-718 In Participants With Mild Cognitive Impairment Or Mild Dementia Due To Alzheimer's Disease

Rationale for Protocol Amendment

The primary purpose for this protocol amendment is to align procedures across protocols in the program and to clarify the procedures to be followed in the study. Several additional changes are being implemented as outlined below:

- To address changing public health advisories and the possibility of local travel restrictions at the time of enrolment, assessments scheduled to be conducted at the study site may be performed via telephone, video, or in-home visits, if necessary and feasible.
- The requirement for participants to attend all clinic visits in a fasted state for clinical laboratory assessments has been removed to reduce the burden on participants.
- Exclusion Criterion 2 has been expanded to exclude patients with chronic conditions that are unstable and /or require more than 2 medications to control, in order to protect patient safety and facilitate the interpretation of pharmacokinetic data.
- A new eligibility criterion has been added to exclude those with possible or probable cerebral amyloid angiopathy, to protect patient safety, as this condition could increase exposure to the investigational product (IP).
- Benzodiazepines have been removed from the prohibited medications list to allow investigators to make case-by-case decisions in the context of each patient's medical history and concomitant medications using the American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults.
- Positive hepatitis B/C test results have been removed from the exclusion criteria, in order to expand the number of patients who may safely participate in the study.

█ [REDACTED]

- An explanation was added that study partners must provide informed consent during Screening to participate.
- Descriptions of safety assessments have been expanded for clarity.

█ [REDACTED]

- Signatories have been changed to reflect current staffing at Sage Therapeutics.

A detailed summary of changes is provided in [Table 1](#). Corrections to typographical errors, punctuation, grammar, abbreviations, and formatting are not detailed.

Table 1: Protocol Amendment 1 Detailed Summary of Changes

The primary section of the protocol affected by the changes in Protocol Amendment 1 is indicated. The corresponding related text has been revised throughout the protocol. Deleted text is indicated by ~~strikeout~~; added text is indicated by **bold** font.

Purpose: *To address changing public health advisories and the possibility of local travel restrictions at the time of enrolment, assessments scheduled to be conducted at the study site may be performed via telephone, video, or in-home visits, if necessary and feasible.*

The primary change occurs in Section 7.1, Overall Study Design.

Added text:

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

Sections also affected by this change:

- Synopsis
- Section 11, Efficacy and Clinical Pharmacology Assessments

Purpose: *The requirement for participants to attend all clinic visits in a fasted state for clinical laboratory assessments has been changed to fasting only for screening clinical laboratory assessments, in order to reduce the burden on participants.*

The primary change occurs in Section 7.1, Overall Study Design.

Revised text:

Beginning on Day 1 and continuing through Day 14, participants will self-administer 3.0 mg SAGE 718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after ~~e~~**initiating** a meal containing approximately 30 g of fat, in accordance with the guidelines provided in a nutritional information brochure. Participants will complete daily remote assessments of [REDACTED]. Treatment Period **clinic** visits will occur on Day 1, Day 7, (**±1 day**), and Day 14. ~~For each Treatment Period clinic visit, participants will arrive at the clinic after an overnight fast.~~ Following predose procedures, participants will eat a morning meal and take the IP under staff supervision within 1 hour after **initiating** the meal.

Sections also affected by this change:

- Synopsis
- Section 12.1.7, Laboratory Assessments

Purpose: *Exclusion criterion 2 has been expanded to exclude those with chronic conditions that are unstable and /or require more than 2 medications to control, in order to protect patient safety and facilitate the interpretation of pharmacokinetic data.*

The primary change occurs in: Section 8.2, Participant Exclusion Criteria.

Added text:

2. Have clinically significant comorbid medical conditions, **a chronic condition that is unstable or requires more than 2 medications to be controlled**, or be taking concomitant medications that, in the opinion of the investigator, may make the participant unsuitable for inclusion or have the potential to compromise safety and/or compliance with study requirements

Sections also affected by this change:

- Synopsis
-

Purpose: *A new eligibility criterion has been added to exclude those with possible or probable cerebral amyloid angiopathy, in order to protect patient safety, as this condition could increase exposure to the investigational product (IP).*

The primary change occurs in: Section 8.2, Participant Exclusion Criteria.

Added text:

- 10. Have a history of possible or probable cerebral amyloid angiopathy (CAA), according to the Boston Criteria (Greenberg 1995)**

Sections also affected by this change:

- Synopsis
-

Purpose: *Specific prohibitions and allowances for benzodiazepines have been removed from the exclusion criteria to allow investigators to make case-by-case decisions using the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.*

The primary change occurs in: Section 8.2, Participant Exclusion Criteria.

Revised text:

12. Be receiving any of the following prohibited medications:
 - a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine, amantadine, ketamine, or related compounds
 - b. Ezetimibe or similar medications that inhibit cholesterol absorption
 - c. Bile acid sequestrants (eg, colestevlam, cholestyramine)
 - d. ~~Long acting benzodiazepines (eg, clonazepam). Shorter acting benzodiazepines (eg, lorazepam) are allowed if dose is stable for 8 weeks prior to the first IP administration.~~ Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as described in the 2019 American Geriatrics Society Updated Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults

Sections also affected by this change:

- Synopsis
-

Purpose: *The history or presence of serologic positive hepatitis B and hepatitis C have been removed from the exclusion criteria, in order to expand the number of patients who may safely participate in the study.*

The primary change occurs in Section 8.2, Participant Exclusion Criteria.

Revised text:

14. Have a history, presence, and/or current evidence of serologic positive results ~~hepatitis B surface antigen, hepatitis C antibodies, or HIV 1 or 2~~ for HIV-1 or HIV-2

Sections also affected by this change:

- Synopsis
-

Revised text:

12.1.7.1 Virus Serology

Subjects will be tested for hepatitis B surface antigen, anti-hepatitis C virus antibody or hepatitis C antigen (RNA), and human immunodeficiency virus (HIV-1 and HIV-2) antibody during Screening.

12.1.7.2 Pregnancy Screen Testing

~~A~~ Serum pregnancy (**human chorionic gonadotropin**) tests will be conducted for all female participants ~~at~~**during** Screening; a urine pregnancy tests will be conducted for all female participants that are not postmenopausal or surgically sterile at other scheduled time points. Follicle stimulating hormone testing will be conducted during Screening to confirm whether a participant with ≥ 12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1). **A urine pregnancy test will also be performed as part of the early termination assessments for subjects who discontinue the study early.**

If a participant becomes pregnant during the study, the process for reporting the pregnancy and guidance for collection of information related to the pregnancy is outlined in Section 12.3.

Sections also affected by this change: Synopsis

Purpose: *The abbreviated physical examination has been defined to provide clarity and consistency.*

The primary change occurs in Section 12.1.3..

Revised text:

Thereafter, abbreviated physical examinations will include ~~a brief medical history~~ **assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems**, followed by a targeted physical examination **as needed**.

Sections also affected by this change: Synopsis

Purpose: *Oxygen saturation has been removed from the list of vital signs to be documented, in alignment with other SAGE-718 protocols, as well as the specification that temperature must be taken orally.*

The primary change occurs in Section 12.1.4..

Revised text:

Vital signs comprise heart rate, respiratory rate, ~~oral~~ temperature ($^{\circ}\text{C}$), **oxygen saturation**, and blood pressure.

Sections also affected by this change: Synopsis

Purpose: [REDACTED]

The primary change occurs in Section 11.2.2, Pharmacodynamic Assessments.

Revised text:

11.2.2 Pharmacodynamic Assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sections also affected by this change: Synopsis

Purpose: *Correct typographical errors, punctuation, grammar, abbreviations, and formatting.*
These changes are not listed individually.