Official Title: A Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Effect of Sage-718 on Cognitive Function in Participants With Huntington's Disease

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A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE THE EFFECT OF SAGE-718 ON COGNITIVE FUNCTION IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

SHORT TITLE: A STUDY TO EVALUATE THE EFFECT OF SAGE-718 ON COGNITIVE FUNCTION IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

PROTOCOL NUMBER: 718-CIH-201

IND NUMBER: 145563

EUDRACT NUMBER: 2021-005577-16

Investigational Product: SAGE-718

Clinical Phase: 2

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Date of Amendment 3 - 21 June 2022

Date of Amendment 4 - 03 November 2023

Date of Amendment 5 – 19 August 2024

*Sponsor address effective 01 September 2024 will be: 55 Cambridge Parkway, Cambridge, MA 02142

Confidentiality Statement

INVESTIGATOR'S AGREEMENT

I have read the 718-CIH-201 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD Month YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician and 24-Hour Emergency Contact	[redacted], MD	215 First Street* Cambridge, MA 02142 Phone: [redacted] e-mail: [redacted]
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Product Complaints Sage Therapeutics	Product Complaints Sage Therapeutics	Phone: 1-833-554-7243 e-mail: productcomplaints@sagerx.com

*Sponsor address effective 01 September 2024 will be: 55 Cambridge Parkway, Cambridge, MA 02142

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 Randomized, Placebo-controlled, Double-Blind Study to Evaluate the Effect of SAGE-718 on Cognitive Function in Participants with Huntington's Disease

Number of Sites and Study Location: Approximately 50 sites globally.

Phase of Development: 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final Follow-up visit) for each participant is estimated to be up to 136 days.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of SAGE-718 on cognitive performance in participants with Huntington's Disease (HD)	• Change from Baseline (CFB) to Day 84 on the Symbol Digit Modalities Test (SDMT)
Secondary	
• To evaluate the effect of SAGE-718 on cognition and daily function in participants with HD	Key Secondary Endpoints: 1. CFB to Day 84 on the Unified Huntington's Disease Rating Scale (UHDRS) - Independence Scale 2. CFB to Day 84 on the Trail Making Test Part B [a] 3. CFB to Day 84 on the One Touch Stockings of Cambridge (OTS) 4. CFB to Day 84 on the Paced Tapping Test (PTAP) 5. CFB to Day 84 in Huntington's Disease Everyday Functioning (Hi-DEF) – at home subdomain score 6. CFB to Day 84 in Clinical Global Impression – Severity (CGI-S) – cognitive status subdomain score
• To evaluate the safety and tolerability of SAGE-718 in participants with HD	Safety Endpoint: • Proportion of participants experiencing treatment-emergent adverse events (TEAEs)

[redacted]

following daily administration of SAGE-718	
• To evaluate additional safety and tolerability parameters of SAGE-718 in participants with HD	• CFB in vital signs, clinical laboratory analyses, electrocardiograms (ECGs), [redacted] • [redacted]

[a] Applicable only to the subgroup of participants who can complete Trail Making Part B within the allowable time limit at baseline.

Study Description:

This is a randomized, placebo-controlled, double-blind study to evaluate the cognitive effects, safety, tolerability, [redacted] of SAGE-718 in participants with premanifest or 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 UHDRS scores and CAG-Age-Product [CAP] scores within specific ranges).

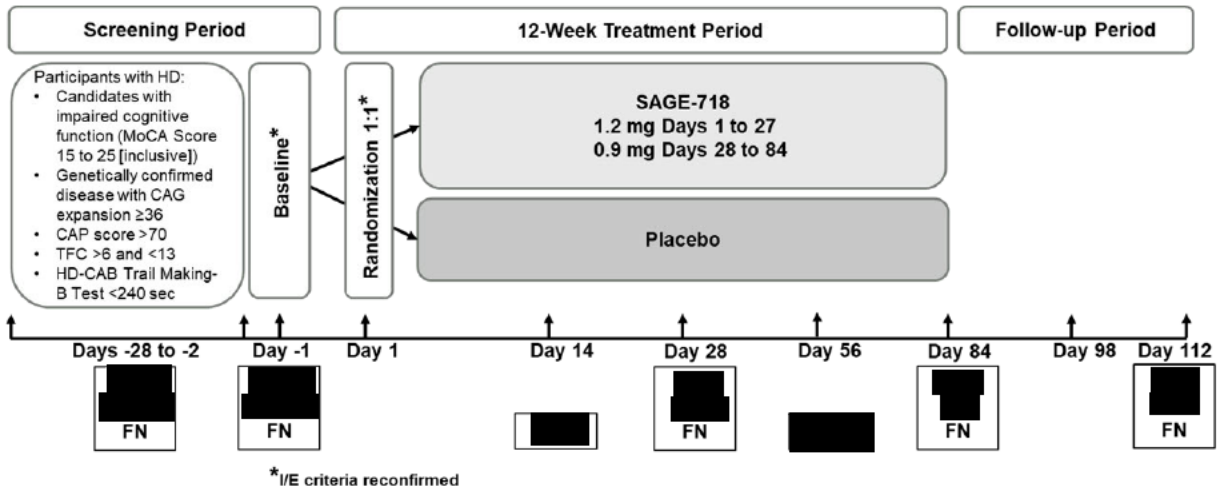
An adult study partner is optional but highly recommended for each participant to support completion of study activities and to answer questions about the participant's condition. For prospective participants and study partners (if applicable), the study will begin with the informed consent process.

Screening, safety, and efficacy assessments will be performed according to the schedule presented in Table 2, [redacted] will be performed according to the schedule presented in Table 3.

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 will be randomized 1:1 to receive either SAGE-718,-or placebo for 84 days. Beginning on Day 1 and continuing through Day 84, participants will self-administer blinded investigational product (IP) once per day in the morning. IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. At clinic visits, participants 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 review of the medication adherence monitoring platform, examination of the used packaging, and counting any returned tablets.

Study Schematic



Abbreviations: HD = Huntington's Disease; CAG = cytosine, adenine, and guanine; CAP = CAG-Age-Product; [redacted]; FN = Functional Scales; HD-CAB = Huntington's Disease Cognitive Assessment Battery; I/E = Inclusion/Exclusion; MoCA = Montreal Cognitive Assessment; [redacted]; TFC = Total Functional Capacity.

During the Treatment Period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. SAGE-718 1.2 mg or placebo will be provided as oral softgel lipid capsule for self-administration once daily in the morning through the day prior to Day 28 visit. Beginning at the Day 28 visit, SAGE-718 0.9 mg or placebo will be provided as oral softgel lipid capsule for self-administration once daily in the morning for the remainder of the Treatment Period. Participants who cannot tolerate 1.2 mg will receive 0.9 mg for the remainder of the Treatment Period. At the discretion of the investigator, participants who cannot tolerate the 0.9 mg dose will be discontinued from IP. Participants who discontinue IP early should complete the remaining study visits as scheduled unless the participant withdraws consent or loses the capacity to grant consent. If a participant withdraws from the study/stops study participation early, an early termination (ET) visit should be conducted. Treatment with SAGE-718 can be ended without down titration.

After completing the Treatment Period, participants will return to the clinic for follow-up visits on Days 98 and 112 to collect continued safety and efficacy data.

End of study will be achieved when last study participant completes Follow-Up Visit at Day 112 (or ET) or in accordance with local regulation.

[redacted]

Number of Participants (Planned): Approximately 178 participants will be randomized in the study to obtain 142 evaluable participants. Additional participants may be randomized and dosed to ensure a sufficient number of evaluable participants or if the early discontinuation rate is higher than expected.

Eligibility Criteria:

Inclusion Criteria

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

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.
5. Be at least 25 years old but no older than 65 years of age at Screening.
6. Meet all the following criteria for HD at Screening (Days -28 to -2):
   a. Genetically confirmed disease with CAG expansion ≥36.
   b. At Screening, UHDRS-TFC score >6 and <13, suggesting no more than a moderate level of functional impairment
   c. No features of juvenile HD
7. CAP score >70, as calculated using the CAP formula: AGE × (CAG – 30) / 6.49.
8. Score of 15 to 25 (inclusive) on the MoCA at Screening indicating the presence of cognitive impairment.
9. 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.
10. Be ambulatory (use of assistance devices such as a walker or cane is acceptable, as is occasional use of wheelchair, as judged by the investigator. 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.
11. 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 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicular stimulation hormone [FSH] >40 mIU/mL), permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), or does not engage in sexual relations which carry a risk of pregnancy.
12. Agree, if male, to use an acceptable method of effective contraception for the duration of study and for 21 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.
13. Agree, if male, to abstain from sperm donation during the Treatment Period and for 21 days after receiving the last dose of IP.
14. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.
15. Completion of HD-CAB Trail Making-B Test in <240 seconds at Screening (Days -28 to -2).

Exclusion criteria

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

1. Have participated in a previous clinical study of SAGE-718; have previous exposure to gene therapy; 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.)
2. 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.

3. 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.
4. Had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
5. Plans to undergo elective surgery during participation in the study.
6. Receive any of the following 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).
    d. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as determined by the investigator.
    e. Tetrahydrocannabinol (THC)-containing substances (any route of administration).
7. 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 5 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.
8. 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.
9. 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.
10. 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):
    a. Heart rate <50 or >100 bpm,
    b. Systolic blood pressure <100 or >160 mmHg,
    c. Diastolic blood pressure <60 or >100 mmHg.
11. 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.
12. Have a history of significant hand injury that would preclude either writing or rapid bimanual computerized responding.
13. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood.
14. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1 or HIV-2, hepatitis B, or hepatitis C.
15. 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.
16. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion).

17. Have a positive pregnancy test, be pregnant, is lactating, or intend to breastfeed during the study.
18. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
19. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.

Investigational Product, Dosage, and Mode of Administration: SAGE-718 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: 84 days.

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.

Database lock will occur in two parts. The first database lock will include all data from all participants who have completed Day 84 or the ET visit. The second database lock will include all the data from all participants through the follow-up visit (Day 112).

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, median, and maximum value. Categorical data will be summarized using frequency counts and percentages.

Analysis Sets

The Randomized Set will include all participants who have been randomized.

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

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

[redacted]

Efficacy Analysis

The change from baseline in cognitive assessments will be analyzed using a mixed-effects model for repeated measures; the model will include treatment, baseline scores, assessment time point, and time point-by-treatment as explanatory variables. All postbaseline time points will be included in the model. The primary comparison will be between SAGE-718 and placebo at the Day 84 time point. Model-based point estimates (eg, least squares means), 95% confidence intervals, and p-values will be reported. An unstructured covariance structure will be used to model the within-participant errors. Other continuous efficacy endpoints, including [redacted], functional outcomes, and [redacted], will be analyzed using similar methods. Additional analyses will be detailed in the SAP.

Safety Analysis

Adverse events (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 and relationship to IP and by treatment group. Vital signs, laboratory parameters, ECGs, [redacted] data will be summarized by treatment group. Additional analyses will be detailed in the SAP. [redacted]

Sample Size

The study is designed to detect a difference between placebo and the SAGE-718 group in the change from baseline to Day 84 for the primary endpoint, SDMT score. Using a 2-sided test at an alpha level of 0.05, a sample size of approximately 71 evaluable participants per treatment group would provide 90% power to detect a difference of 4 points between SAGE-718 and placebo arms in the change from baseline to Day 84 in SDMT values, assuming that the SD of the change from baseline in SDMT is 7.3 points.

Assuming a 20% dropout and a 1:1 randomization ratio, approximately 178 randomized participants (89 per treatment group) will be required to obtain 71 evaluable participants per treatment group. Evaluable participants are defined as those randomized participants who receive IP and have a valid baseline and at least 1 postbaseline SDMT assessment. Additional participants may be randomized to ensure a sufficient number of evaluable participants or if the dropout rate is higher than 20%.

Table 2: Schedule of Assessments

Assessments	Screening Period		Treatment Period					Follow-Up	
	Days -28 to -2	Day -1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (±2 days)	Day 98 (±2 days)	Day 112 (±2 days) or ET
Informed consent[a]	X								
Inclusion/exclusion criteria	X	X	X						
Family/Medical history and demographics[b]	X	X							
Participant training[c]	X	X							
Body weight	X		X		X	X	X		X
Body height	X								
Vital signs (including orthostatics)[d]	X		X	X	X	X	X	X	X
Physical examination[e]	X				X		X		X
CAG test[f] (if not collected as part of medical history)	X								
FSH test[g]	X								
Serology test[h]	X								
12-lead ECG[i]	X				X		X		X
Clinical laboratory assessments[j]	X		X		X		X		X
Urine drug test	X		X	X	X	X	X	X	X
Alcohol test[k]	X		X	X	X	X	X	X	X
Cigarette/tobacco use assessment[l]	X		X	X	X	X	X	X	X
Pregnancy test[m]	X		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 56 (±2 days)	Day 84 (±2 days)	Day 98 (±2 days)	Day 112 (±2 days) or ET
[redacted]									
C-SSRS (Screening/Baseline)	X								
[redacted]									
UHDRS[p]	X	X					X		
Montreal Cognitive Assessment	X								
Global Impression – Severity[q]	X	X					X		
[redacted]									
Cognitive battery[r]	X								
[redacted]									
Hi-DEF Scale		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 56 (±2 days)	Day 84 (±2 days)	Day 98 (±2 days)	Day 112 (±2 days) or ET
Randomization			X						
IP self-administration[v]			X (once daily in the morning)						
IP dispensation[w]			X	X	X	X			
IP Adherence[x]			X						
IP Accountability/Return[y]			X	X	X	X	X		
AEs/SAEs	X (from time of ICF throughout the duration of participation)								
Prior and concomitant medications	X								

Abbreviations: AE = adverse event, ASO = anti-sense oligonucleotide; 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; Hi-DEF = Huntington's Disease Everyday Functioning Scale; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; [redacted]; [redacted]; [redacted]; SAE = serious adverse event; UHDRS = Unified Huntington's Disease Rating Scale.

Note: If needed, participant-reported outcomes and study partner-reported outcomes can be completed remotely/at home via the web.

a. Both participants and study partners (if applicable) will be consented during the Screening Period. [redacted]
b. In addition to full medical history, all medications and supplements taken within 8 weeks prior to Screening, all medications used to treat HD (including ASO therapies) regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD are to be recorded. Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at screening and throughout the study. Confirmed (genetically tested) or suspected family history of HD will be collected.
c. 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.
d. Vital signs to include body temperature, respiratory rate, heart rate, and blood pressure. On dosing days, vital signs will be measured prior to dosing. Blood pressure and heart rate will be measured after the participant has been in the supine position for at least 5 minutes and then repeated approximately 1 and 3 minutes after standing at all scheduled time points. Vital signs can be repeated once per visit if out of range.
e. A full physical examination is to be conducted during Screening and at Day 112. At other visits, physical examinations will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems and followed by a targeted physical assessment as needed. A symptom-directed examination may be conducted at any time at the discretion of the investigator.
f. 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 the local practice.

g. Serum FSH test will be conducted at Screening for the female participants to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal.
h. To include hepatitis B and C screening tests, HIV-1 and -2 antibody.
i. Single ECG will be measured after the participant has been in the supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, blood draws should be carried out after ECG and vital signs.
j. Clinical laboratory assessments will include blood samples for hematology, clinical chemistry, biochemistry, coagulation, serology, genetic testing, and urinalysis. Samples will be collected ≤2 hours prior to dosing on dosing days. On non-dosing days, collection may occur at any time.
k. A breath test for alcohol will be performed.
l. 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.
m. 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 permanently sterile.

[redacted]

p. Total Functional Capacity [redacted] scores will be collected at Screening, [redacted]. Independence Scale will be conducted at [redacted] 84 [redacted].

[redacted]

r. Cognitive tests at all time points are to be performed at the same time of day (±2 hours) and postdose on dosing days. [redacted]

[redacted]

v. On visit Days 1, 14, 28, 56, and 84, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing and all scheduled cognitive tests will be administered post dosing.
w. Study staff will dispense enough IP for the participant to take daily at home until the next scheduled visit.
x. IP administration will be monitored using the [redacted]. Participants will complete the training within the application. Thereafter participants should use the application each time they take IP and sites should regularly use the dashboards to follow up on instances of non-adherence with IP. IP adherence will not be captured after participants discontinue IP.
y. Participants will bring all used packaging and unused IP to the clinic at each visit for study staff to review and document.

Table 3: [redacted]

[redacted]

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

TABLE OF CONTENTS

1. TITLE PAGE 1
2. SYNOPSIS 4
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 17
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 23
5. INTRODUCTION 26
5.1. Overall Risk/Benefit Assessment 26
5.2. Dose Justification 27
6. STUDY OBJECTIVES AND ENDPOINTS 28
7. INVESTIGATIONAL PLAN 30
7.1. Overall Study Design 30
7.1.1. Screening Period 30
7.1.2. Treatment Period 31
7.1.3. Follow-up Period 31
7.1.4. End of Study 31
7.2. Number of Participants 33
7.3. Treatment Assignment 33
7.4. Dose Adjustment Criteria 33
7.4.1. Stopping criteria 33
7.4.2. Dose Evaluation Committee 33
7.4.3. Safety Criteria for Adjustment or Stopping Doses 34
7.5. Criteria for Study Termination 34
7.6. End of Study Definition 34
8. SELECTION AND WITHDRAWAL OF PARTICIPANTS 35
8.1. Participant Inclusion Criteria 35
8.2. Participant Exclusion Criteria 36
8.3. Screen Failures 37
8.4. Investigational Product Discontinuation and Early Termination from the Study 38
8.4.1. Investigational Product Discontinuation 38

8.4.2. Early Termination from the Study 38
8.4.3. Loss to Follow-up 39
8.4.4. Replacement of Participants 39
9. TREATMENT OF PARTICIPANTS 40
9.1. Description of Investigational Product 40
9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements 40
9.2.1. Prior and Concomitant Medications and/or Supplements 40
9.2.2. Prohibited Medications 40
9.2.3. Other Restrictions and Recommendations 41
9.2.4. Acceptable Forms of Contraception 41
9.3. Intervention After the End of the Study 42
9.4. Treatment Adherence 42
9.5. Randomization and Blinding 42
9.5.1. Emergency Unblinding 43
10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT 44
10.1. Investigational Product 44
10.2. Investigational Product Packaging and Labeling 44
10.3. Investigational Product Storage 44
10.4. Investigational Product Preparation 45
10.5. Investigational Product Administration 45
10.5.1. Medication Adherence and Reminder System 45
10.5.1.1. Registration in the [redacted] 45
10.5.1.2. Ongoing Use and Monitoring of Medication Adherence 45
10.6. Investigational Product Accountability, Handling, and Disposal 46
10.7. Product Complaints 47
10.8. Ancillary Supplies 47
11. SCREENING, EFFICACY, [redacted] ASSESSMENTS 48
11.1. Screening Assessments 48
11.1.1. Montreal Cognitive Assessment 48
11.1.2. Cigarette and(or) Tobacco Use Assessment 48
11.2. Efficacy Assessments 49

11.2.1. Symbol Digit Modalities Test 49
11.2.2. Unified Huntington's Disease Rating Scale – Independence Scale 49
11.2.3. [redacted] 49
11.2.3.1. One Touch Stockings of Cambridge 50
11.2.3.2. Trail Making 50
11.2.3.3. [redacted] 50
11.2.3.4. Paced Tapping Test 51
11.2.3.5. [redacted] 51
11.2.4. [redacted] 51
11.2.4.1. [redacted] 51
11.2.4.2. [redacted] 51
11.2.4.3. [redacted] 51
11.2.4.4. [redacted] 51
11.2.4.5. [redacted] 52
11.2.5. [redacted] 52
11.2.6. [redacted] 52
11.2.7. Patient-Reported Outcomes 52
11.2.7.1. [redacted] 52
11.2.7.2. [redacted] 52
11.2.7.3. Huntington's Disease Everyday Functioning Scale 53
11.2.7.4. [redacted] 53
11.2.7.5. [redacted] 53
11.2.7.6. [redacted] 53
11.2.7.7. [redacted] 54
11.2.7.8. [redacted] 54
11.2.7.9. [redacted] 54
11.2.8. [redacted] 54
11.2.8.1. [redacted] 54
11.2.8.2. [redacted] 54
11.2.8.3. [redacted] 55
11.2.9. Clinical Global Impression Severity [redacted] 55
11.2.10. [redacted] 55

11.2.11. [redacted] 55
11.2.12. [redacted] 56
11.3. [redacted] 56
11.3.1. [redacted] 56
11.3.1.1. [redacted] 56
11.3.1.2. [redacted] 56
11.3.2. [redacted] 57
11.3.2.1. [redacted] 57
11.3.2.2. [redacted] 57
12. SAFETY ASSESSMENTS 58
12.1. Safety Parameters 58
12.1.1. Demography and Medical History 58
12.1.2. Weight and Height 58
12.1.3. Physical Examination 58
12.1.4. COVID-19 Questions 58
12.1.5. Vital Signs 58
12.1.6. Electrocardiogram 59
12.1.7. Laboratory Assessments 59
12.1.7.1. Drugs of Abuse, Alcohol 60
12.1.7.2. Pregnancy Testing 60
12.1.8. [redacted] 60
12.1.9. [redacted] 60
12.2. Adverse and Serious Adverse Events 60
12.2.1. Adverse Event Definition 60
12.2.2. Serious Adverse Event Definition 61
12.2.3. Definition of Urgent Safety Measure and Unanticipated Problem 62
12.2.4. Relationship to Investigational Product 62
12.2.5. Recording Adverse Events 63
12.2.6. Reporting Serious Adverse Events 63
12.2.7. Assessment of Liver Biochemistry for Hy's Law Screening, or Hy's Law Laboratory Criteria 64
12.3. Pregnancy 65
12.4. Special Considerations 65

13. STATISTICS 67
13.1. Data Analysis Sets 67
13.2. Handling of Missing Data 67
13.3. General Considerations 67
13.4. Demographics and Baseline Characteristics 68
13.5. Efficacy Analysis 68
13.5.1. Multiplicity Adjustment for Primary and Key Secondary Endpoints 69
13.6. Safety Analyses 69
13.6.1. Adverse Events 69
13.6.2. Clinical Laboratory Evaluations 70
13.6.3. Physical Examinations 70
13.6.4. Vital Signs 70
13.6.5. 12-Lead Electrocardiogram 70
13.6.6. Prior and Concomitant Medications 70
13.6.7. [redacted] 71
13.6.8. [redacted] 71
13.6.9. Other Safety Analysis 71
13.7. [redacted] 71
13.8. Sample Size and Power 71
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 72
14.1. Study Monitoring 72
14.2. Audits and Inspections 72
14.3. Institutional Review Board or Independent Ethics Committee 73
15. QUALITY CONTROL AND QUALITY ASSURANCE 74
16. ETHICS 75
16.1. Ethics Review 75
16.2. Ethical Conduct of the Study 75
16.3. Written Informed Consent 75
16.4. Data Protection 76
17. DATA HANDLING AND RECORDKEEPING 77
17.1. Inspection of Records 77
17.2. Retention of Records 77
18. PUBLICATION POLICY 78

19. LIST OF REFERENCES 79

20. APPENDICES 82

Appendix 1: Country-Specific Changes 82

LIST OF TABLES

Table 1: Emergency Contact Information 3

Table 2: Schedule of Assessments 12

Table 3: [redacted] 16

Table 4: Abbreviations and Specialist Terms 23

Table 5: Investigational Product 44

Table 6: Summary of Clinical Laboratory Analytes 59

LIST OF FIGURES

Figure 1: Study Design 32

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]
ASO	anti-sense oligonucleotide
ECG	electrocardiogram
[redacted]	[redacted]
BMI	body mass index
CAG	cytosine, adenine, and guanine
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CAP	CAG-Age-Product
CFR	Code of Federal Regulations
[redacted]	[redacted]
CGI-S	Clinical Global Impression Severity
COVID-19	coronavirus disease 2019
C_{max}	maximum concentration
CS	clinically significant
C-SSRS	Columbia–Suicide Severity Rating Scale
eCRF	electronic case report form
[redacted]	[redacted]
DEC	Dose Evaluation Committee
ET	Early Termination
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration

Abbreviation	Definition
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEE	generalized estimating equation
GMP	Good Manufacturing Practice
[redacted]	[redacted]
HD	Huntington's Disease
HD-CAB	Huntington's Disease Cognitive Assessment Battery
[redacted]	[redacted]
Hi-DEF	Huntington's Disease Everyday Functioning
HIV	human immunodeficiency virus
HTT	Huntingtin gene
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
NCS	not clinically significant
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
OTS	One Touch Stockings of Cambridge
PAM	positive allosteric modulator
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic
[redacted]	[redacted]
PRO	patient-reported outcome

Abbreviation	Definition
PTAP	Paced Tapping Test
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDMT	Symbol Digit Modalities Test
[redacted]	[redacted]
Study partner	synonymous with care partner
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TFC	Total Functional Capacity
THC	tetrahydrocannabinol
UHDRS	Unified Huntington's Disease Rating Scale
UP	unanticipated problem
US	United States
USM	urgent safety measure
VAS	Visual Analogue Scale
[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 HD patients (Albin 1990). Together, these data suggest that lowered NMDA receptor tone may contribute to cognitive dysfunction in HD (Paul 2013).

Preclinical data illustrate that HD patients 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.

Sage believes that pre-clinical findings, combined with our early-stage clinical data in patients with HD, support the hypothesis that SAGE-718 may work to restore aberrant NMDA receptor activity in patients with early HD and thereby help to ameliorate cognitive deficits seen in these patients.

5.1. Overall Risk/Benefit Assessment

Currently, there are no therapies approved to treat the cognitive or psychiatric changes associated with HD.

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

In a radiolabeled rat absorption, distribution, metabolism and excretion study, there was no selective distribution or retention of radioactive SAGE-718 to pigmented tissues and no quantifiable concentration of radioactivity was observed in the eye lens in Long Evans rats, implying that potential risk of phototoxicity is low.

Due to an unexplained mortality early in the 14-day oral repeat-dose rat study at 30 mg/kg/day, a human maximum concentration (C_{max}) cap for clinical studies was established from the Day 0 mean C_{max} (443 ng/mL) in female rats at the 15 mg/kg/day dose level. A 10-fold safety factor

was used to derive the 45 ng/mL clinical exposure cap (see Section 5.2). Across rat and dog nonclinical studies a C_{max} threshold for observation of convulsions occurred at exposures 20 to 40 times greater than clinically relevant exposures.

No deaths, serious adverse events (SAEs) or treatment emergent adverse events (TEAEs) leading to discontinuation were reported in the completed studies with SAGE-718. A maximum tolerated dose has not been identified yet and no characteristic safety signals have been identified to date. No clinically relevant mean changes from baseline were observed in electrocardiograms (ECGs) or electroencephalograms (EEGs). In addition, there were no treatment-emergent adverse events reported in patients with Huntington's disease that were enrolled in the completed SAGE-718 open label study (718-CLP-102).

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

The effect of SAGE-718 on cognitive function in participants with Huntington's disease will be evaluated in this randomized, placebo-controlled, double-blind study. Additional data on the effects of SAGE-718 in participants with HD will be collected throughout, [redacted].

5.2. Dose Justification

SAGE-718 has been well tolerated in both healthy participants 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 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 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. The dose is selected to provide pharmacokinetic (PK) exposures similar to those achieved in prior studies that have shown evidence consistent with NMDA target engagement and beneficial effects on assessments of cognition. [redacted]

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of SAGE-718 on cognitive performance in participants with Huntington's Disease (HD)	• Change from Baseline (CFB) to Day 84 on the Symbol Digit Modalities Test (SDMT)
Secondary	
• To evaluate the effect of SAGE-718 on cognition and daily function in participants with HD	<u>Key Secondary Endpoints:</u> 1. CFB to Day 84 on the Unified Huntington's Disease Rating Scale (UHDRS) - Independence Scale 2. CFB to Day 84 on the Trail Making Test Part B [a] 3. CFB to Day 84 on the One Touch Stockings of Cambridge (OTS) 4. CFB to Day 84 on the Paced Tapping Test (PTAP) 5. CFB to Day 84 in Huntington's Disease Everyday Functioning (Hi-DEF) – at home subdomain score 6. CFB to Day 84 in Clinical Global Impression – Severity (CGI-S) – cognitive status subdomain score
• To evaluate the safety and tolerability of SAGE-718 in participants with HD	<u>Safety Endpoint:</u> • Proportion of participants experiencing treatment-emergent adverse events (TEAEs)
[redacted]	

[redacted]

• To evaluate additional safety and tolerability parameters of SAGE-718 in participants with HD	• CFB in vital signs, clinical laboratory analyses, electrocardiograms (ECGs), and suicidal ideation [redacted] • [redacted]

[a] Applicable only to the subgroup of participants who can complete Trail Making Part B within the allowable time limit at baseline.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, placebo-controlled, double-blind study to evaluate the cognitive effects, safety, tolerability, [redacted] of SAGE-718 in participants with premanifest or 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 UHDRS scores and CAG-Age-Product [CAP] scores within specific ranges).

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

Screening, safety, and efficacy will be performed according to the schedule presented in Table 2, [redacted] will be performed according to the schedule presented in and Table 3.

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 will be randomized 1:1 to receive either SAGE-718 (1.2 mg at Day 1 visit through the day prior to Day 28 visit and 0.9 mg from Day 28 visit until End of Treatment [EOT]) or placebo for 84 days. Beginning on Day 1 and continuing through Day 84, participants will self-administer blinded investigational product (IP) once per day in the morning. IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. At clinic visits, participants 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 review of the medication adherence monitoring platform, examination of the used packaging, and counting any returned tablets.

During the Treatment Period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. Participants who cannot tolerate 1.2 mg will receive 0.9 mg for the remainder of the Treatment Period. At the discretion of the investigator, participants who cannot tolerate the 0.9 mg dose will be discontinued from IP. Participants who discontinue IP early should complete the remaining study visits as scheduled unless the participant withdraws consent or loses the capacity to grant consent. If a participant withdraws from the study/stops study participation early, an early termination (ET) visit should be conducted. Treatment with SAGE-718 can be ended without down titration.

7.1.1. Screening Period

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

7.1.2. Treatment Period

Eligible participants will be randomized 1:1 to receive either SAGE-718, or placebo for 84 days. Beginning on Day 1 and continuing through the 12-week treatment period, participants will self-administer SAGE-718 or placebo once per day in the morning. Participants who utilize the ±2-day window at Day 84 should continue to self-administer IP within the visit window. IP administration will be monitored using the [redacted].

At clinic visits, participants will take the IP under staff supervision, followed by assessments of cognitive function, [redacted] as outlined in Table 2 and Figure 1. 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 review of the medication adherence monitoring platform, examination of the used packaging, and counting any returned tablets. [redacted]

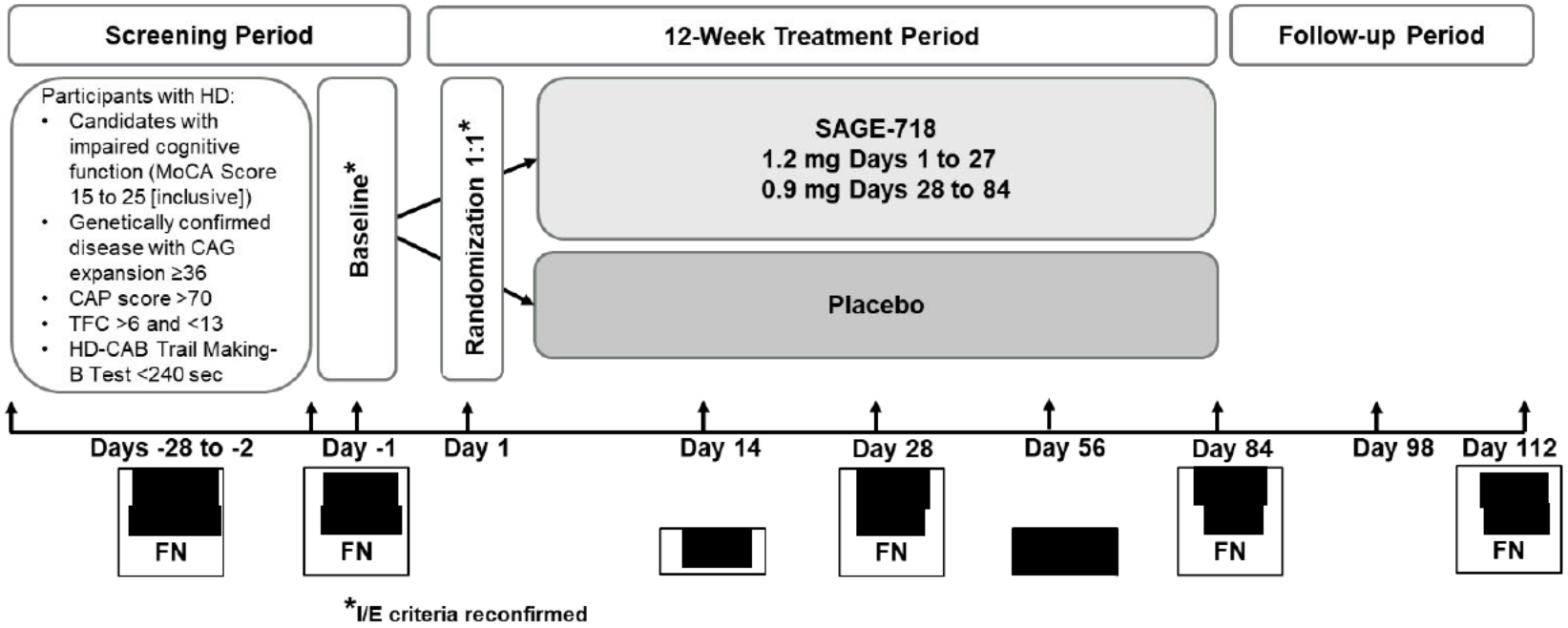
7.1.3. Follow-up Period

Follow-up period starts after Day 84 and continuing through Day 112. After completing the Treatment Period, participants will return to the clinic for follow-up visits on Days 98 and 112 (or ET) to collect continued safety and efficacy data.

7.1.4. End of Study

End of study will be achieved when last study participant completes Follow-Up Visit at Day 112 (or ET) or as defined by local country specific requirements, see Section 20 (Appendix 1).

Figure 1: Study Design



Abbreviations: HD = Huntington's Disease; CAG = cytosine, adenine, and guanine; CAP = CAG-Age-Product; [redacted]; FN = Functional Scales; HD-CAB = Huntington's Disease Cognitive Assessment Battery; I/E = Inclusion/Exclusion; MoCA = Montreal Cognitive Assessment; [redacted]; TFC = Total Functional Capacity.

7.2. Number of Participants

Approximately 178 participants will be randomized in the study to obtain 142 evaluable participants. Additional participants may be randomized and dosed to ensure a sufficient number of evaluable participants or if the early discontinuation rate is higher than expected.

7.3. Treatment Assignment

Eligible participants will be randomized 1:1 to receive either SAGE-718, or placebo for 84 days. Additional details on randomization and blinding are provided in Section 9.5.

7.4. Dose Adjustment Criteria

Individual dose reductions will be permitted.

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

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

At the discretion of the investigator, participants who cannot tolerate the 0.9-mg dose will be discontinued from IP (refer to Section 8.4 for procedures for early IP discontinuation). Participants are encouraged to continue to come in for assessments following IP discontinuation.

7.4.1. Stopping criteria

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

7.4.2. Dose Evaluation Committee

A Dose Evaluation Committee (DEC) will be convened as needed [redacted]

7.4.3. Safety Criteria for Adjustment or Stopping Doses

Dose Modification in Potential Hy's Law Cases

Dosing with IP for study participants meeting potential Hy's Law criteria (described in Section 12.2.7) should be interrupted until drug-induced living injury (DILI) is ruled out. Participants should be treated accordingly if hepatic laboratory elevations are due to other causes (eg, viral hepatitis, alcohol ingestion, congestive heart failure). If DILI is not ruled out, IP should be permanently discontinued; if DILI is ruled out and upon liver biochemistry returning to normal or baseline levels, dosing with IP may resume, if clinically appropriate and with agreement from the sponsor.

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. See Section 20 (Appendix 1) for country-specific requirements.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

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

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.
5. Be at least 25 years old but no older than 65 years of, at the time informed consent is obtained.
6. Meet all the following criteria for HD at Screening (Days -28 to -2):
    a. Genetically confirmed disease with CAG expansion ≥36.
    b. At Screening, UHDRS-TFC score >6 and <13, suggesting no more than a moderate level of functional impairment.
    c. No features of juvenile HD.
7. CAP score >70, as calculated using the CAP formula: AGE × (CAG – 30) / 6.49.
8. Score of 15 to 25 (inclusive) on the Montreal Cognitive Assessment (MoCA) at Screening.
9. 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.
10. Be ambulatory (use of assistance devices such as a walker or cane is acceptable, as is occasional use of wheelchair, as judged by the investigator. 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.
11. 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 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicular stimulation hormone [FSH] >40 mIU/mL), permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), or does not engage in sexual relations which carry a risk of pregnancy.
12. Agree, if male, to use an acceptable method of effective contraception for the duration of study and for 21 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 methos of effective contraception are listed in Section 9.2.4.
13. Agree, if male, to abstain from sperm donation during the Treatment Period and for 21 days after receiving the last dose of IP.

14. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.
15. Completion of HD-CAB Trail Making-B Test in <240 seconds at Screening (Days -28 to -2).

8.2. Participant Exclusion Criteria

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

1. Have participated in a previous clinical study of SAGE-718; have previous exposure to gene therapy; have participated in any 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.)
2. 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.
3. 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.
4. Had gastric bypass surgery, has a gastric sleeve or lap band, or has had any related procedures that interfere with gastrointestinal transit.
5. Plans to undergo elective surgery during participation in the study.
6. Receive any of the following 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).
   d. Other medications given at doses or in combinations that are likely to have a deleterious effect on cognitive performance, as determined by the investigator.
   e. Tetrahydrocannabinol (THC)-containing substances (any route of administration), regardless of whether or not they are prescribed.
7. 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 5 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.

8. 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.
9. 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.
10. 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):
    a. Heart rate <50 or >100 bpm,
    b. Systolic blood pressure <100 or >160 mmHg,
    c. Diastolic blood pressure <60 or >100 mmHg.
11. 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.
12. Have a history of significant hand injury that would preclude either writing or rapid bimanual computerized responding.
13. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood.
14. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1 or HIV-2, hepatitis B, or hepatitis C.
15. 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.
16. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion).
17. Have a positive pregnancy test, be pregnant, is lactating, or intend to breastfeed during the study.
18. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
19. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.

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

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's 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 at contact and the reason for discontinuation will be documented. If the investigator becomes aware of a change in the participant's status or receives more information about a participant's disposition, this information will be documented.

8.4.4. Replacement of Participants

Participants who discontinue or withdraw from the study will not be replaced. However, additional participants may be randomized and dosed to ensure a sufficient number of evaluable participants or if the early discontinuation rate is higher than expected.

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 (including anti-sense oligonucleotide [ASO] therapies) regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD are to be recorded.

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

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

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

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 (eg, 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) eg, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

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

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

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

- Sexual abstinence
- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation;
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation;
- Intrauterine device;

- Intrauterine hormone-releasing system;
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening);
- Vasectomized partner (performed at least 3 months prior to screening) (Note: 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

Not applicable.

9.4. Treatment Adherence

Beginning on Day 1 and continuing through Day 84, participants will self-administer blinded IP once per day in the morning. IP administration will be monitored via a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. At clinic visits, participants 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 review of the medication adherence monitoring platform, examination of the used packaging, and counting any returned tablets. This information will be documented in the source files and eCRF, along with any deviations from the prescribed dosage regimen. Details about IP accountability are included in Section 10.6.

9.5. Randomization and Blinding

This is a randomized, placebo-controlled, double-blind study. Eligible participants will be randomized 1:1 to receive either SAGE-718, or placebo for 84 days.

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

Database lock will occur in 2 parts (see Section 13). A selected team of Sponsor personnel will be unblinded after Part 1 of database lock to conduct Part 1 data analyses, but site personnel, participants, and other Sponsor personnel will remain blinded until after Part 2 of database lock.

9.5.1. Emergency Unblinding

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

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

The composition and pharmaceutical quality of the oral softgel lipid capsule will be maintained according to current Good Manufacturing Practice (GMP). Labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/Good Clinical Practice (GCP) guidelines and all other applicable regulations will be prepared by Sage Therapeutics. 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 oral softgel lipid capsule for self-administration once daily in the morning through the day prior to the Day 28 visit.

Beginning at the Day 28 visit, SAGE-718 0.9 mg or placebo will be provided as an oral softgel lipid capsule for self-administration once daily in the morning for the remainder of the Treatment Period.

10.5. Investigational Product Administration

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

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

SAGE-718 or placebo will be self-administered by participants once daily in the morning. Sites will dispense a 2-week or 4-week supply of IP to the participants to take at home with instructions for use (see Table 2).

This study will use a medication adherence monitoring platform for all participants in the study. The platform is provided on the [redacted]. Built-in reminders and a communication system allow real-time intervention in case of missed doses. Use of the platform is required for all participants in the study to reinforce the proper dosing schedule and improve data integrity (Section 10.5.1).

In addition, the participant will be instructed to bring their dosing kit to the site as outlined in Table 2. All participants should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the participant source records.

10.5.1. Medication Adherence and Reminder System

10.5.1.1. Registration in the [redacted]

The platform may be downloaded as an app on the participant's personal smartphone. If a participant does not own a smartphone or prefers not to use his/ her personal smartphone, one of the backup provisioned devices should be provided.

- Participants will be registered in the platform.
- Participant training is automated within the application.

10.5.1.2. Ongoing Use and Monitoring of Medication Adherence

Participants should use the application to record each intake of study medication throughout the study, both at home between visits and during the visits when study drug is taken at the site.

Site personnel should regularly check the dashboard to ensure consistent medication adherence throughout the study. In cases of missed doses or pending data, site personnel should follow up with the participant as soon as possible to assess the reason for nonadherence and reinforce the importance of complying with the study drug dosing schedule. If the participant reports that a dose was taken but not logged in the app, site personnel should reclassify this dose to "site reported" using the dashboard.

Participants 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 IB and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

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

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

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

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

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during 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 (eg, 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 in accordance with study-specific Pharmacy Manual; disposition of IP will be documented.

More detailed information can be found in the SAGE-718 Investigator's Brochure and 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 listed in Table 1. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

10.8. Ancillary Supplies

Not applicable.

11. SCREENING, EFFICACY, [redacted] ASSESSMENTS

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

The eligible participants 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 MoCA 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.

Note: In addition to Screening this assessment is also performed [redacted], as outlined in Table 2.

Refer to Table 2 and Table 3 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 Days 1, 14, 28, 56, 84, 98 and Day 112 (or ET), as outlined in Table 2.

11.2. Efficacy Assessments

The assessments described below provide broad neurocognitive evaluation across the domains of executive function, [redacted].

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

These assessments are to be administered after the daily dose of SAGE-718 during the Treatment Period, and at approximately the same time of day (±2 hours) throughout the study.

11.2.1. Symbol Digit Modalities Test

The SDMT is a widely utilized tool for tracking cognitive function over time and for the early detection of cognitive impairment. This paper-and-pencil test assesses sustained attention, processing speed, visual scanning, and psychomotor speed (Smith 1991). The test requires participants to use a reference key to match numbers with geometric figures, with the total score reflecting the number of correct pairings (out of 110 possible) completed within 90 seconds.

The SDMT is considered one of the most sensitive and broadly accepted measures of cognitive performance in multiple sclerosis (Strober 2019) and has been used in numerous therapeutic trials (Mohammadian Nejad 2023; Rezaeimanesh 2024; Morrow 2013; De Giglio 2019). It has also been used in Parkinson's disease research as a sensitive measure of progression of the disease, particularly at early stages (Cao 2024; Han 2021; Bayram 2019). In HD, the SDMT has been designated as a Stage 2 cognitive landmark in the HD Integrated Staging System (HD-ISS) (Tabrizi 2022). This was due to its prevalence in clinical research, robust psychometric properties (such as consistency, test-retest reliability, sensitivity, and validity), and minimal susceptibility to practice effects (Stout 2014a; Braisch 2019). The National Institute of Neurological Disorders and Stroke (NINDS) - Common Data Elements project deemed the SDMT to be supplemental - highly recommended for cognitive assessments in HD studies (NINDS 2024).

The SDMT has been employed in several registries, including PREDICT-HD, TRACK-HD, and ENROLL-HD, where it has proven sensitive to disease progression across various TFC stages (Siesling 1998; Dorsey 2013; Tabrizi 2013; Hamilton 2023). In a study analyzing datasets from IMAGE, TRACK, and PREDICT, the SDMT was identified as the most effective marker for describing longitudinal changes across CAG-Age Product (CAP) groups (Abeyasinghe 2021).

11.2.2. Unified Huntington's Disease Rating Scale – Independence Scale

The UHDRS was developed as a multi-domain clinical rating scale for assessment of functional capacity in HD.

Part V of the UHDRS is the Independence Scale, which is intended to assess the ability of the participant to function independently in activities of daily living across the full spectrum of the disease. A single independence rating is provided on a scale ranging from 10 to 100, with higher scores reflecting better functioning.

11.2.3. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

11.2.3.1. One Touch Stockings of Cambridge

The OTS 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

11.2.3.2. Trail Making

The Trail Making test is a speeded graphomotor test of visual attention and task switching, [redacted] 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.

Standard administration of Part B uses a 300 second time limit, at which point the test is stopped and scored using the maximum allowable time if not yet completed. The developers of the HD-CAB have adopted a briefer limit of 240 seconds to reduce overall duration of testing, fatigue, and frustration (Stout 2014b). However, a floor effect is an acknowledged concern that reduces Part B's ability to distinguish impairment levels among individuals unable to complete within the standard time limit (Smith Watts 2019; Abreu 2021). This shorter time limit used by the HD-CAB may further compromise the test's sensitivity to measure drug effects when scored using the maximum allowable time. For this reason, inclusion criterion #15 was added to the study protocol (in effect since Amendment 4, Version 5). Accordingly, scores of 240 at baseline are considered unevaluable for purposes of this study and the key secondary endpoint will be tested within a subgroup of participants who were able to complete the test within the allowable time.

11.2.3.3. [redacted]

[redacted]

11.2.3.4. Paced Tapping Test

In the PTAP, 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).

11.2.3.5. [redacted]

[redacted]

11.2.4. [redacted]

11.2.4.1. [redacted]

[redacted]

11.2.4.2. [redacted]

[redacted]

11.2.4.3. [redacted]

[redacted]

11.2.4.4. [redacted]

[redacted]

11.2.4.5. [redacted]

[redacted]

11.2.5. [redacted]

[redacted]

11.2.6. [redacted]

[redacted]

11.2.7. Patient-Reported Outcomes

11.2.7.1. [redacted]

[redacted]

11.2.7.2. [redacted]

[redacted]

11.2.7.3. Huntington's Disease Everyday Functioning Scale

The Hi-DEF Scale is a self-reported measure to capture difficulties experienced in daily life due to HD across four different areas of functioning, including (1) At home, (2) At work, (3) Driving, and (4) Relationships. The 47-item questionnaire asks patients to rate their functioning difficulty using a 5-point Likert scale from 1 (No Difficulty) to 5 (Cannot do this anymore) on the first three domains, and a 4-point scale from 1 (Never) to 4 (Always) for Relationships. The measure was developed from qualitative interviews with HD patients and study partners who were still functionally independent and often working but reported cognitive changes that impacted their daily life tasks. The Hi-DEF Scale is currently undergoing psychometric validation, and the scoring will be available following that outcome.

11.2.7.4. [redacted]

[redacted]

11.2.7.5. [redacted]

[redacted]

11.2.7.6. [redacted]

[redacted]

[redacted]

11.2.7.7. [redacted]

[redacted]

11.2.7.8. [redacted]

[redacted]).

11.2.7.9. [redacted]

[redacted]

11.2.8. [redacted]

11.2.8.1. [redacted]

[redacted]

11.2.8.2. [redacted]

[redacted]

11.2.8.3. [redacted]

[redacted]

[redacted]

11.2.9. Clinical Global Impression Severity [redacted]

The Clinical Global Impressions Severity [redacted] (CGI-S [redacted]) scales are validated instruments developed by the National Institute of Mental Health specifically for use in clinical studies. For global impression severity scales, clinicians, participants, and study partners separately rate the severity of the participant's condition over the past 7 days (including the day of the clinic visit) (Guy 1976, Busner 2007). For this study, [redacted], cognitive status, [redacted].

[redacted]

11.2.10. [redacted]

[redacted]

11.2.11. [redacted]

[redacted]

11.2.12. [redacted]

[redacted]

11.3. [redacted]

11.3.1. [redacted]

[redacted]

11.3.1.1. [redacted]

[redacted]

11.3.1.2. [redacted]

[redacted]

11.3.2. [redacted]

[redacted]

11.3.2.1. [redacted]

[redacted]

11.3.2.2. [redacted]

[redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2) [redacted] (Table 3).

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

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity, highest level 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 112 (or 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. 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, isolation, 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 are to be measured after the participant has been supine for at least 5 minutes prior to the measurement. Orthostatic blood pressure and heart rate will also be measured after the participant has been in the supine position for at least 5 minutes and then repeated approximately 1 and 3 minutes after standing.

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 2. At each time point, a single ECG will be recorded. The standard intervals (heart rate, PR, QRS, QT, and QT corrected according to Fridericia's formula [QTcF]) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, 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 (low density lipoprotein [LDL], high density lipoprotein [HDL]), creatine phosphokinase, TSH and reflex to free T3/T4 if TSH is abnormal
Hematology	Red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, RBC indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]).
Urinalysis	Protein, glucose, pH, blood, leukocyte esterase, leukocytes (reflex to leukocytes via microscopy if urinalysis is abnormal) 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]

[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 permanently 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 drugs of abuse (including 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 permanently sterile.

12.1.8. [redacted]

[redacted]

12.1.9. [redacted]

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Adverse Event Definition

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

Laboratory abnormalities and changes from baseline in vital signs, and ECGs are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be 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 in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

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

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

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

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

12.2.3. Definition of Urgent Safety Measure and Unanticipated Problem

In accordance with Article 10(b) of Directive 2001/20/EC, some reported events may result in an urgent safety measure (USM), defined as an action that the sponsor and investigator may take 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)/IECs(s).

12.2.4. Relationship to Investigational Product

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

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

12.2.5. Recording Adverse Events

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

Intensity will be assessed according to the following scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria 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 (See Section 20 [Appendix 1]). Sage, or designee, will submit SUSARS to investigators in a blinded fashion.

12.2.7. Assessment of Liver Biochemistry for Hy's Law Screening, or Hy's Law Laboratory Criteria

Hy's Law is a principle outlining specific criteria to indicate when an individual is at high risk of a severe drug-induced liver injury (DILI) as a result of incurring hepatocellular injury sufficient to impair bilirubin excretion.

Potential Hy's Law is defined as an elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3× upper limit of normal (ULN) and an elevated total bilirubin ≥2× ULN with alkaline phosphatase <2× ULN at any time during the study. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IP. The elevations of transaminases and bilirubin may occur together or at different time points during the study, therefore, to identify cases of potential Hy's Law, a comprehensive review of liver biochemistry must be performed.

The investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study. If a participant has elevations in liver biochemistry, further evaluation may be required and, if elevations meet the potential Hy's Law criteria, it must be reported as an SAE within 24 hours of Investigator awareness (see Section 12.2.6 for procedure on reporting an SAE). All results of laboratory tests including alkaline phosphatase testing should also be appended to the SAE form. The investigator must continue to follow the participant until liver biochemistry returns to normal or baseline levels, or for as long as clinically indicated. In addition, the investigator should perform any necessary diagnostic evaluations to investigate the etiology of the event and update the SAE report accordingly.

These events must also be recorded as an SAE in the eCRF with the investigator's assessment of seriousness, severity, and causality, and a detailed narrative must be provided on the SAE form.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting AEs and SAEs in line with standard safety reporting procedures (see Section 12.2.5 and Section 12.2.6).

IP dose modifications for participants who meet potential Hy's Law criteria should be made according to Section 7.4.

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 (eg, spontaneous abortion, stillbirth, neonatal death,), the investigator should follow the procedures for reporting an SAE.

See Section 20 (Appendix 1) for country-specific requirements.

12.4. Special Considerations

Drug abuse is the persistent or sporadic, intentional excessive use of IP which is accompanied by harmful physical or psychological effects in the participant. If an event of drug abuse occurs during the study it must be reported to the sponsor and/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 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 or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE or 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.

Database lock will occur in two parts. The first database lock will include all data from all participants who have completed Day 84 or the ET visit. The second database lock will include all the data from all participants through the follow-up visit (Day 112).

13.1. Data Analysis Sets

The Randomized Set will include all participants who have been randomized.

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

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

[redacted]

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all non-missing data available. A sensitivity analysis will be used to investigate the impact of missing data if ≥5% of participants in any treatment group have missing data in the primary endpoint.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant data 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, median, and maximum value. Categorical data will be summarized using frequency counts and percentages.

13.4. Demographics and Baseline Characteristics

Demographic characteristics (age, race, sex, ethnicity, highest level of education, total years of employment, and current employment status) 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.

The estimand for the primary efficacy analysis is defined as follows:

1. The treatment regimen for participants is placebo or SAGE-718 for 84 days.
2. The target population is adult participants with premanifest or early manifest HD.
3. The variable of interest is the change from baseline in SDMT score at Day 84.
4. The intercurrent events could be:
    a. The premature discontinuation of treatment for any reason. The treatment policy strategy will be used.
    b. Taking certain medications including, but not limited to, medications with potent effects at the NMDA receptor, including memantine, amantadine, ketamine, or related compounds or other medications, given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance, or prescribed THC-containing substances. The treatment policy strategy will be used.
5. The population summary level deals with the difference between SAGE-718 and placebo treatments in mean change from baseline in SDMT score at Day 84.

The change from baseline in cognitive assessments will be analyzed using a mixed-effects model for repeated measures; the model will include treatment, baseline scores, assessment time point, and time point-by-treatment as explanatory variables. All postbaseline time points will be included

in the model. The primary comparison will be between SAGE-718 and placebo at the Day 84 time point. Model-based point estimates (eg, least squares means), 95% confidence intervals, and p-values will be reported. An unstructured covariance structure will be used to model the within-participant errors. Other continuous efficacy endpoints, including [redacted] functional outcomes, [redacted], will be analyzed using similar methods.

Generalized estimating equation (GEE) methods will be used for the analysis of Clinical Global Impression response. GEE models will include terms for treatment, baseline CGI-S assessment, time point, and time point-by-treatment as explanatory variables. The comparison of interest will be the difference between SAGE-718 and matching placebo at the Day 84 time point. Model-based point estimates (eg, odds ratios), 95% confidence intervals, and p-values will be reported.

Additional analyses will be detailed in the SAP.

13.5.1. Multiplicity Adjustment for Primary and Key Secondary Endpoints

The statistical comparisons for the primary and the key secondary endpoints will be carried out using a fixed-sequence procedure which tests hypotheses in a hierarchical order to control the familywise type I error rate. This means that statistically significant results for the comparison in the higher rank (primary) for no difference between SAGE-718 versus placebo is required to initiate the testing of the next comparison in the lower rank (key secondary) for no difference between SAGE-718 versus placebo. The hierarchical testing of key secondary endpoints will follow the order shown in Section 6. Details will be provided in the study SAP. Since a hierarchical procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved.

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, [redacted]. [redacted] Safety data will be listed by participant and summarized by treatment group, maximum severity and relationship to IP. Vital signs, laboratory parameters, ECGs, [redacted] 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/SAEs 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 incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). 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 non-dosing 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 112. At other visits, physical examinations will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems and followed by a targeted physical assessment as needed. A symptom-directed examination may be conducted at any time at the discretion of the investigator. The occurrence of a physical examination (yes/no) and the date performed will be listed by participant.

13.6.4. Vital Signs

Vital signs will include body temperature, respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position and standing position at all scheduled time points. Vital sign results at each visit and mean changes from baseline will be summarized by scheduled visit. Potentially CS values will be summarized by treatment. Vital sign results will be listed by participant and timing of collection.

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 (including ASO therapies) 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”. Medications will be presented according to whether they are “Prior” or “Concomitant” as defined above. If medication dates

are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

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

13.6.7. [redacted]

[redacted]

13.6.8. [redacted]

[redacted]

13.6.9. Other Safety Analysis

Not applicable.

13.7. [redacted]

[redacted]

13.8. Sample Size and Power

The study is designed to detect a difference between the placebo and SAGE-718 group in the change from baseline to Day 84 for the primary endpoint, SDMT score. Using a 2-sided test at an alpha level of 0.05, a sample size of approximately 71 evaluable participants per treatment group would provide 90% power to detect a difference of 4 points between the SAGE-718 and placebo arms in the change from baseline to Day 84 in SDMT values, assuming that the SD of the change from baseline in SDMT is 7.3 points.

Assuming a 20% dropout and a 1:1 randomization ratio, approximately 178 randomized participants (89 per treatment group) will be required to obtain 71 evaluable participants per treatment group. Evaluable participants are defined as those randomized participants who receive IP and have a valid baseline and at least 1 postbaseline SDMT assessment. Additional participants may be randomized to ensure a sufficient number of evaluable participants or if the dropout rate is higher than 20%.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

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

- Confirm the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, IP management, GCP/ICH GCP compliance, and the responsibilities of Sage Therapeutics or its representatives. Agreed upon site responsibilities will be documented in a Clinical Trial Agreement between Sage 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 eCRF, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRF with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, medical records, source documents, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

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

14.2. Audits and Inspections

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

14.3. Institutional Review Board or Independent Ethics Committee

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

When the participant decides to participate in the study, the participant 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 documentation. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant.

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

provided. [redacted]

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 visits at the investigation site and/or supporting facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant medical records and study source documents, and other records relative to study conduct.

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

17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The retention of records must be in accordance with local regulations (Section 20 [Appendix 1]) and Sage Therapeutics is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

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

19. LIST OF REFERENCES

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20. APPENDICES

Appendix 1: Country-Specific Changes

Country	Section Number	Original Language in Country-Specific Amendment	Updated Language for Country-Specific Amendment
United Kingdom (UK)	Section 7.1.4	End of study will be achieved when last study participant completes Follow-Up Visit at Day 112 (or ET).	End of study will be achieved when last study participant completes Follow-up Visit at Day 112 (or ET). Additionally, for UK participants, end of study will be achieved when all sample analyses are completed, with the exception of any consented exploratory analyses as described in Informed Consent Form and in adherence with local regulation.
Australia	Section 12.3	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.	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. For participants in Australia, pregnancy follow-up will be required for not less than 12 months. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
Australia	Section 17.2	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.	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. The sponsor will maintain all data relating to the study for a period of 50 years after the completion of the study. [redacted]

Country	Section Number	Original Language in Country-Specific Amendment	Updated Language for Country-Specific Amendment
Canada	Section 12.2.6	IRBs/IECs will be notified of SAEs and/or SUSARs as required by local law.	IRBs/IECs will be notified of SAEs and/or SUSARs as required by local law. The sponsor will report all SUSARs to Health Canada within 7 days (if fatal or life threatening) or 15 days (if neither fatal nor life threatening) after becoming aware of the information.
Canada	Section 17.2	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.	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. The sponsor will maintain all documentation relating to the study for a period of 15 years after the completion of the study as outlined in Section C.05.012 (4) of the Food and Drug Regulations.

Abbreviations: ET = early termination; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IRB = institutional review board; IEC = independent ethics committee; IP = investigational product; [redacted]; SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; UK = United Kingdom

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