Official Title: A 28-Day Randomized, Placebo-Controlled, Double-Blind, Parallel Groups and Normative Comparison Study to Evaluate the Effect of SAGE-718 on Functioning Capacity in Participants with Huntington's Disease

NCT ID: NCT05358821

Document Date: Protocol Version 3.0: 06 June 2023

A 28-DAY RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL GROUPS AND NORMATIVE COMPARISON STUDY TO EVALUATE THE EFFECT OF SAGE-718 ON FUNCTIONING CAPACITY IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

SHORT TITLE: 28-DAY PLACEBO-CONTROLLED STUDY OF SAGE-718 ON FUNCTIONING CAPACITY IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

PROTOCOL NUMBER: 718-CIH-202

IND NUMBER: 145563

Investigational Product	SAGE-718
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] PhD [redacted] Cambridge, MA 02142 Phone: [redacted]
Sponsor Medical Monitor	[redacted], MD [redacted] Cambridge, MA 02142 Phone: [redacted]

Date of Original Protocol	10 January 2022
Date of Amendment 1	15 July 2022
Date of Amendment 2	26 May 2023

Confidentiality Statement

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

SPONSOR APPROVAL

Protocol Number:	718-CIH-202
Study Title:	A 28-Day Randomized, Placebo-Controlled, Double-Blind, Parallel Groups and Normative Comparison Study to Evaluate the Effect of SAGE-718 on Functioning Capacity in Participants with Huntington's Disease
Protocol Version and Date	Version 3, 26 May 2023

{see appended electronic signature page}

[redacted] MD — Date (DD Month YYYY)
[redacted]

{see appended electronic signature page}

[redacted] MD, PhD — Date (DD Month YYYY)
[redacted]

{see appended electronic signature page}

[redacted] PhD — Date (DD Month YYYY)
[redacted]

{see appended electronic signature page}

[redacted] — Date (DD Month YYYY)
[redacted]

{see appended electronic signature page}

[redacted] MLA
[redacted]

Date (DD Month YYYY)

{see appended electronic signature page}

[redacted] MS
[redacted]

Date (DD Month YYYY)

{see appended electronic signature page}

[redacted] PhD
[redacted]

Date (DD Month YYYY)

INVESTIGATOR'S AGREEMENT

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD Month YYYY)

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician and 24-Hour Emergency Contact	[redacted] MD [redacted]	215 First Street Cambridge, MA 02142 Phone: [redacted]
SAE Reporting	IQVIA Lifecycle Safety IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 e-mail: Sage.Safety@iqvia.com Fax: +1-855-638-1674 SAE Hotline: +1-855-564-2229
	[redacted] MD [redacted]	[redacted]
	[redacted] MD	[redacted]
Product Complaints Contact	Product Complaints, Sage Therapeutics	e-mail: productcomplaints@sagerx.comPhone: 1-833-554-7243

2. SYNOPSIS

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

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

Name of Active Ingredient:
SAGE-718

Title of Study:
A 28-Day Randomized, Placebo-Controlled, Double-Blind, Parallel Groups and Normative Comparison Study to Evaluate the Effect of SAGE-718 on Functioning Capacity in Participants with Huntington's Disease

Number of Sites and Study Location: This study will take place at approximately 10 sites in the United States and Canada.

Phase of Development: 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the Follow-up Visit) for each participant is estimated to be up to 70 days.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the magnitude of the baseline difference between participants with Early Huntington's Disease (HD) and healthy participants (HP) with respect to measures of cognitive performance.	• Difference in baseline measures of the Huntington's Disease Cognitive Assessment Battery (HD-CAB) cognitive composite score in participants with HD and HP.
Secondary	
• To evaluate safety and tolerability of SAGE-718 in participants with HD.	• Safety and tolerability of SAGE-718 as assessed by the incidence of adverse events (AEs)/serious adverse events (SAEs), and by changes in vital signs and clinical laboratory parameters.

[redacted]

[redacted]

• To evaluate additional safety and tolerability parameters of SAGE-718 in participants with HD.	• Change from Baseline and between-group effects (SAGE-718 and placebo) [redacted], electrocardiograms (ECGs), and responses on the Columbia-Suicide Severity Rating Scale (C-SSRS).

[redacted]

[redacted]

Study Description:

This is a randomized, placebo-controlled, double-blind, parallel group study with a 28-day treatment duration to evaluate the effects of SAGE-718 on functioning capacity, safety, and tolerability in participants with early manifest HD. Participants will be adults with genetically-confirmed expansion of the Huntingtin (HTT) gene cytosine, adenine, and guanine (CAG) trinucleotide repeat at Screening who meet diagnostic criteria detailed in the inclusion criteria below [including Unified Huntington's Disease Rating Scale (UHDRS) scores and CAG-Age-Product [CAP] scores within specific ranges].

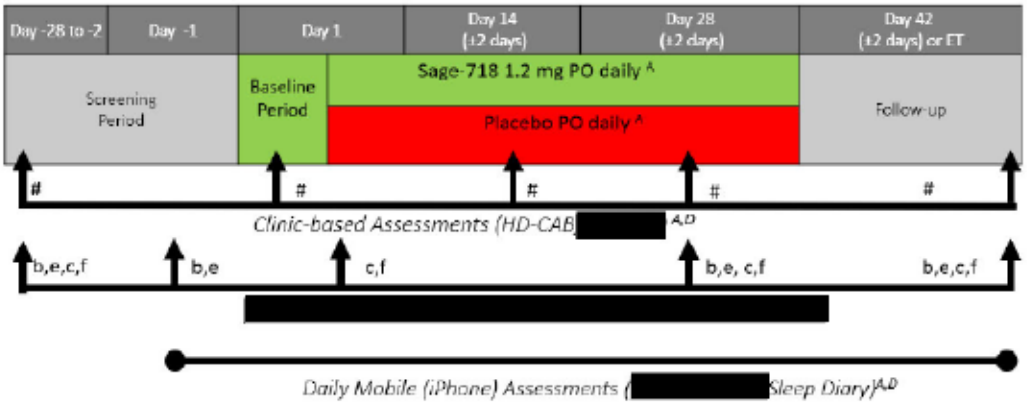
HP enrolled in the study will follow the same assessment schedule as participants with HD, but will not receive SAGE-718 or placebo, and will complete assessments only on performance-based tests (HD-CAB[redacted], not HD-specific measures of functioning and HD symptomatology.

An adult study partner for participants with HD is optional but highly recommended for each participant with HD to support completion of study activities and to answer questions about the participant's condition. For prospective participants with HD and study partners (if applicable), the study will begin with the informed consent process.

Screening, safety, and efficacy assessments will be performed according to the schedule presented in Table 1 (HD) and Table 2 (HP). [redacted]

Screening assessments will be performed to determine eligibility. Participants and study partners (if applicable) will receive training on the study procedures and devices.

Eligible participants with HD will be randomized 1:1 in a stratified manner based on previous intake of antisense oligonucleotide drugs (yes/no) to receive 1.2 mg of SAGE-718 or placebo for up to 28 days. Beginning on Day 1 and continuing through Day 28, participants with HD will self--administer blinded investigational product (IP) once per day in the morning. At clinic visits, participants with HD will take the IP under staff supervision, followed by assessments of cognitive function, [redacted]. Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by examination of the used packaging and counting any returned capsules.



Abbreviations: [redacted] HD = Huntington's Disease, HD-CAB = Huntington's Disease Cognitive Assessment Battery, HP = healthy participants, PO = by mouth, [redacted]

[A] **Participants with HD:**

[b] [redacted]

[c] [redacted]

[D] **HP: (Assessments Only)**

[e] [redacted]

[f] [redacted]

[g] [redacted]

During the Treatment Period, participants with HD will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants with HD who discontinue IP early should complete the remaining study visits as scheduled, unless the participant with HD withdraws consent or loses the capacity to grant consent. If a participant with HD withdraws from the study or stops study participation, an early termination (ET) visit should be conducted. After completing the Treatment period or Reliability Assessment Period, all participants will return to the clinic for follow-up visits on Day 42 (±2 days) to collect continued safety and efficacy data.

Number of Participants (Planned): Approximately 40 participants with early HD (n = 20 per treatment arm) will be randomized in the study to obtain 32 evaluable participants with HD (16 participants per arm). Additional participants may be randomized if the early discontinuation rate is higher than expected (20%). Approximately 40 matched healthy participants (eg, age, sex, race, and education) will be enrolled in an "assessment only" arm and will complete specific assessment procedures following the same schedule as the treatment arm participants.

Eligibility Criteria:

Inclusion Criteria

Each eligible participant must:

For All

1. Be capable of providing informed consent, in the opinion of the investigator.
2. Have signed an informed consent form (ICF) prior to any study-specific procedures being performed.
3. Agree to adhere to the study requirements.
4. Be capable of complying with study procedures, in the opinion of the investigator. The investigator may determine a participant's capability of being able to complete the Driving Simulator at Screening based on the outcome of the simulator sickness screening interview.
5. Be at least 25 years old but no older than 65 years of age at Screening.
6. Currently hold a valid driver's license, 5+ years driving experience, and participants opting in the driving simulator assessment are currently driving at least 1 × weekly.
7. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.

Additional criteria for participants with HD only

8. Be ambulatory (use of assistance devices such as a walker or cane is acceptable, as is occasional use of wheelchair. Individuals requiring a wheelchair on a regular basis are excluded), able to travel to the study center, and, judged by the investigator, is likely to be able to continue to travel to the study center to complete study visits for the duration of the study.
9. Have:
    a. Genetically confirmed disease with CAG expansion ≥36.
    b. At Screening, UHDRS TFC >6 and <13, suggesting no more than a moderate level of functional impairment.
    c. No features of juvenile HD.
10. CAP score >70, as calculated using the CAP formula: AGE × (CAG – 30) / 6.49.
11. Score of 15 to 25 (inclusive) on the MoCA at Screening, indicating the presence of cognitive impairment.
12. Be willing to invite a study partner, if available, who is reliable, competent, and at least 18 years of age to participate in the study.
13. Agree, if female, to use at least one method of highly effective contraception (refer to Section 9.2.4 for further details on acceptable forms of contraception) during participation in the study and for 155 days following the last dose of IP, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle-stimulating hormone [FSH] > 40 mIU/mL), surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), or does not engage in sexual relations which carry a risk of pregnancy.

14. Agree, if male, to use an acceptable method of effective contraception for the duration of study and for 215 days after receiving the last dose of the IP, unless the participant does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
15. Agree, if male, to abstain from sperm donation during the Treatment Period and for 215 days after receiving the last dose of IP.

Additional criteria for HP only

16. Score ≥26 on the MoCA at Screening.
17. Have no known family history of HD; or, have known family history of HD but have genetic test results available that show a normal CAG repeat length for both HTT alleles (<36).

Exclusion criteria

Each eligible participant must not:

For All

1. Have been diagnosed with and/or treated for any type of cancer (excluding basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
2. Plans to undergo elective surgery during participation in the study.
3. Have current or recent suicidality, defined as follows:
   a. Suicidal ideation within the past month, as evidenced by a "Yes" on question 4 (active suicidal ideation with some intent to act, without specific plan) or question 5 (active suicidal ideation with specific plan and intent) on the C-SSRS.
   b. Suicidal behavior within the past year, as evidenced by a "Yes" on any of the C-SSRS Suicidal Behavior items (actual attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, or suicidal behavior) on the C-SSRS.
   c. Presenting a serious risk of suicide in the opinion of the investigator.
4. Take any psychotropic medications, including antidepressants and anxiolytics, unless the dose and frequency have been stable for at least 30 days prior to the first IP administration and are expected to remain stable for the duration of the study.
5. Have an ongoing medical or psychiatric condition that, in the opinion of the investigator, may compromise the participant's safety or compliance with study requirements.
6. Have supine vital signs outside of the following ranges at Screening or Baseline (vital sign measurements may be repeated once for initial values outside these ranges):
   - Heart rate <50 or >100 bpm,
   - Systolic blood pressure <100 or >160 mmHg,
   - Diastolic blood pressure <60 or >100 mmHg.
7. Have an alcohol or drug use disorder within the past 2 years, as assessed by the investigator. A positive urine drug screen is exclusionary unless deemed by the investigator to reflect a prescribed medication.
8. Have a history of significant hand injury that would preclude either writing or rapid bimanual computerized responding.

9. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood.
10. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1 or HIV-2 or hepatitis B or C.
11. Have a history of brain surgery, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury.
12. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion).
13. Have a positive pregnancy test, is lactating, or intend to breastfeed during the study.
14. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
15. Have participated in a previous clinical study of SAGE-718; have previous exposure to gene therapy; or have participated in any Huntington's Disease (HD) investigational drug, biologic, or device trial within 180 days, or a non-HD drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer).

    (Note: Participants with confirmation of enrollment in the placebo arm of these trials would not be excluded.)
16. Receive any prohibited medications within 30 days of Screening and during participation in the study:
    a. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as determined by the investigator.
    b. Tetrahydrocannabinol (THC)-containing substances (any route of administration), regardless of whether or not they are prescribed.
17. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.

<u>Additional criteria for participants with HD only</u>

18. Had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
19. Receive any prohibited medications within 30 days of Screening and during participation in the study:
    a. Medications with potent effects at the N-methyl-D-aspartate (NMDA) receptor, including memantine, amantadine, ketamine, cycloserine, or related compounds.
    b. Medications that inhibit cholesterol absorption (eg, ezetimibe).
    c. Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine).
20. Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease.

<u>Additional criteria for HP only</u>

21. Have a diagnosis of an ongoing neurodegenerative condition, including but not limited to HD, Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease.

Investigational Product, Dosage, and Mode of Administration: SAGE-718 1.2 mg or placebo will be provided as oral softgel lipid capsule for self-administration once daily in the morning.

Reference Therapy, Dosage, and Mode of Administration: None.

Duration of Treatment: 28 days (4 weeks)

Statistical Methods:

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be finalized and approved prior to database lock.

General Considerations:

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

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

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

Analysis Sets

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

The Safety Set will include all participants with HD who were administered IP or HP and will be used to describe the safety data. The Safety Set will be further subdivided to describe participants with HD and healthy participants separately.

The Full Analysis Set will include all participants who meet the eligibility criteria and have at least 1 baseline assessment of HD-CAB (participants with HD and HP).

The Full Analysis Set 1 will include all participants who initiate IP and have baseline and at least 1 postbaseline efficacy evaluation (participants with HD only).

The Full Analysis Set 2 will include all participants with HD who initiate IP or HP who meet eligibility criteria and have baseline and at least 1 postbaseline efficacy evaluation (participants with HD and HP).

The Healthy Participant Set will include all the healthy participants who meet the eligibility criteria and have more than one evaluation (baseline and at least one postbaseline).

Efficacy Analysis

Baseline differences between participants with HD and HP will be assessed across candidate endpoint using T-test. The mean differences, its 95% confidence interval (CI) and corresponding p value will be reported. For a given endpoint, if the 95% CI does not span zero, then it will be concluded that the participants with HD are statistically significantly different from their healthy comparators at Baseline

for that endpoint; otherwise, it will be concluded that there is not enough evidence to declare them statistically different.

[redacted]

Safety Analysis

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA™) Version 22.0 or higher. The proportion of participants experiencing treatment-emergent adverse events (TEAEs) will be displayed by treatment group and by System Organ Class and Preferred Term. The frequency of TEAEs will also be presented by maximum severity, relationship to IP, and by treatment group. Vital signs, [redacted], laboratory parameters, ECGs, and C-SSRS data will be summarized by treatment group.

Sample Size

Using a two-sided alpha level of 0.05, a sample size of at least 80 participants (40 HP and 40 participants with HD) would provide at least 80% power to detect a baseline difference in HD-CAB composite score assuming Cohen's D effect size equal to 0.63, which is in the range of effect sizes reported in the literature.

Using a CI approach for sample size estimation a sample size of 32 evaluable participants with HD (16 per treatment arm) will provide 80% confidence level for estimating the population mean with 0.50 precision or margin of error.

Assuming a 20% dropout rate in participants with HD, a sample size of approximately 40 participants with HD will be randomized in a 1:1 ratio to SAGE-718 and placebo to obtain 32 evaluable participants with HD. Additional participants may be randomized if the dropout rate is higher than 20%.

Evaluable participants with HD are defined as those randomized participants who receive IP and have a valid baseline and at least 1 postbaseline efficacy assessment.

Table 1: Schedule of Assessments -Huntington's Disease

Assessments	Screening Period		Treatment Period			Follow-up
	Days -28 to -2	Day-1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 42 (±2 days) or ET
Informed consent[a]	X					
Inclusion/exclusion criteria	X	X	X			
Randomization[b]			X			
Family/medical history and demographics[c]	X					
Participant training[d]	X	X	X			
Body weight	X				X	X
Body height	X					
Vital signs (including orthostatics)[e]	X	X		X	X	X
Physical examination[f]	X	X			X	X
CAG test (if not collected as part of medical history)[g]	X					
FSH test[h]	X					
Serology test[i]	X					
12-lead ECG[j]	X	X			X	X
Clinical laboratory assessments[k]	X	X			X	X
Urine drug test[l]	X	X	X	X	X	X
Alcohol test[l]	X	X	X	X	X	X
Cigarette/tobacco use assessment[m]	X		X	X	X	X
Pregnancy test[n]	X		X		X	X
[redacted]						
C-SSRS (Screening)	X					
C-SSRS (since last visit)			X	X	X	X
[redacted]						

Assessments	Screening Period		Treatment Period			Follow-up
	Days -28 to -2	Day-1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 42 (±2 days) or ET
[redacted]						
Cognitive test (HD-CAB[redacted])[t]	X		X			
[redacted]						
Daily Mobile Assessments[x]		X----------X				
IP self-administration[y]			X (once daily in the morning)			
IP dispensation[z]			X	X		
IP accountability/return[aa]				X	X	
AEs/SAEs	X (from time of ICF throughout the duration of participation)					
Prior and concomitant medications	X----------X					

Abbreviations: AE = adverse event; CAP = CAG-Age-Product; [redacted]; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia–Suicide Severity Rating Scale; [redacted]
ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HD = Huntington's Disease; HD-CAB = Huntington's Disease Cognitive Assessment Battery; [redacted] HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; [redacted]
SAE = serious adverse event; [redacted]

a. Both participants and study partners (if applicable) will be consented during the Screening Period.
b. Randomization will take place on Day 1, following all safety assessments (vital signs, physical examinations, 12-lead ECGs and clinical laboratory), eligibility requirements (C-SSRS, urine drug, alcohol and pregnancy testing) and confirmation of inclusion/exclusion criteria.
c. In addition to full medical history, all medications and supplements taken within 8 weeks prior to Screening, all medications used to treat HD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD will be recorded. Information regarding diagnosis and/or hospitalization due to COVID-19 will be documented as part of medical history regardless of timing. The following demographics will be collected: age, race, sex, ethnicity, years of education, employment history, and current employment status.
d. Participants and study partners (if applicable) will be trained by study staff on the use of software applications and devices necessary for the conduct of the study.
e. Vital signs will 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.

f. A full physical examination is to be conducted during Screening (Days -28 to -2) and at Day 42 (±2 days)/ET. At other visits [eg, Day 28 (±2 days) for participants with HD], 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.
g. Test results of genetically confirmed disease with CAG expansion ≥36 collected as part of medical history is acceptable in lieu of central laboratory confirmation. For any genetic counseling, the study sites should follow their local practice.
h. Serum FSH test will be conducted at Screening for the female participants who are not surgically sterile to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal.
i. To include hepatitis B and C screening tests, HIV-1 and -2 antibody.
j. A single ECG will be measured after the participant has been in the supine position for at least 5 minutes. When ECG measurements coincide with vital signs assessment or blood draws, blood draws should be carried out after ECG and vital signs.
k. Clinical laboratory assessments will include blood samples for hematology, clinical chemistry, biochemistry, coagulation, genetic testing, and urinalysis. Samples will be collected ≤2 hours prior to dosing on Days 1 to 28. On nondosing days, collection may occur at any time.

[redacted]

m. Data on cigarette use will be collected using the question: "How many packs of cigarettes did you smoke over the past 7 days?" at the time points specified.
n. Serum pregnancy tests will be conducted for all female participants at Screening; urine pregnancy tests will be conducted at other scheduled time points for female participants that are not postmenopausal or surgically sterile.

[redacted]

r. To be administered to participant, study partner (if applicable), and clinician. Measures directed to study partner may be administered remotely or in person.
s. Study partner involvement is optional.
t. Cognitive tests at all time points will be performed at the same time of day (±2 hours) and will be conducted predose on Day 1 only, [redacted] The cognitive tests include the Huntington's Disease Cognitive Assessment Battery (HD-CAB; Symbol Digit Modalities Test, One Touch Stockings of Cambridge, Trail Making A and Trail Making B, Hopkins Verbal Learning Test_Revised, Paced Tapping Test, and Emotion Recognition Test) [redacted]

x. Daily reminders will be sent to participants via a mobile device to complete assessments on remote device. Daily assessments include [redacted] the National Sleep Foundation Sleep Diary. It is recommended that these assessments are completed at approximately the same time each day, within 1 hour following IP administration. Daily mobile assessments should be completed in a quiet area of participant's home. If in conflict with clinic visit schedule, remote assessment may be completed in the clinic under observation by the study staff.
y. On Days 1, 14, and 28 study visits, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing. All scheduled cognitive tests will be administered predose on Day 1 Visit only and postdose on Day 14 Visit (±2 days) and Day 28 Visit (±2 days). Participants will record the date and time of each dose taken at home and in-clinic using an application.
z. Study staff will dispense enough IP for the participant to take daily at home until the next scheduled visit.
aa. Participants will bring all used packaging and unused IP to the clinic at each visit for study staff to review and document.

Note: On screening (Days -28 to -2), Day 28, and Day 42, safety assessments [redacted] may be done on separate day(s) than the cognitive assessments, if need be, provided that all assessments are completed within the specified visit window (±2 days).

Table 2: Schedule of Assessments -Healthy Participants

Assessments	Screening Period		Reliability Assessment Period			Follow-up
	Days -28 to -2	Day -1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 42 (±2 days) or ET
Informed consent[a]	X					
Inclusion/exclusion criteria	X	X	X			
Medical history and demographics[b]	X					
Participant training[c]	X	X	X			
Body weight	X					X
Body height	X					
Vital signs (including orthostatics)[d]	X	X				X
Physical examination[e]	X	X				X
FSH test[f]	X					
Serology test[g]	X					
12-lead ECG[h]	X	X				X
Clinical laboratory assessments[i]	X	X				X
Urine drug test	X	X	X	X	X	X
Alcohol test	X	X	X	X	X	X
Cigarette/tobacco use assessment[j]	X		X	X	X	X
Pregnancy test[k]	X		X			X
C-SSRS (Screening)	X					
[redacted]						
Montreal Cognitive Assessment	X				X	
[redacted]						
Daily Mobile Assessments[p]		X----------				----------X
AEs/SAEs	X (from time of ICF throughout the duration of participation)					
Prior and concomitant medications	X----------					----------X

Abbreviations: AE = adverse event; [redacted]
COVID-19 = coronavirus disease 2019; C-SSRS = Columbia–Suicide Severity Rating Scale;
ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HD = Huntington's Disease; HD-CAB = Huntington's Disease Cognitive Assessment Battery, HIV = human immunodeficiency virus;

ICF = informed consent form; [redacted] SAE = serious adverse event; [redacted]

a. Participants will be consented during the Screening Period.
b. In addition to full medical history, all medications and supplements taken within 8 weeks prior to Screening. Information regarding diagnosis and/or hospitalization due to COVID-19 will be documented as part of medical history. The following demographics will be collected: age, race, sex, ethnicity, years of education, employment history, and current employment status.
c. Participants will be trained by study staff on the use of software applications and devices necessary for the conduct of the study.
d. Vital signs will 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 (Days -28 to -2) and at Day 42 (±2 days)/ET. A symptom-directed examination may be conducted at any time at the discretion of the investigator.
f. Serum FSH test will be conducted at Screening for the female participants who are not surgically sterile to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal.
g. To include hepatitis B and C screening tests, HIV-1 and -2 antibody.
h. A single ECG will be measured after the participant has been in the supine position for at least 5 minutes.
i. Clinical laboratory assessments will include blood samples for hematology, clinical chemistry, biochemistry, coagulation, and urinalysis. Sample collection may occur at any time.
j. Data on cigarette use will be collected using the question: "How many packs of cigarettes did you smoke over the past 7 days?" at the time points specified.
k. Serum pregnancy tests will be conducted for all female participants at Screening; urine pregnancy tests will be conducted at other scheduled time points for female participants that are not postmenopausal or surgically sterile.
[redacted]
m. Cognitive tests at all time points will be performed at the same time of day (±2 hours). The cognitive tests include the Huntington's Disease Cognitive Assessment Battery (HD-CAB; Symbol Digit Modalities Test, One Touch Stockings of Cambridge, Trail Making A and Trail Making B, Hopkins Verbal Learning Test_Revised, Paced Tapping Test, and Emotion Recognition Test) [redacted]
[redacted]
[redacted]
p. Daily reminders will be sent to participants via a mobile device to complete assessments on remote device. Daily assessments include [redacted] the National Sleep Foundation Sleep Diary. It is recommended that assessments are completed at approximately the same time each day. Daily mobile assessments should be completed in a quiet area of participant's home. If in conflict with clinic visit schedule, remote assessment may be completed in the clinic under observation by the study staff.

Note: On Days 28 and 42, safety assessments [redacted] may be done on separate day(s) than the cognitive assessments, if need be, provided that all assessments are completed within the specified visit window (±2 days).

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

TABLE OF CONTENTS

1. TITLE PAGE 1
2. SYNOPSIS 7
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 23
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 29
5. INTRODUCTION 32
5.1. Dose Justification 32
6. STUDY OBJECTIVES AND ENDPOINTS 34
6.1. Objectives and Endpoints 34
7. INVESTIGATIONAL PLAN 36
7.1. Overall Study Design 36
7.1.1. Screening Period 37
7.1.2. Baseline Period 37
7.1.3. Treatment Period 37
7.1.4. Follow-up Period 37
7.2. Number of Participants 39
7.3. Treatment Assignment 39
7.4. Dose Criteria 39
7.4.1. Stopping Criteria 39
7.5. Criteria for Study Termination 39
7.6. End of Study Definition 39
8. SELECTION AND WITHDRAWAL OF PARTICIPANTS 40
8.1. Participant Inclusion Criteria 40
8.2. Participant Exclusion Criteria 41
8.3. Screen Failures 43
8.4. Investigational Product Discontinuation and Early Termination from the Study 43
8.4.1. Investigational Product Discontinuation 43
8.4.2. Early Termination from the Study 43
8.4.3. Loss to Follow-up 44
8.4.4. Replacement of Participants 44

9. TREATMENT OF PARTICIPANTS 45
9.1. Description of Investigational Product 45
9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements 45
9.2.1. Prior and Concomitant Medications and/or Supplements 45
9.2.2. Prohibited Medications 45
9.2.3. Other Restrictions and Recommendations 46
9.2.4. Acceptable Forms of Contraception 46
9.3. Intervention After the End of the Study 47
9.4. Treatment Adherence 47
9.5. Randomization and Blinding 47
9.5.1. Emergency Unblinding 48
10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT 49
10.1. Investigational Product 49
10.2. Investigational Product Packaging and Labeling 49
10.3. Investigational Product Storage 49
10.4. Investigational Product Preparation 50
10.5. Investigational Product Administration 50
10.5.1. Medication Adherence and Reminder System 50
10.5.1.1. Ongoing Use and Monitoring of Medication Adherence 50
10.6. Investigational Product Accountability, Handling, and Disposal 50
10.7. Product Complaints 51
11. SCREENING, EFFICACY, AND CLINICAL PHARMACOLOGY ASSESSMENTS 52
11.1. Screening Assessments 52
11.1.1. Montreal Cognitive Assessment 52
11.1.2. Cigarette and/or Tobacco Use Assessment 52
11.2. Efficacy Assessments 53
11.2.1. Huntington's Disease-Cognitive Assessment Battery Individual Assessments 53
11.2.1.1. Symbol Digit Modalities Test 53
11.2.1.2. One Touch Stockings of Cambridge 53
11.2.1.3. Trail Making 53
11.2.1.4. Hopkins Verbal Learning Test_Revised 53

11.2.1.5. Paced Tapping Test....54
11.2.1.6. Emotion Recognition Task....54
[redacted]....54
[redacted]....54
[redacted]....54
[redacted]....54
[redacted]....55
[redacted]....55
[redacted]....55
[redacted]....55
[redacted]....55
[redacted]....55
[redacted]....56
[redacted]....56
[redacted]....56
[redacted]....56
11.2.5. Daily Mobile Assessments....56
[redacted]....56
[redacted]....57
11.2.5.3. National Sleep Foundation Sleep Diary....57
[redacted]....57
[redacted]....57
[redacted]....57
[redacted]....58
[redacted]....58
[redacted]....59
[redacted]....59
[redacted]....59
11.3. Clinical Pharmacology Assessments....59
[redacted]....59
[redacted]....60
[redacted]....60
11.3.2. Pharmacodynamic Assessments....60

[redacted] [redacted] 60
[redacted] [redacted] 60
12. SAFETY ASSESSMENTS 62
12.1. Safety Parameters 62
12.1.1. Demography and Medical History 62
12.1.2. Weight and Height 62
12.1.3. Physical Examination 62
12.1.4. COVID-19 Questions 62
12.1.5. Vital Signs 62
12.1.6. Electrocardiogram 63
12.1.7. Laboratory Assessments 63
12.1.7.1. Drugs of Abuse, Alcohol 64
12.1.7.2. Pregnancy Testing 64
12.1.8. Columbia-Suicide Severity Rating Scale (C-SSRS) 64
12.2. Adverse and Serious Adverse Events 64
12.2.1. Adverse Event Definition 64
12.2.2. Serious Adverse Event Definition 65
12.2.3. Relationship to Investigational Product 66
12.2.4. Definition of Urgent Safety Measure (USM) and Unanticipated Problem (UP) 66
12.2.5. Recording Adverse Events 67
12.2.6. Reporting Serious Adverse Events 67
12.3. Pregnancy 68
12.4. Overdose 68
12.5. Special Considerations 68
13. STATISTICS 70
13.1. Data Analysis Sets 70
13.2. Handling of Missing Data 70
13.3. General Considerations 70
13.4. Demographics and Baseline Characteristics 71
13.5. Efficacy Analysis 71
13.6. Safety Analyses 71
13.6.1. Adverse Events 72

13.6.2. Clinical Laboratory Evaluations 72
13.6.3. Physical Examinations 72
13.6.4. Vital Signs 72
13.6.5. 12-Lead Electrocardiogram 72
13.6.6. Prior and Concomitant Medications 73
13.6.7. Columbia Suicide Severity Rating Scale 73
13.6.8. Other Safety Analysis 73
13.7. Clinical Pharmacology Analyses 73
13.8. Sample Size and Power 73
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 75
14.1. Study Monitoring 75
14.2. Audits and Inspections 75
14.3. Institutional Review Board or Ethics Committee 76
15. QUALITY CONTROL AND QUALITY ASSURANCE 77
16. ETHICS 78
16.1. Ethics Review 78
16.2. Ethical Conduct of the Study 78
16.3. Written Informed Consent 78
16.4. Data Protection 79
17. DATA HANDLING AND RECORDKEEPING 80
17.1. Inspection of Records 80
17.2. Retention of Records 80
18. PUBLICATION POLICY 81
19. LIST OF REFERENCES 82
[redacted] [redacted] 84
[redacted] [redacted] 84

LIST OF TABLES

Table 1: Schedule of Assessments -Huntington's Disease 16
Table 2: Schedule of Assessments -Healthy Participants 20
[redacted] 22
Table 4: Abbreviations and Specialist Terms 29
Table 5: Investigational Product 49
Table 6: Summary of Clinical Laboratory Analytes 63

LIST OF FIGURES

Figure 1: Study Design 38

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
[redacted]	[redacted]
BMI	body mass index
[redacted]	[redacted]
CAG	cytosine, adenine, and guanine
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CAP	CAG-Age-Product
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
CS	clinically significant
C-SSRS	Columbia–Suicide Severity Rating Scale
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
eCRF	electronic case report form
ECG	electrocardiogram
EC	Ethic Committee
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

Abbreviation	Definition
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
GMP	Good Manufacturing Practice
[redacted]	[redacted]
HD	Huntington's Disease
HD-CAB	Huntington's Disease Cognitive Assessment Battery
[redacted]	[redacted]
[redacted]	[redacted]
HIV	human immunodeficiency virus
HP	healthy participant(s)
[redacted]	[redacted]
HTT	Huntington gene
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	a participant identification
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MoCA	Montreal Cognitive Assessment
mRNA	messenger ribonucleic acid
NCS	not clinically significant
[redacted]	[redacted]
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
NSF	National Sleep Foundation

Abbreviation	Definition
PAM	positive allosteric modulator
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic
PO	by mouth
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
Study partner	Synonymous with care partner
TEAE	treatment-emergent adverse event
TFC	Total Functional Capacity
THC	tetrahydrocannabinol
UHDRS	Unified Huntington's Disease Rating Scale
UP	unanticipated problem
USM	urgent safety measure
[redacted]	[redacted]

5. INTRODUCTION

Huntington's Disease (HD) is a rare hereditary neurodegenerative disease characterized by specific motor symptoms, including chorea and rigidity, and deterioration of psychiatric and cognitive function. The motor symptoms can manifest at any age, after which disease progression leads to incapacitation and death. Before the appearance of motor symptoms, psychiatric and cognitive dysfunction predominate (Tabrizi 2012). Cognitive impairment is always present in the course of the disease, even in premanifest gene carriers (Cardoso 2017).

The mechanisms of cognitive changes in HD have not been fully described, but changes in glutamatergic neurotransmission appear to be involved. Reduced glutamate in the posterior cingulate cortex has been correlated with cognitive dysfunction in early manifest HD (Unschuld 2012). N-methyl-D-aspartate (NMDA) receptors are a subtype of glutamate receptor with a fundamental and well documented role in regulating synaptic strength, health, and plasticity (Vyklicky 2014, Yao 2017). NMDA receptors have been found to be dysfunctional in the postmortem brains of patients with HD (Albin 1990). Together, these data suggest that lowered NMDA receptor tone may contribute to cognitive dysfunction in HD (Paul 2013).

Preclinical data illustrate that patients with HD have reduced plasma levels of a specific oxysterol, 24(S)-hydroxycholesterol (Leoni 2013). This molecule acts as an endogenous positive allosteric modulator (PAM) of the NMDA receptor (Paul 2013) and has been correlated with performance on several cognitive tasks in HD (Lewis 2019). SAGE-718 is a novel oxysterol-based PAM of NMDA receptors with the potential to restore NMDA receptor tone to ameliorate cognitive deficits in HD. SAGE-718 only affects receptor function in the presence of endogenous glutamate, thus it does not directly activate the receptor and is not expected to cause NMDA receptor-associated excitotoxicity.

The effect of SAGE-718 on cognitive and function outcomes in participants with HD will be evaluated in a randomized, placebo-controlled, double-blind, parallel group and normative comparison study. Additional data on the effects of SAGE-718 in participants with HD will be collected throughout, including assessments of neuropsychiatric and motor symptoms.

5.1. Dose Justification

SAGE-718 has been well tolerated in both healthy participants (HP) and a small cohort of participants with HD in previous clinical studies. However, based on nonclinical findings, the United States Food and Drug Administration (FDA) imposed a median maximum concentration (C_{max}) cap of 45 ng/mL. To date, clinical studies with SAGE-718 have used doses that resulted in exposures within this cap and no related adverse events (AEs) leading to discontinuation have been reported. For additional information on the exposure caps, see the SAGE-718 investigator's brochure.

From a previous study of SAGE-718 administered as an oral solution in healthy participants, repeat doses of 1 mg and a single dose of 3 mg demonstrated evidence consistent with NMDA target engagement. From a 14-day study of SAGE-718 administered as an oral solution in participants with HD, repeat doses of 1 mg showed beneficial effects on cognition assessments. Similarly, from a 14-day study of SAGE-718 administered as a solid tablet in participants with Parkinson's Disease, repeat doses of 3 mg when taken with a meal containing approximately 30 g of dietary fat showed beneficial effects on cognition assessments. The pharmacokinetic

(PK) exposures in the above scenarios were similar, with individual C_{max} values ranging from 19.7 to 29.7 ng/mL.

In the present study, SAGE-718 will be administered as a lipid based softgel formulation at a daily dose of 1.2 mg. The lipid formulation has improved bioavailability characteristics compared to solution and tablet forms. [redacted]

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the magnitude of the baseline difference between participants with Early Huntington's Disease (HD) and healthy participants (HP) with respect to measures of cognitive performance.	• Difference in baseline measures of the Huntington's Disease Cognitive Assessment Battery (HD-CAB) cognitive composite score in participants with HD and HP.
Secondary	
• To evaluate safety and tolerability of SAGE-718 in participants with HD.	• Safety and tolerability of SAGE-718 as assessed by the incidence of adverse events (AEs)/serious adverse events (SAEs), and by changes in vital signs and clinical laboratory parameters.
[redacted]	

[redacted]

• To evaluate additional safety and tolerability parameters of SAGE-718 in participants with HD.	• Change from Baseline and between-group effects (SAGE-718 and placebo) for [redacted], electrocardiograms (ECGs), and responses on the Columbia-Suicide Severity Rating Scale (C-SSRS).

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, placebo-controlled, double-blind, parallel group study with a 28-day treatment duration to evaluate the effects of SAGE-718 on functioning capacity, safety, and tolerability in participants with early manifest HD. Participants will be adults with genetically-confirmed expansion of the Huntingtin (HTT) gene cytosine, adenine, and guanine (CAG) trinucleotide repeat at screening who meet diagnostic criteria detailed in the inclusion criteria below [including Unified Huntington's Disease Rating Scale (UHDRS) scores and CAG-Age-Product [CAP] scores within specific ranges).

HP enrolled in the study will follow the same assessment schedule as participants with HD, but will not receive SAGE-718 or placebo, and will complete assessments only on performance-based tests (HD-CAB[redacted]), not HD-specific measures of functioning and HD symptomatology.

An adult study partner for participants with HD is optional but highly recommended for each participant with HD to support completion of study activities and to answer questions about the participant's condition. For prospective participants with HD and study partners (if applicable), the study will begin with the informed consent process.

Screening, safety, and efficacy assessments will be performed according to the schedule presented in Table 1 (HD) and Table 2 (HP). [redacted]

Screening assessments will be performed to determine eligibility. Participants and study partners (if applicable) will receive training on the study procedures and devices.

Eligible participants with HD will be randomized 1:1 in a stratified manner based on previous intake of antisense oligonucleotide drugs (yes/no) to receive 1.2 mg of SAGE-718 or placebo for up to 28 days. Beginning on Day 1 and continuing through Day 28, participants with HD will self-administer blinded investigational product (IP) once per day in the morning. At clinic visits, participants with HD will take the IP under staff supervision, [redacted] Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by examination of the used packaging and counting any returned tablets.

During the Treatment Period, participants with HD will be able to receive IP as long as there are no dose-limiting safety/tolerability concerns. Participants with HD who discontinue IP early should complete the remaining study visits as scheduled, unless the participant with HD withdraws consent or loses the capacity to grant consent. If a participant with HD withdraws from the study or stops study participation, an early termination (ET) visit should be conducted.

After completing the Treatment Period or Reliability Assessment Period, all participants will return to the clinic for follow-up visits on Day 42 (±2 days) to collect continued safety and efficacy data.

7.1.1. Screening Period

The Screening Period begins with the informed consent process for prospective participants, including study partners for participants with HD. Subsequent screening assessments will be performed between Day -28 and Day -1 for participants with HD and HP to determine eligibility, including assessments of cognitive function.

7.1.2. Baseline Period

The Baseline Period will be completed by Day 1 for participants with HD and HP. During this period, participants will visit the clinic for confirmation of continued eligibility and collection of baseline cognitive and safety data.

7.1.3. Treatment Period

Eligible participants with HD will be randomized 1:1 to receive SAGE-718, or placebo for 28 days. Beginning on Day 1 and continuing through the 4-week treatment period, participants with HD will self-administer blinded 1.2 mg SAGE-718 (as 1.2-mg softgel lipid capsules) or placebo, once per day in the morning. Participants who utilize the ±2 day window at Day 28 should continue to self-administer IP within the visit window. HP will not receive SAGE-718 or placebo.

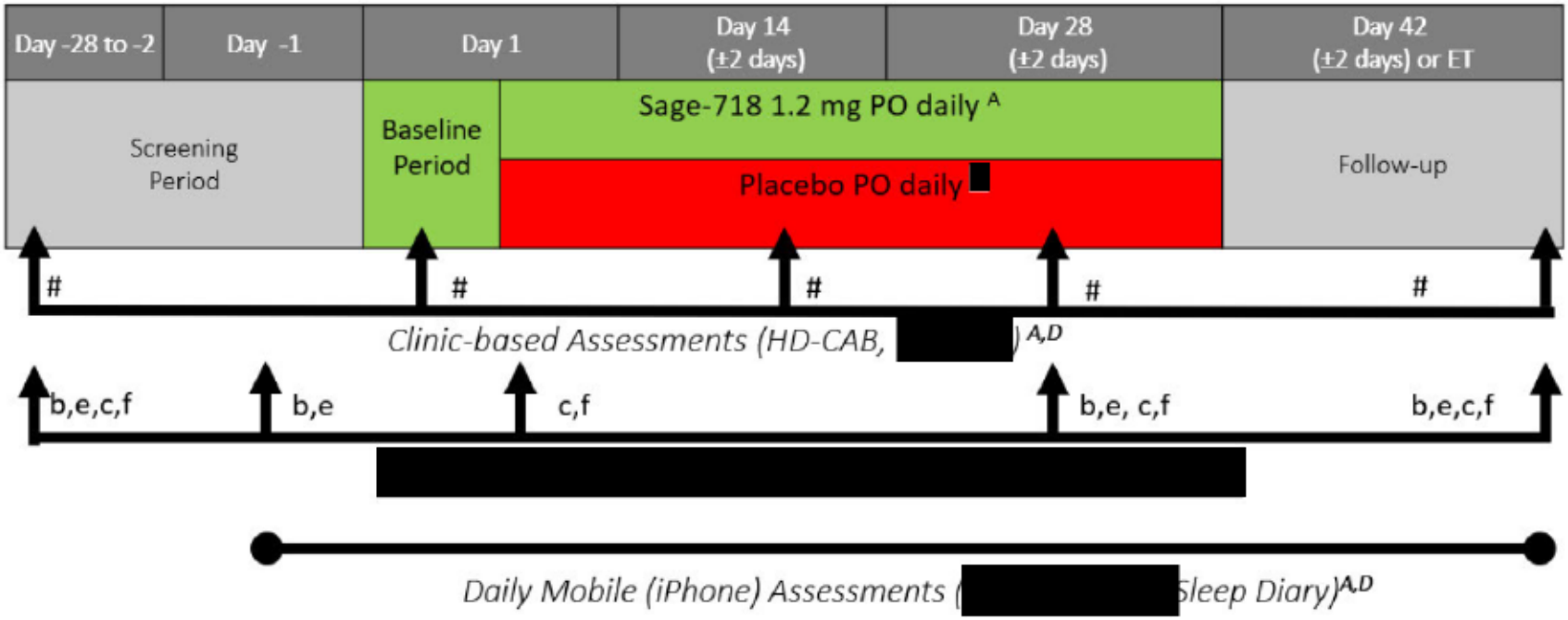
At clinic visits, participants with HD will take the IP under staff supervision, [redacted] Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by examination of the used packaging and counting any returned tablets.

During the Treatment Period, participants with HD will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants with HD who discontinue IP early should complete the remaining study visits as scheduled, unless the participant with HD withdraws consent or loses the capacity to grant consent. If a participant with HD withdraws from the study or stops study participation early, an ET visit should be conducted.

7.1.4. Follow-up Period

After completing the Treatment Period or Reliability Assessment Period, all participants will return to the clinic for follow-up visits on Day 42 (±2 days) to collect continued safety and efficacy data (Table 1 and Table 2).

Figure 1: Study Design



Abbreviations: HD = Huntington's Disease, HD-CAB = Huntington's Disease Cognitive Assessment Battery, HP = healthy participants, PO = by mouth,

[A] **Participants with HD:**

[b]

[c]

[D] **HP: (Assessments Only)**

[e]

[f]

[#]

7.2. Number of Participants

Approximately 40 participants with early HD (n = 20 per treatment arm) will be randomized in the study to obtain 32 evaluable participants with HD (n = 16 per treatment arm). Additional participants may be randomized if the early discontinuation rate is higher than expected (20%). Approximately 40 matched healthy participants (eg. age, sex, race and education) will be enrolled in an "assessment only" arm and will complete specific assessment procedures following the same schedule as the treatment arm participants.

7.3. Treatment Assignment

Eligible participants with HD will be randomized 1:1 to receive 1.2 mg of SAGE-718, or placebo for up to 28 days. Additional details on randomization and blinding are provided in Section 9.5.

7.4. Dose Criteria

During the Treatment Period, participants with HD will be able to receive IP as long as there are no dose limiting safety/tolerability concerns.

7.4.1. Stopping Criteria

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

7.5. Criteria for Study Termination

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

7.6. End of Study Definition

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

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

Each eligible participant must:

For All

1. Be capable of providing informed consent, in the opinion of the investigator.
2. Have signed an informed consent form (ICF) prior to any study-specific procedures being performed.
3. Agree to adhere to the study requirements.
4. Be capable of complying with study procedures, in the opinion of the investigator. The investigator may determine a participant's capability of being able to complete the Driving Simulator at Screening based on the outcome of the simulator sickness screening interview.
5. Be at least 25 years old but no older than 65 years of age at Screening.
6. Currently hold a valid driver's license, 5+ years driving experience, and participants opting in the driving simulator assessment are currently driving at least 1 × weekly.
7. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.

Additional criteria for participants with HD only

8. Be ambulatory (use of assistance devices such as a walker or cane is acceptable, as is occasional use of wheelchair. Individuals requiring a wheelchair on a regular basis are excluded), able to travel to the study center, and, judged by the investigator, is likely to be able to continue to travel to the study center to complete study visits for the duration of the study.
9. Have:
    a. Genetically confirmed disease with CAG expansion ≥36.
    b. At Screening, UHDRS TFC >6 and <13, suggesting no more than a moderate level of functional impairment.
    c. No features of juvenile HD.
10. CAP score >70, as calculated using the CAP formula: AGE × (CAG – 30) / 6.49.
11. Score of 15 to 25 (inclusive) on the MoCA at Screening, indicating the presence of cognitive impairment.
12. Be willing to invite a study partner, if available, who is reliable, competent, and at least 18 years of age to participate in the study.
13. Agree, if female, to use at least one method of highly effective contraception (refer to Section 9.2.4 for further details on acceptable forms of contraception) during participation in the study and for 155 days following the last dose of IP, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical

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

14. Agree, if male, to use an acceptable method of effective contraception for the duration of study and for 215 days after receiving the last dose of the IP, unless the participant does not engage in sexual relations which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
15. Agree, if male, to abstain from sperm donation during the Treatment Period and for 215 days after receiving the last dose of IP.

Additional criteria for HP only

16. Score ≥26 on the MoCA at Screening.
17. Have no known family history of HD; or, have known family history of HD but have genetic test results available that show a normal CAG repeat length for both HTT alleles (<36).

8.2. Participant Exclusion Criteria

Each eligible participant must not:

For All

1. Have been diagnosed with and/or treated for any type of cancer (excluding successfully treated locally excised basal cell carcinoma and melanoma in situ) within the past year prior to Screening.
2. Plans to undergo elective surgery during participation in the study.
3. Have current or recent suicidality, defined as follows:
   - Suicidal ideation within the past month, as evidenced by a "Yes" on question 4 (active suicidal ideation with some intent to act, without specific plan) or question 5 (active suicidal ideation with specific plan and intent) on the C-SSRS.
   - Suicidal behavior within the past year, as evidenced by a "Yes" on any of the C-SSRS Suicidal Behavior items (actual attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, or suicidal behavior) on the C-SSRS.
   - Presenting a serious risk of suicide in the opinion of the investigator.
4. Take any psychotropic medications, including antidepressants and anxiolytics, unless the dose and frequency have been stable for at least 30 days prior to the first IP administration and are expected to remain stable for the duration of the study.
5. Have an ongoing medical or psychiatric condition that, in the opinion of the investigator, may compromise the participant's safety or compliance with study requirements.
6. Have supine vital signs outside of the following ranges at Screening or Baseline (vital sign measurements may be repeated once for initial values outside these ranges):
   - Heart rate <50 or >100 bpm,
   - Systolic blood pressure <100 or >160 mmHg,

- Diastolic blood pressure <60 or >100 mmHg.

7. Have an alcohol or drug use disorder within the past 2 years, as assessed by the investigator. A positive urine drug screen is exclusionary unless deemed by the investigator to reflect a prescribed medication.
8. Have a history of significant hand injury that would preclude either writing or rapid bimanual computerized responding.
9. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood.
10. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1 or HIV-2 or hepatitis B or C.
11. Have a history of brain surgery, a significant head injury causing loss of consciousness greater than 30 minutes, or hospitalization due to a brain injury.
12. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion).
13. Have a positive pregnancy test, is lactating, or intend to breastfeed during the study.
14. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
15. Have participated in a previous clinical study of SAGE-718; have previous exposure to gene therapy; or have participated in any Huntington's Disease (HD) investigational drug, biologic, or device trial within 180 days, or a non-HD drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer).

    (Note: Participants with confirmation of enrollment in the placebo arm of these trials would not be excluded.)
16. Receive any prohibited medications within 30 days of Screening and during participation in the study:
    a. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as determined by the investigator.
    b. Tetrahydrocannabinol (THC)-containing substances (any route of administration), regardless of whether or not they are prescribed.
17. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.

<u>Additional criteria for participants with HD only</u>

18. Had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
19. Receive any prohibited medications within 30 days of Screening and during participation in the study:
    a. Medications with potent effects at the NMDA receptor, including memantine, amantadine, ketamine, cycloserine, or related compounds.
    b. Medications that inhibit cholesterol absorption (eg, ezetimibe).

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

20. Have a diagnosis of an ongoing neurodegenerative condition other than HD, including but not limited to Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease.

Additional criteria for HP only

21. Have a diagnosis of an ongoing neurodegenerative condition, including but not limited to HD, Alzheimer's Disease, vascular dementia, dementia with Lewy bodies, or Parkinson's Disease.

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/entered in the study. A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any AE or SAE.

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 ET 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 ET Visit.

8.4.2. Early Termination from the Study

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

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

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

Possible reasons for study discontinuation include but are not limited to the following:

- AE
- Pregnancy
- Protocol deviation
- Non-compliance with study drug
- Lost to follow-up
- Withdrawal by subject
- Screen failure
- Study terminated by sponsor
- Physician decision
- Other

8.4.3. Loss to Follow-up

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

8.4.4. Replacement of Participants

Participants who discontinue or withdraw from the study will not be replaced. However, additional participants with HD may be randomized if the dropout rate is higher than 20%.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

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

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

9.2.1. Prior and Concomitant Medications and/or Supplements

All medications and supplements taken within 8 weeks prior to Screening, all medications used to treat HD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD will be recorded. Information regarding diagnosis and/or hospitalization due to coronavirus disease 2019 (COVID-19) will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

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

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

9.2.2. Prohibited Medications

Prohibited medications prior to and during the study include:

- Gene therapy
- HD investigational drug, biologic, or device within 180 days prior to Screening and until the final visit
- Non-HD investigational drug, biologic, or device within 30 days or 5 half-lives (whichever is longer) prior to Screening and until the final visit

Use of the following medications is prohibited within 30 days of screening and during the entire course of the study:

- Medications that inhibit cholesterol absorption (eg, ezetimibe).
- Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine).

- Medications with potent effects at the NMDA receptor, including memantine, amantadine, cycloserine, ketamine, or related compounds.
- THC-containing substances (any route of administration), regardless of whether or not they are prescribed

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.

9.2.3. Other Restrictions and Recommendations

Participants must agree to refrain from drugs of abuse for the duration of the study (unless deemed by the investigator to reflect a prescribed medication) and from alcohol during the 48 hours preceding each study visit.

Psychotropic medications and medications that are known to affect cognitive performance (ie, antidepressants, anxiolytics, stimulants, benzodiazepines, antipsychotics, anticholinergics) must be at a stable dose for at least 30 days prior to the first IP administration. Additions and/or modifications to these medications should be minimized throughout the course of the study.

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 are to be avoided as much as possible.

Any additions or modifications to medications during the course of the study will be recorded in the concomitant medications log and source documentation.

9.2.4. Acceptable Forms of Contraception

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

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

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

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

- Sexual abstinence;
- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation;

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

Acceptable forms of contraception for male participants include:

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

9.3. Intervention After the End of the Study

If eligible, participants with HD who complete this study may continue or begin treatment with SAGE-718 by participating in the long-term open-label study 718-CIH-301.

9.4. Treatment Adherence

Beginning on Day 1 and continuing through Day 28, participants with HD will self-administer blinded IP once per day in the morning. At clinic visits, participants with HD will take the IP under staff supervision, [redacted] Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. IP adherence diary will be collected daily via the [redacted] application. This information will be documented in the source files and eCRF, along with any deviations from the prescribed dosage regimen. Adherence will be assessed during the visit and documented. Any reasons for non-adherence will also be documented. Details about IP accountability are included in Section 10.6.

9.5. Randomization and Blinding

This is a randomized, placebo-controlled, double-blind, parallel group study. Eligible participants with HD will be randomized 1:1 in a stratified manner by previous intake of antisense oligonucleotide drugs (yes/no) to receive SAGE-718, or matching placebo for 28 days. Stratified randomization will ensure the treatment balance within each stratum of prior antisense oligonucleotide drug intake (yes or no) with the consideration that participants with or without prior exposure to antisense oligonucleotide drug may respond to treatment differently. Randomization will take place on Day 1.

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

Similarly for HP on Day 1, site staff will access the IRT and provide the necessary participant identifying information, including participant identification (ID) number assigned at Screening to register the eligible HP in the IRT system as enrolled status, and set as inactive for treatment assignment.

9.5.1. Emergency Unblinding

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

In all cases where the study personnel are unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's source documentation and on the eCRF. At the time of withdrawal from the study/stopping participation, if possible, an ET visit should be conducted.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

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

Table 5: Investigational Product

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

[a] US only

10.2. Investigational Product Packaging and Labeling

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

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

10.3. Investigational Product Storage

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

The IP must be carefully stored at the temperature specified in the investigator's brochure and Pharmacy Manual. The IP may not be used for any purpose other than the present study. After the study is completed, all unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s) in accordance with the study-specific Pharmacy Manual.

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

10.4. Investigational Product Preparation

SAGE-718 1.2 mg or placebo will be provided as softgel lipid capsules for self-administration once daily in the morning for up to 28 days.

10.5. Investigational Product Administration

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

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

SAGE-718 or placebo will be self-administered by participants with HD once daily in the morning. Sites will dispense a 2-week supply of IP to the participants with HD to take at home with instructions for use (see Table 1).

In addition, the participant with HD will be instructed to bring their dosing kit to the site as outlined in Table 1. All participants with HD should be reinstructed about the dosing requirements during study contacts. The authorized study personnel conducting the re-education must document the process in the participants with HD source records.

The investigator(s) will record any reasons for noncompliance in the source documents.

10.5.1. Medication Adherence and Reminder System

10.5.1.1. Ongoing Use and Monitoring of Medication Adherence

In cases of missed doses, site personnel should follow up with the participant with HD as soon as possible to assess the reason for nonadherence and reinforce the importance of complying with the IP dosing schedule.

Participants with HD who are consistently noncompliant with study medication should be discussed with the medical monitor.

10.6. Investigational Product Accountability, Handling, and Disposal

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

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in Table 1.

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

Refer to Section 9.5 for the IRT assignment and registration process for HP.

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

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

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

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

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

More detailed information can be found in the SAGE--718 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 emergency contact information. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. SCREENING, EFFICACY, AND CLINICAL PHARMACOLOGY ASSESSMENTS

A variety of measures will be employed in this study to evaluate [redacted] All assessments will be completed according to the Schedules of Assessments (Table 1 and Table 2) [redacted].

The eligible participants with HD in this study will be in the earliest stages of HD and are expected to be able to independently care for themselves. However, some of these assessments include information provided by caregivers. For the purposes of this study, the word "caregiver" refers to the participant's study partner.

11.1. Screening Assessments

11.1.1. Montreal Cognitive Assessment

The MoCA is a measure designed as a cognitive screening instrument that is widely used in clinical settings. This 1 page, 30-point questionnaire assesses several different cognitive domains, including attention and concentration, executive functions, memory, language, visuospatial skills, conceptual thinking, calculations, and orientation.

The Montreal Cognitive Assessment Memory Total Score includes all cognitive domains measured and represented global cognitive function. This assessment is expected to take approximately 10 minutes to complete. The test is scored from zero to 30, with scores 26 or higher indicating normal cognition (Nasreddine 2005).

A subset of MoCA will be audio recorded and reviewed with the goal of minimizing the variability in assessment data. Personal participant identifiers should not be included in the recordings.

The recorded study interviews will be encrypted and stored on the study devices with password-protected access for authorized users only. Recordings will be removed from the study devices once they are transferred via secure portal to the study server, where they will remain until study completion when Sage Therapeutics provides destruction authorization or other instructions.

[redacted]

Refer to Table 1 and Table 2 for a listing of screening assessments.

11.1.2. Cigarette and/or Tobacco Use Assessment

Data on cigarette use will be collected using the question: "How many packs of cigarettes did you smoke over the past 7 days?".

Note: In addition to Screening, this assessment is also performed at additional timepoints, as outlined in Table 1 and Table 2.

11.2. Efficacy Assessments

The assessments described below provide broad neurocognitive evaluation across the domains of executive function, learning and memory, motor coordination, and social cognition.

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 will be administered predose on Day 1 only and after the daily dose of SAGE-718 during the Treatment Period on Day 14 (±2 days) and Day 28 (±2 days) for participants with HD (Table 1), and at approximately the same time of day (±2 hours) throughout the study for participants with HD and HP.

11.2.1. Huntington's Disease-Cognitive Assessment Battery Individual Assessments

The HD-CAB is a cognitive assessment battery designed for clinical trials in HD (Stout 2014). The battery consists of the 6 following subtests: Symbol Digit Modalities Test, One Touch Stockings of Cambridge, Trail Making, Hopkins Verbal Learning Test_Revised, Paced Tapping Test, and Emotion Recognition Test.

11.2.1.1. Symbol Digit Modalities Test

The Symbol Digit Modalities Test is widely used to monitor changes in cognitive function over time and for early detection of cognitive dysfunction. The task requires participants to use a reference key to pair specific numbers with geometric figures. The number of correct pairings (out of 110 possible) achieved within 90 seconds is summed to generate a total score.

11.2.1.2. One Touch Stockings of Cambridge

One Touch Stockings of Cambridge is a computerized test of executive function. For this task, participants must imagine stacking a set of colored balls to match an example by moving 1 ball at a time into 1 of 2 possible locations. The goal is to imagine the fewest number of moves needed to perform the task. The participant selects that number from the response options on the screen. The primary measure for analysis is time to correct response.

11.2.1.3. Trail Making

The Trail Making test is a speeded graphomotor test of visual attention and task switching, administered in two parts. Part A requires the examinee to connect a series of numbers in order from lowest to highest as quickly as possible. Part B includes an additional set-switching component, requiring the examinee to connect a series of alternating numbers and letters in order from lowest to highest, as in 1-A-2-B-3-C..., in the shortest time possible. The primary measure for analysis is time to completion.

11.2.1.4. Hopkins Verbal Learning Test_Revised

The Hopkins Verbal Learning Test_Revised is used to assess verbal learning and memory. The test consists of three learning trials over which a 12-item semantically categorized list is read aloud by an examiner. The examinee is asked to recall as many items as possible from memory immediately following each trial (immediate recall) and again following a delay (delayed recall).

The primary measure for analysis is the total words correctly recalled over 4 trials (3 immediate and 1 delayed) with a maximum of 48 correct.

11.2.1.5. Paced Tapping Test

In paced tapping, examinees are presented with auditory pacing tones and instructed to harmonize their fingertaps with the pacing tones. A self-paced phase follows, in which the auditory pacing cue is removed, and ends with another auditory cue demarking the end of the test. The primary measure of analysis is paced tapping consistency, calculated as 1/standard deviation (SD) of the intertap interval (1/msec).

11.2.1.6. Emotion Recognition Task

The Emotion Recognition Task has participants identify the emotions expressed on a series of computer-generated human faces (ie, sadness, happiness, fear, anger, disgust, and surprise). The responses can be analyzed by total errors, response latency, and the number of errors for each emotion. The primary measure for analysis is the number of correct negative emotion trials (out of 24).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.2.5. Daily Mobile Assessments

[redacted]

[redacted]

[redacted]

11.2.5.3. National Sleep Foundation Sleep Diary

Once daily in the morning, participants will briefly answer 5 questions about sleep length, sleep latency, night awakenings, and sleep quality. These questions have been modified from version 6 of the National Sleep Foundation Sleep Diary (National Sleep Foundation). This diary will be completed each morning during the Treatment Period using a mobile device. At scheduled clinic visits, the task will be performed in the clinic under observation by study staff, otherwise the participant will perform this task remotely (at home).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.3. Clinical Pharmacology Assessments

[redacted]

[redacted]

[redacted]

11.3.2. Pharmacodynamic Assessments

Blood samples will be collected, stored, and analyzed to identify biochemical and/or genetic markers associated with SAGE-718. 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]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 1 and Table 2) [redacted].

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity, years of education, employment history, and current employment status) and a full medical history will be documented. Confirmed (genetically tested) or suspected family history of HD will also be documented.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Full physical examinations will be performed at Screening and Day 42 (±2 days)/Early Termination (ET), and include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as cognitive and neurological examination, and mental status examination. At other visits (eg, Day 28 for participants with HD), 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. Unscheduled physical examinations may also be conducted per the investigator's discretion.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

12.1.4. COVID-19 Questions

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

12.1.5. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Systolic and diastolic blood pressure will 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.

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

12.1.6. Electrocardiogram

A 12-lead ECG will be performed at the time points described in Table 1 and Table 2. The standard intervals (heart rate, PR, QRS, QT, and QT corrected according to Fridericia's formula (QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiogram will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with vital signs assessment or blood draws, blood draws should be carried out after ECG and vital signs.

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

12.1.7. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 6.

Table 6: Summary of Clinical Laboratory Analytes

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

Abbreviations: CAG = cytosine, adenine, and guanine, HDL = high density lipoprotein, HIV = human immunodeficiency virus, LDL = low density lipoprotein, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, RBC = Red blood cell, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid-stimulating hormone.
a Genetically confirmed disease with CAG expansion ≥36 collected as part of medical history is acceptable in lieu of central laboratory confirmation. For any genetic counseling, the study sites should follow their local practice.

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

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

12.1.7.1. Drugs of Abuse, Alcohol

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

12.1.7.2. Pregnancy Testing

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

12.1.8. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

The "Baseline/Screening" C-SSRS form will be completed at Screening (lifetime, past 1 year and past month) (Table 1 and Table 2). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points outlined in Table 1.

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

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

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

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

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

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

12.2.2. Serious Adverse Event Definition

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

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

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

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

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

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

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

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

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

In accordance with FDA Guidance 21 CFR Part 312.66, some reported events may qualify as an unanticipated problem (UP), defined as any incident, experience, or outcome that meets all of the following criteria:

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

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

12.2.5. Recording Adverse Events

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

Intensity will be assessed according to the following scale:

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

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

12.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage Therapeutics and 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 Therapeutics and designee.

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

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

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

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

12.3. Pregnancy

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

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

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

12.4. Overdose

Overdose is described in Section 12.5.

12.5. Special Considerations

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

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

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

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

13. STATISTICS

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

13.1. Data Analysis Sets

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

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

The Full Analysis Set will include all participants who meet the eligibility criteria and have at least 1 baseline assessment of HD-CAB (participants with HD and HP).

The Full Analysis Set 1 will include all participants who initiate IP and have baseline and at least 1 postbaseline efficacy evaluation (participants with HD only).

The Full Analysis Set 2 will include all participants with HD who initiate IP or HP who meet eligibility criteria and have baseline and at least 1 postbaseline efficacy evaluation (participants with HD and HP).

The Healthy Participant Set will include all the healthy participants who meet the eligibility criteria and have more than one evaluation (baseline and at least one postbaseline).

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 non-missing data available. Imputation process will be applied and described in the SAP if needed.

13.3. General Considerations

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

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

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

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

Continuous data will be summarized in terms of the number of participants, mean, SD, minimum value, first quartile (Q1), median, third quartile (Q3), and maximum value. Categorical data will be summarized using frequency 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 BMI, will be summarized using the Safety Set.

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

Medical history will be listed by participant.

13.5. Efficacy Analysis

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods, where applicable; participant listings will be provided for all efficacy data. Participants will be analyzed according to randomized treatment.

Baseline differences between participants with HD and HP will be assessed across candidate endpoint based on enrollment set using T-test. The mean differences, its 95% confidence interval (CI) and corresponding p value will be reported. For a given endpoint, if the 95% CI does not span zero, then it will be concluded that the participants with HD are statistically significantly different from their healthy comparators at Baseline for that endpoint; otherwise, it will be concluded that there is not enough evidence to declare them statistically different.

[redacted]

Additional analyses will be detailed in the SAP.

13.6. Safety Analyses

Safety and tolerability of SAGE-718 will be evaluated by the frequency of TEAEs and change from baseline in vital signs, clinical laboratory analytes, ECGs, and responses on the C-SSRS. Safety data will be listed by participant and summarized by treatment group, maximum severity and relationship to IP. Vital signs, laboratory parameters, ECGs, and C-SSRS 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 (MedDRA) 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 proportion of subjects experiencing TEAEs will be displayed by treatment group and by System Organ Class (SOC) 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 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

Clinical laboratory assessments will include blood samples for hematology, clinical chemistry, and urinalysis. Samples will be collected ≤2 hours prior to dosing on dosing days. On nondosing days, collection may occur at any time.

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

13.6.3. Physical Examinations

A full physical examination is to be conducted during Screening and at Day 42 (±2 days). At other visits (eg, Day 28 for participants with HD), physical examinations will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems and followed by a targeted physical assessment as needed. A symptom-directed examination may be conducted at any time at the discretion of the investigator. The occurrence of a physical examination (yes/no) and the date performed will be listed by participant.

13.6.4. Vital Signs

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

13.6.5. 12-Lead Electrocardiogram

A single ECG will be measured after the participant has been in the supine position for at least 5 minutes. The following ECG parameters will be listed for each participant: heart rate, PR, QRS, QT, and QTcF. ECG data will be summarized by visit. Potentially CS values of QTcF will be summarized by treatment. ECG findings will be listed by participant and visit.

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 8 weeks prior to Screening, all medications used to treat HD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD will be recorded. Those medications taken prior to the initiation of the start of IP will be denoted "Prior". Those medications taken prior to the initiation of the 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".

Information regarding diagnosis and/or hospitalization due to coronavirus disease 2019 (COVID-19) will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

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 for participants with HD and HP and by visit during the Treatment Period and Follow-up for participants with HD will be listed and summarized. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

13.6.8. Other Safety Analysis

Not applicable.

[redacted]

13.8. Sample Size and Power

Using a two-sided alpha level of 0.05, a sample size of at least 80 participants (40 HP and 40 participants with HD) would provide at least 80% power to detect baseline difference in HD-CAB composite score assuming Cohen's D effect size equal to 0.63, which is in the range of effect sizes observed for individual tests from HD-CAB (Stout 2014).

Using a CI approach for sample size estimation a sample size of 32 evaluable participants with HD (16 per treatment arm) will provide 80% confidence level for estimating the population mean with 0.50 precision or margin of error.

Assuming a 20% dropout rate in participants with HD, a sample size of approximately 40 participants with HD will be randomized in a 1:1 ratio to SAGE-718 and placebo to obtain 32 evaluable participants with HD. Additional participants may be randomized if the dropout rate is higher than 20%.

Evaluable participants with HD are defined as those randomized participants who receive IP and have a valid baseline and at least 1 postbaseline efficacy assessment.

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 eCRFs, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRFs 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 ethics committee.

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 Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/IEC about an inspection.

14.3. Institutional Review Board or Ethics Committee

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

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/EC per the IRB/EC's written procedures.

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

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial 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 EC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or EC must supply to the sponsor a list of the IRB/EC membership and a statement to confirm that the IRB/EC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or EC 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 EC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/EC and sponsor of any changes significantly affecting the conduct of the trial 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 trial 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 trial, 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 Informed Consent Form must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the trial 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.

16.4. Data Protection

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

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 IP. Sage Therapeutics is responsible to inform the investigator/institution as to when study documents no longer need to be retained. [redacted]

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

Albin RL, Young AB, Penney JB, et al. Abnormalities of striatal projection neurons and N-methyl-D-aspartate receptors in presymptomatic Huntington's disease. N Engl J Med. 1990;322(18):1293-1298.

[redacted]

Cardoso, F. Nonmotor Symptoms in Huntington Disease. Int Rev Neurobiol. 2017;134:1397-1408.

[redacted]

Leoni V, Long JD, Mills JA, et al. PREDICT-HD study group. Plasma 24Shydroxycholesterol correlation with markers of Huntington disease progression. Neurobiol Dis. 2013;55:37-43.

Lewis et al. Cognitive Deficits in Huntington's Disease and Altered 24(S) Hydroxycholesterol. Poster at HSG Annual Meeting. 2019.

Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 ;53(4):695-699.

NSF Sleep Diary, the nsf.org, Rev-2, 2021.

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

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-1277.

Stout JC, Queller S, Baker KN, et al. HD-CAB: a cognitive assessment battery for clinical trials in Huntington's disease. Mov Disord. 2014;29(10):1281-1288.

Tabrizi SJ, Reilmann R, Roos RA, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol. 2012;11(1):42-53.

[redacted]

Unschuld PG, Edden RA, Carass A, et al. Brain metabolite alterations and cognitive dysfunction in early Huntington's disease. Mov Disord. 2012;27(7):895-902.

Vyklicky V, Korinek M, Smejkalova T, et al. Structure, function, and pharmacology of NMDA receptor channels. Physiol Res. 2014;63 Suppl 1:S191-S203.

Yao L, Zhou Q. Enhancing NMDA receptor function: recent progress on allosteric modulators. Neural Plast. 2017; 2017:2875904.

[redacted]

Signature Page for VV-CLIN-002651 v1.0

eSignature Approval Task	[redacted] 01-Jun-2023 20:46:45 GMT+0000
eSignature Approval Task	[redacted] 01-Jun-2023 21:00:10 GMT+0000
eSignature Approval Task	[redacted] 02-Jun-2023 00:37:36 GMT+0000
eSignature Approval Task	[redacted] 02-Jun-2023 14:19:42 GMT+0000
eSignature Approval Task	[redacted] 02-Jun-2023 16:15:39 GMT+0000
eSignature Approval Task	[redacted] 05-Jun-2023 18:07:21 GMT+0000
eSignature Approval Task	[redacted] 06-Jun-2023 14:23:38 GMT+0000

Signature Page for VV-CLIN-002651 v1.0