Official Title: A Phase 3, Multicenter, Open-Label Safety Study to Evaluate the Long-Term Safety and Tolerability of SAGE-718 in Participants with Huntington's Disease

NCT Number: NCT05655520

Document Date: Protocol Version 3: 05 February 2024

A PHASE 3, MULTICENTER, OPEN-LABEL SAFETY STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF SAGE-718 IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

SHORT TITLE: PHASE 3 OPEN-LABEL SAFETY STUDY OF SAGE-718 IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

PROTOCOL NUMBER: 718-CIH-301
IND NUMBER: 145563

Investigational Product	SAGE-718
Clinical Phase	3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], PhD [redacted] Cambridge, MA 02142 Phone: [redacted]
Medical Monitor	[redacted], MD [redacted] Cambridge, MA 02142 Phone: [redacted]
Date of Original Protocol	20 September 2022
Date of Amendment #1	01 June 2023
Date of Amendment #2	05 February 2024

INVESTIGATOR'S AGREEMENT

I have received and read the investigator's brochure for SAGE-718. I have read the 718-CIH-301 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]
SAE Reporting	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 Fax: +1 (855) 638-1674 SAE Hotline: +1 (855) 564-2229 e-mail: Sage.Safety@iqvia.com
	[redacted], MD	Phone: [redacted] e-mail: [redacted]
Product Complaints Sage Therapeutics	Sage Therapeutics	Phone: 1 (833) 554-7243 e-mail: productcomplaints@sagerx.com
Inspection Notification Contact	Sage Therapeutics	e-mail: InspectionNotification@sagerx.com

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

Protocol Number: 718-CIH-301

IND Number: 145563

Title of Study:
A Phase 3, Multicenter, Open-label Safety Study to Evaluate the Long-term Safety and Tolerability of SAGE-718 in Participants with Huntington's Disease.

Short Title: Phase 3 Open-label Safety Study of SAGE-718 in Participants with Huntington's Disease

Number of Sites and Study Location: This study will take place at approximately 60 sites globally.

Phase of Development: 3

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final Safety Follow-up Visit) for each participant is projected to be up to approximately 4 years or study termination by the sponsor.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of SAGE-718 softgel lipid capsule in participants with Huntington's Disease (HD)	• Proportion of participants experiencing treatment-emergent adverse events (TEAEs) and severity of TEAEs • Number of participants who withdraw due to adverse events (AEs) • Change from Baseline in vital signs, clinical laboratory parameters, electrocardiograms (ECGs), and Columbia Suicide Severity Rating Scale (CSSRS) responses.
Other	
[redacted]	

[redacted]

Study Description:

This is a long-term, open-label study to evaluate the safety and tolerability of SAGE-718 in rollover participants from Phase 2 placebo-controlled studies and de novo participants with premanifest or early manifest HD.

Participants will be adults with genetically confirmed expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat within the huntingtin gene, who meet the eligibility criteria. An adult study partner is

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

There will be 3 cohorts of participants:

- Cohort 1 (Direct rollover) includes rollover participants from the 718-CIH-201 and 718-CIH-202 studies for whom 718-CIH-301 informed consent date is ≤7 days after the last day of the corresponding parent study and who had previously met the corresponding parent studies' eligibility criteria.
- Cohort 2 (Gap rollover) includes rollover participants from the 718-CIH-201 and 718-CIH-202 studies who have experienced a gap of >7 days between completion of the corresponding parent study and signing of the 718-CIH-301 informed consent and who had previously met the corresponding parent studies' eligibility criteria.

Cohorts 1 and 2 include participants who exhibited a measurable functional impairment (6 < TFC < 13) and cognitive impairment (Montreal Cognitive Assessment [MoCA] < 26) at the time of screening for the parent study.

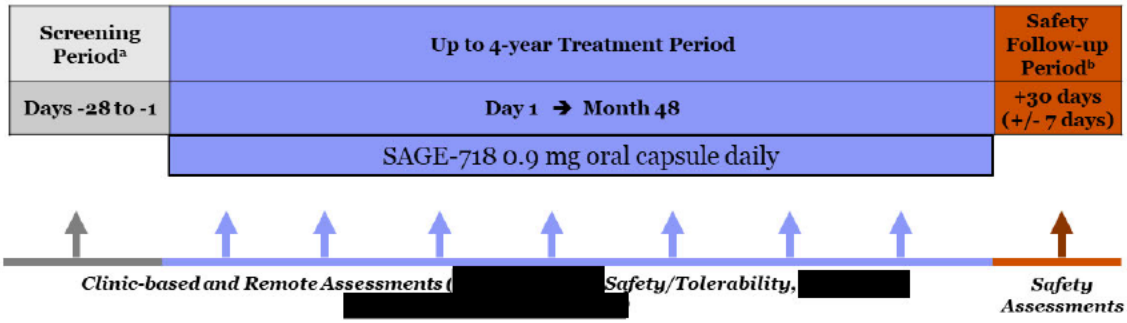
- Cohort 3 (De novo) includes de novo participants not previously included in a SAGE-718 clinical study. Enrollment of this cohort allows for assessment of the effect of SAGE-718 in a population that does not exhibit measurable functional impairment (TFC=13 [with MoCA ≤25]) or that meets the criteria of normal cognitive performance (MoCA >25 [with TFC ≤12]) (one or the other; not both). These participants must meet additional 718-CIH-301 study eligibility criteria for the de novo cohort outlined within this protocol.

Data from these 3 cohorts will contribute to a comprehensive safety database in a broadly defined group of individuals affected by HD.

Screening (for Cohorts 2 and 3) and safety, [redacted] will be performed according to the schedule presented in Table 2, Table 3, Table 4, Table 5, Table 6, Section 20.2, and Figure 1.

Screening assessments will be performed to determine eligibility for the de novo cohort with premanifest or early manifest HD, as specified in Table 2. The participants who rollover from the parent studies 718-CIH-201/202 with >7 days gap will confirm their eligibility and undergo selected screening/baseline assessments, as specified in Table 2. For the participants who rollover directly from the parent studies 718-CIH-201/202, the results of selected assessments will be carried over from the parent studies to 718-CIH-301 study, as specified in Table 3.

Study Schematics



Abbreviation: [redacted].

[a] De novo and gap (>7 days) rollover participants only. For direct (≤7 days) rollover participants, results of selected last parent study assessment to be used as Day 1 assessments when applicable.

[b] The Safety Follow-Up Visit will take place 30 days (±7 days) after the Month 48 or ET visit.

[redacted]

Beginning on Day 1, participants will self-administer investigational product (IP) once per day in the morning and will track IP intake in a participant diary. At clinic visits, participants will take the IP under staff supervision, [redacted] Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by examination of the used packaging, counting any returned capsules, and reviewing the participant diary.

During the treatment period, participants will be able to receive IP as long as there are no dose-limiting safety/tolerability concerns. At the discretion of the investigator, participants who cannot tolerate the 0.9 mg dose will be discontinued from IP. Treatment with SAGE-718 can be discontinued without down titration. Participants who complete the Treatment Period (ie, through the Month 48 Visit) or who discontinue IP early and complete an early termination (ET) visit will be asked to return to the clinic for a Safety Follow-Up Visit 30 days ±7 days after the Month 48 or ET visit.

The Safety Follow-Up Visit will be used to assess AEs and concomitant medications or procedures/therapies; participants will undergo a urine pregnancy test (females of childbearing potential [FOCBP] only), physical examination, vital signs, C-SSRS, [redacted]. End of study will be achieved when the last study participant completes the last study visit unless required differently in the operating country (refer to appendix for country specific requirements).

[redacted]

Participants who have completed their Day 395 visit under Protocol Version 2 and wish to continue participation under Protocol Version 3 or higher ("718-CIH-301 v2 Completers") will return to the site for a Re-Qualification Visit (Table 4) up to 28 days prior to resuming IP at their Next Scheduled Study Treatment Visit (relative to the date of their Day 1 visit, see Table 5). Relevant inclusion and exclusion criteria (see Section 7.1.3.1) will be re-confirmed at the Re-Qualification Visit, and participants will re-consent to study participation prior to continuing in the study. Thirty (30) days after resuming IP at their Next Scheduled Study Treatment Visit (Table 5), 718-CIH-301 v2 Completers will return to the site for a Post Re-Qualification Safety Check-in visit to evaluate safety (Table 4).

Participants who have completed their Day 365 visit but not their Day 395 visit under Protocol Version 2 when Protocol Version 3 or higher is implemented will NOT be considered "718-CIH-301 v2 Completers". Instead, these participants will return to the site as soon as possible for a Study Continuation Visit (Appendix 2, Section 20.2) during which they will consent to Protocol Version 3 or higher, complete safety assessments, and be dispensed SAGE-718 to resume study treatment. They will continue their study visits per Table 5 and will not have a Day 395 visit.

Number of Participants (Planned): There will be 3 cohorts in the study, including an estimated 128 rollover participants from 718-CIH-201 study, an estimated 28 rollover participants from the 718-CIH-202 study, and approximately 144 participants enrolled as a de novo cohort, comprising an estimated 300 participants total.

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

For all participants:

1. Completed 718-CIH-201 or 718-CIH-202 studies or meet eligibility criteria for the de novo cohort.
2. Be capable of providing informed consent in the opinion of the investigator (all cohorts) or be willing to have a legally authorized representative provide informed consent on their behalf (for 718-CIH-201 or 718-CIH-202 completers only).
3. Have signed (or a legally authorized representative has signed, if applicable) an informed consent form prior to any study-specific procedures being performed.
4. Agree to adhere to the study requirements.
5. Be capable of complying with study procedures, in the opinion of the investigator.
6. 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.
7. Be 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.
8. *[Revised in protocol version 3.0]*

8.A. 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 IP, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle-stimulating hormone >40 mIU/mL), permanently sterile, or does not engage in sexual relations which carry a risk of pregnancy.

9. *[Revised in protocol version 3.0]*

9.A. 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 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.

10. *[Revised in protocol version 3.0]*

10.A. Agree, if male, to abstain from sperm donation during the treatment period and for **21** days after receiving the last dose of IP.

11. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.

Additional inclusion criteria for the de novo cohort (Cohort 3)

12. Be at least 25 years old, but not older than 65 years of age at Screening.
13. Meet all of the following criteria for HD:
    a. Genetically confirmed disease with CAG expansion ≥40
    b. No features of juvenile HD
    c. CAG-Age-Product (CAP) score ≥90, as calculated using the CAP formula: AGE × (CAG – 30) / 6.49.
14. *[Revised in protocol version 3.0]*

14.A. At Screening, scores of EITHER

a. UHDRS-TFC=13 and MoCA ≤25, OR
b. UHDRS-TFC ≤12 and MoCA >25

15. Completion of HD-CAB Trail Making-B Test in <240 seconds at Screening (Days -28 to -1).

Exclusion criteria

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

For all participants

1. 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.
2. Have been diagnosed with and/or treated for any type of cancer (except successfully treated, locally excised basal cell carcinoma and melanoma in situ) within the past year prior to screening.
3. Had gastric bypass surgery, have a gastric sleeve or lap band, or have had any related procedures that interfere with gastrointestinal transit.
4. Plan to undergo elective surgery during participation in the study.
5. 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 amantadine, memantine, 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-containing substances (any route of administration), regardless of whether they are prescribed.
6. 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.
7. 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.
8. Have supine vital signs outside of the following ranges at Screening or Baseline (vital sign measurements may be repeated once per visit 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.
9. 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.
10. Have a history of significant hand injury that would preclude either writing or rapid bimanual computerized responding.

11. Have a history of seizures or epilepsy, except for a single episode of febrile seizures in childhood.
12. 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.
13. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion).
14. Have a positive pregnancy test, be pregnant, be lactating, or intend to breast feed during the study.
15. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
16. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.

Additional exclusion criteria for 718-CIH-201/202 completers who enroll after a gap of >7 days since completion of the parent study (Cohort 2) and for the de novo cohort (Cohort 3):

17. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1/HIV-2 or hepatitis B or hepatitis C.

Additional exclusion criteria for the de novo cohort (Cohort 3):

18. Have previous exposure to gene therapy, or have participated in any other 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). Participants with confirmation of enrollment in the placebo arm of these investigational trials would not be excluded. Additionally, participants who have received treatment with antisense oligonucleotides or an mRNA splicing modifier will be excluded.
19. 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 ‘suicidal ideation’ items on the C-SSRS.
    b. Suicidal behavior **within the past year**, as evidenced by a "Yes" on any of the Suicidal Behavior items on the C-SSRS.
    c. Presenting a serious risk of suicide in the opinion of the investigator.

Additional exclusion criteria for 718-CIH-201/202 completers (Cohorts 1 and 2):

20. Have current or recent suicidality, defined as follows:
    a. Suicidal ideation **since last visit**, 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 ‘suicidal ideation’ items on the C-SSRS.
    b. Suicidal behavior **since last visit**, as evidenced by a "Yes" on any of the Suicidal Behavior items on the C-SSRS.
    c. Presenting a serious risk of suicide in the opinion of the investigator.
21. Have one or more ongoing serious adverse events from the parent study that were assessed as related to IP.
22. Have ongoing, unresolved AE(s), which in the opinion of the investigator or sponsor, are likely to interfere with study conduct or compliance.

Investigational Product, Dosage, and Mode of Administration: SAGE-718 0.9 mg will be provided as a softgel lipid capsule for self-administration once daily orally in the morning.

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

Duration of Treatment: Each participant will receive SAGE-718 from the Day 1 Visit up to the Month 48 Visit.

Statistical Methods:

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

General Considerations:

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

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

Analysis Sets

The Safety Set is defined as all participants who were administered IP during the study and will be used to describe the safety data.

The Full Analysis Set is defined as all participants who were administered IP during the study and have baseline and at least 1 post-baseline efficacy evaluation.

[redacted]

Safety Analysis

Safety and tolerability of SAGE-718 will be evaluated by the number and severity of TEAEs, the number of participants who withdraw due to AEs, and the change from baseline in vital signs, clinical laboratory analyses, ECGs, and responses on the C-SSRS. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™). The proportion of participants experiencing TEAEs will be displayed by system organ class and preferred term for cohort and overall. The frequency of TEAEs will also be presented by maximum severity and relationship to IP and by cohort and overall. Vital signs, laboratory parameters, ECGs, and C-SSRS data will be summarized by cohort. Additional analyses will be detailed in the SAP. [redacted]

[redacted]

Sample Size

This is a long-term, open-label, safety study; there is no formal sample size calculation. The de novo cohort sample size of 144 or more was chosen to demonstrate the long-term safety for this de novo cohort. Approximately 156 participants are expected to rollover from the parent studies 718-CIH-201 and 718-CIH-202 assuming 10% dropout rate and 80% of completers from these 2 studies will be rolled over. If the rollover rate is lower than 80%, more de novo participants will be enrolled to achieve the target enrollment of 300 participants.

Table 2: Schedule of Assessments: Screening to Month 12 [De Novo (Cohort 3) and 718-CIH-201/202 >7 Day Gap Rollover (Cohort 2) Participants]

Assessments	Screening Period	Treatment Period						
	Days -28 to -1	Day 1	Day 30 (±7 days)	Day 60 (±7 days)	Day 90 (±7 days)	Day 180 (±14 days)	Day 270 (±14 days)	Day 365 (±14 days) [b]
Informed consent[a]	X							
Inclusion/exclusion criteria	X	X						
Family history and demographics	X							
Medical history[c]	X							
Participant training[d]	X							
Body weight	X	X				X		X
Body height[e]	X							
Vital signs (including orthostatics)[f]	X	X	X	X	X	X	X	X
Physical examination[g]	X	X	X	X	X	X	X	X
CAG test[e]	X							
FSH test[h]	X							
Serology test[i]	X							
12-lead ECG[j]	X	X	X		X	X		X
Safety laboratory assessments[k]	X	X	X		X	X	X	X
Urine drug test	X	X	X	X	X	X		X
Alcohol breath test	X	X	X	X	X	X		X
Cigarette/tobacco use assessment	X	X	X	X	X	X		X
Pregnancy test[l]	X	X	X		X	X	X	X
[redacted]								

Assessments	Screening Period	Treatment Period						
	Days -28 to -1	Day 1	Day 30 (±7 days)	Day 60 (±7 days)	Day 90 (±7 days)	Day 180 (±14 days)	Day 270 (±14 days)	Day 365 (±14 days) [b]
C-SSRS (Screening/Baseline)[p]	X (Cohort 3 only)							
C-SSRS (Since Last Visit)[p]	X (Cohort 2 only)	X	X	X	X	X	X	X
UHDRS[q]	X	[redacted]						
[redacted]								
MoCA	X							
[redacted]								
IP self-administration[w]		X (once daily in the morning)						
IP dispensation[x]		X	X	X	X	X	X	X
IP accountability/return[y]			X	X	X	X	X	X
IP adherence monitoring		X						
AEs/SAEs[z]	X							

Assessments	Screening Period	Treatment Period						
	Days -28 to -1	Day 1	Day 30 (±7 days)	Day 60 (±7 days)	Day 90 (±7 days)	Day 180 (±14 days)	Day 270 (±14 days)	Day 365 (±14 days) [b]
Prior and concomitant medications and procedures/therapies[aa]	X							

Abbreviations: AE = adverse event, CAG = cytosine-adenine-guanine trinucleotide repeat within the huntingtin gene, [redacted]; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic Case Report Form, FSH = follicle-stimulating hormone; [redacted]; HD = Huntington's Disease; [redacted]; HIV = human immunodeficiency virus; IP = investigational product; MoCA = Montreal Cognitive Assessment; [redacted]; SAE = serious adverse event; [redacted]; UHDRS = Unified Huntington's Disease Rating Scale; [redacted].

NOTE: Any additional parent study data needed to support the 718-CIH-301 data or analyses will be carried over from the applicable parent study.

[a] Both participants and study partners (if applicable) will be consented during the Screening Period. For gap rollovers only, a legally authorized representative may consent on behalf of participants who are not capable of providing informed consent in the opinion of the investigator.

[b] Participants who have completed their Day 395 visit under Protocol Version 2 and wish to continue participation under Protocol Version 3 or higher ("718-CIH-301 v2 Completers") will return to the site for a Re-Qualification visit (Table 4) up to 28 days prior to resuming IP at their Next Scheduled Study Treatment Visit (relative to the date of their Day 1 visit, see Table 5).

[c] Includes full medical history carried over from the parent study for gap rollover participants. Any medical history from the end of the parent study through informed consent for 718-CIH-301 and any resolved AEs from parent study, if clinically relevant, will be recorded as medical history in the eCRF. For de novo participants, full medical history will be collected.

[d] Participants and study partners (if applicable) will be trained by study staff on the use of software applications, devices, and diaries necessary for the conduct of the study. For the rollover participants, training can be customized based on participant's comfort level.

[e] For De Novo (Cohort 3) only. For gap rollover participants (Cohort 2), these tests will be carried over from the corresponding parent studies, 718-CIH-201 or 718-CIH-202.

[f] Vital signs 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.

[g] A full physical and neurological examination is to be conducted during Screening and on Day 180. 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.

[h] Serum FSH test will be conducted at Screening for the de novo female participants and rollover participants who are not surgically sterile and who have ≥12 months of spontaneous amenorrhea to confirm postmenopausal state as defined in this protocol. For the postmenopausal rollover participants (where postmenopausal state was confirmed in parent studies), the preceding results will be carried over from the corresponding parent studies, 718-CIH-201/202, as applicable.

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

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

[k] Safety laboratory assessments will include blood samples for hematology, biochemistry, coagulation, and urine samples for urinalysis. On dosing days, samples will be collected ≤2 hours prior to dosing.

[l] Serum pregnancy tests will be conducted for all female participants at Screening. Urine pregnancy tests will be conducted at other scheduled time points for female participants that are not postmenopausal or surgically sterile.

[o] Only applicable for gap rollover participants that did not provide [redacted] in the parent study and for de novo participants.

[p] For gap rollover participants (Cohort 2), the C-SSRS (Since Last Visit) will be completed during Screening. For de-novo participants (Cohort 3), the C-SSRS (Screening/Baseline) will be completed at Screening. Participants in Cohort 2 and 3 will complete the C-SSRS (Since Last Visit) at all subsequent time points.

[redacted]

[w] At scheduled clinic visits, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing and all scheduled cognitive tests will be administered postdosing. (All Day 1 assessments should be done predose).

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

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

[z] AEs/SAEs will be collected beginning with completion of 718-CIH-301 informed consent through end of study participation. For gap rollover participants, documented ongoing AE/SAE from the parent studies will be collected to follow through resolution.

[aa] All medications, supplements, procedures, and therapies taken within 8 weeks prior to obtaining 718-CIH-301 informed consent will be recorded through the end of the study. All medications, supplements, procedures, and therapies used to treat Huntington's Disease or to treat or prevent COVID, regardless of timing will be recorded through the end of the 718-CIH-301 study.

Table 3: Schedule of Assessments: Day 1 to Month 12 [718-CIH-201/202 Direct (≤7 days) Rollover (Cohort 1) Participants]

Assessments	Carry-over Results of the Last Assessments from Parent Studies when Applicable[a,f]	Treatment Period						
		Day 1	Day 30 (±7 days)	Day 60 (±7 days)	Day 90 (±7 days)	Day 180 (±14 days)	Day 270 (±14 days)	Day 365 (±14 days)[b]
Informed consent[c]		X						
Inclusion/exclusion criteria		X						
Family history and demographics	X							
Medical history[d]	X	X						
Participant training[e]		X						
Body weight		X[f]				X		X
Body height	X							
Vital signs (including orthostatics)[g]		X[f]	X	X	X	X	X	X
Physical examination[h]	X		X	X	X	X	X	X
CAG test	X							
FSH test	X							
Serology test[i]	X							
12-lead ECG[j]	X		X		X	X		X
Safety laboratory assessments[k]	X		X		X	X	X	X
Urine drug test		X[f]	X	X	X	X		X
Alcohol breath test		X[f]	X	X	X	X		X
Cigarette/tobacco use assessment		X[f]	X	X	X	X		X
Pregnancy test[l]	X		X		X	X	X	X
[redacted]								
C-SSRS (Since Last Visit)	X		X	X	X	X	X	X

Assessments	Carry-over Results of the Last Assessments from Parent Studies when Applicable[a,f]	Treatment Period						
		Day 1	Day 30 (±7 days)	Day 60 (±7 days)	Day 90 (±7 days)	Day 180 (±14 days)	Day 270 (±14 days)	Day 365 (±14 days)[b]
UHDRS[p]	X							
[redacted]								
MoCA	X							
[redacted]								
IP self-administration[w]		X (once daily in the morning)						
IP dispensation[x]		X	X	X	X	X	X	X
IP accountability/return[y]			X	X	X	X	X	X
IP adherence monitoring		X						
AEs/SAEs[z]	X							
Prior and concomitant medications and procedures/therapies[aa]	X							

Abbreviations: AE = adverse event, CAG = cytosine-adenine-guanine trinucleotide repeat within the huntingtin gene, [redacted]; COVID-19 = coronavirus disease 2019; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic Case Report Form, FSH = follicle-stimulating hormone; [redacted]; HD = Huntington's Disease; [redacted]; HIV = human immunodeficiency virus; IP = investigational product; MoCA = Montreal Cognitive Assessment; [redacted]; SAE = serious adverse event; [redacted]; UHDRS = Unified Huntington's Disease Rating Scale; [redacted].

NOTE: Any additional parent study data needed to support the 718-CIH-301 data or analyses will be carried over from the applicable parent study.

[a] The carryover assessments constitute the baseline/screening assessments for this extension study.

[b] Participants who have completed their Day 395 visit under Protocol Version 2 and wish to continue participation under Protocol Version 3 or higher ("718-CIH-301 v2 Completers") will return to the site for a Re-Qualification Visit (Table 4) up to 28 days prior to resuming IP at their Next Scheduled Study Treatment Visit (relative to the date of their Day 1 visit, see Table 5).

[c] Both participants and study partners (if applicable) will be consented on Day 1. A legally authorized representative may consent on behalf of participants who are not capable of providing informed consent in the opinion of the investigator. [redacted]

[d] Includes full medical history carried over from the parent study. On Day 1, any medical history from the end of the parent study through informed consent for 718-CIH-301 and any resolved AEs from parent study, if clinically relevant, will be recorded as medical history in the eCRF.

[e] Participants and study partners (if applicable) will be re-trained, if need be based on participant's comfort level, by study staff on the use of software applications, devices, and diaries necessary for the conduct of the study.

[f] Participants completing the final visit day of the parent study (Day 112 in CIH-201 or Day 42 in CIH-202) and Day 1 of this study at the same clinic visit are not required to repeat testing for body weight, vital signs (unless they had supine vital signs outside of the ranges specified in exclusion criterion #8), urine drug test, alcohol breath test, and cigarette/tobacco use assessment twice.

[g] Vital signs 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.

[h] The final physical and neurological examinations will be carried over from the parent study and will serve as Day 1 assessments in the current study. A full physical and neurological examination is to be conducted on Day 180. 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.

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

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

[k] Safety laboratory assessments will include blood samples for hematology, biochemistry, coagulation, and urine samples for urinalysis. On dosing days, samples will be collected ≤2 hours prior to dosing.

[l] Urine pregnancy tests will be conducted at scheduled time points for female participants that are not postmenopausal or surgically sterile.

[redacted]

[o] Only applicable for direct rollover participants that did not provide sample(s) in the parent study.

[redacted]

[w] At scheduled clinic visits, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing and all scheduled cognitive tests will be administered post dosing. (All Day 1 assessments should be done predose).

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

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

[z] AEs/SAEs will be collected beginning with completion of 718-CIH-301 informed consent through end of study participation. Documented ongoing AE/SAE from parent studies will be collected to follow through resolution.

[aa] All medications, supplements, procedures, and therapies taken within 8 weeks prior to obtaining 718-CIH-301 informed consent will be recorded through the end of the study. All medications, supplements, procedures, and therapies used to treat Huntington's Disease or to treat or prevent COVID, regardless of timing will be recorded through the end of the 718-CIH-301 study.

Table 4: Schedule of Assessments: Additional Visits for 718-CIH-301 v2 Completers

Assessments	Re-Qualification Visit[a, b]		Post Re-Qualification Safety Check-in
	Up to 28 days prior to Next Scheduled Study Treatment Visit	Next Scheduled Study Treatment Visit (See Table 5)[c]	30 days (±7 days) after Next Scheduled Study Treatment Visit
Informed re-consent[d]	X		
Reconfirm inclusion/exclusion criteria[e]	X		
Interim medical history[f]	X		
Optional participant training[g]	X		
Body weight	X		
Body height	X		
Vital signs (including orthostatics)[h]	X		X
Physical examination[i]	X		X
Serology test[j]	X		
12-lead ECG[k]	X		X
Safety laboratory assessments[l]	X		X
Urine drug test	X		
Alcohol breath test	X		
Cigarette/tobacco use assessment	X		
Pregnancy test[m]	X		
[redacted]			
C-SSRS (Since Last Visit)	X		X
IP self-administration[n]			X
IP adherence monitoring			X
AEs/SAEs[o]	X		X
Prior and concomitant medications and procedures/therapies[p]	X		X

Abbreviations: AE = adverse event; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic Case Report Form; HIV = human immunodeficiency virus; IP = investigational product; SAE = serious adverse event.

[a] Participants who have completed their Day 395 visit under Protocol Version 2 and wish to continue participation under Protocol Version 3 or higher ("718-CIH-301 v2 Completers") will return to the site for a Re-Qualification Visit (Table 4) up to 28 days prior to resuming IP at their Next Scheduled Study Treatment Visit (relative to the date of their Day 1 visit, see Table 5).

[b] Participants who have NOT completed their Day 395 visit under Protocol Version 2 but have completed their Day 365 visit and wish to continue participation under Protocol Version 3 or higher will NOT return to the site for a Re-Qualification Visit. They will return to the site for a Study Continuation Visit (Appendix 2, Section 20.2) and then continue on to their Month 15 visit (see Table 5). The participant's visit schedule should remain relative to the date of their Day 1 visit.

[c] 718-CIH-301 v2 Completers will resume IP at their Next Scheduled Study Treatment Visit (see Table 5). The Next Scheduled Study Treatment Visit may be any visit within the Treatment Period and will depend on the participant's visit schedule, which will remain relative to the date of their Day 1 visit.

[d] Both participants and study partners (if applicable) will be re-consented at the Re-Qualification Visit. A legally authorized representative may consent on behalf of participants who are not capable of providing informed consent in the opinion of the investigator.

[e] Guidance on eligibility for 718-CIH-301 v2 Completers is provided in Section 7.1.3.1.

[f] Any new or worsening conditions or events with an onset after the end of participation under 718-CIH-301 Protocol Version 2 (Day 395) and before informed consent for 718-CIH-301 Protocol Version 3 or higher will be recorded as Interim Medical History in the eCRF.

[g] Participants and study partners (if applicable) will be re-trained, if need be based on participant's comfort level, by study staff on the use of software applications, devices, and diaries necessary for the conduct of the study.

[h] Vital signs include body temperature, respiratory rate, heart rate, and blood pressure. 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 if out of range. At the Post Re-Qualification Safety Check-in, vital signs will be measured prior to dosing.

[i] A full physical and neurological examination is to be conducted during the Re-Qualification Visit. At the Post Re-Qualification Safety Check-in, 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.

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

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

[l] Safety laboratory assessments will include blood samples for hematology, biochemistry, coagulation, and urine samples for urinalysis. At the Post Re-Qualification Safety Check-in, samples will be collected ≤2 hours prior to dosing.

[m] Serum pregnancy tests will be conducted for all female participants at the Re-Qualification Visit.

[n] At the Post Re-Qualification Safety Check-in, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing.

[o] AEs/SAEs will be collected from the time of informed consent for 718-CIH-301 Protocol Version 3 or higher through end of study participation.

[p] All medications, supplements, procedures, and therapies taken after the completion of Day 395 under 718-CIH-301 Protocol Version 2 will be recorded through the end of the study.

Table 5: Schedule of Assessments: Month 15 to Month 48 – All Participants

Assessments	**Treatment Period[a]**												**Safety Follow-Up**
	M 15 (±14 d)	**M 18 (±14 d)**	**M 21 (±14 d)**	**M 24 (±14 d)**	**M 27 (remote) (±14 d)**	**M 30 (±14 d)**	**M 33 (remote) (±14 d)**	**M 36 (±14 d)**	**M 39 (remote) (±14 d)**	**M 42 (±14 d)**	**M 45 (remote) (±14 d)**	**M 48 or ET[b] (±14 d)**	**+30 days (±7 days)**
Body weight				X				X				X	X
Vital signs (including orthostatics)[c]	X	X	X	X		X		X		X		X	X
Brief physical examination[d]	X	X	X	X		X		X		X		X	X
12-lead ECG[e]		X		X		X		X		X		X	
Safety laboratory assessments[f]	X	X	X	X		X		X		X		X	
Urine drug test		X		X				X				X	
Alcohol breath test		X		X				X				X	
Cigarette/tobacco use assessment				X				X				X	
Pregnancy test[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
C-SSRS (Since Last Visit)	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													

Assessments	Treatment Period[a]												Safety Follow-Up
	M 15 (±14 d)	M 18 (±14 d)	M 21 (±14 d)	M 24 (±14 d)	M 27 (remote) (±14 d)	M 30 (±14 d)	M 33 (remote) (±14 d)	M 36 (±14 d)	M 39 (remote) (±14 d)	M 42 (±14 d)	M 45 (remote) (±14 d)	M 48 or ET[b] (±14 d)	+30 days (±7 days)
[redacted]													
IP accountability/return[p]	X	X	X	X		X		X		X		X	
IP dispensation[q]	X	X	X	X	X	X	X	X	X	X	X		
IP self-administration[r]	X (once daily in the morning)												
IP adherence monitoring[s]	X												
AEs/SAEs	X												
Prior and concomitant medications and procedures/therapies	X												

Abbreviations: AE = adverse event; AI = Apathy Inventory; [redacted]; C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; ECG = electrocardiogram; ET = early termination; [redacted] IP = investigational product; M = Month; MoCA = Montreal Cognitive Assessment; [redacted]; SAE = serious adverse event; [redacted]; UHDRS = Unified Huntington's Disease Rating Scale; [redacted].

[a] For 718-CIH-301 v2 Completers, the "Next Scheduled Study Treatment Visit" may be any visit within the Treatment Period and will depend on the participant's visit schedule, which will remain relative to the date of their Day 1 visit.

[b] Participants who terminate the study early should complete an ET visit (Table 5) within 7 days of IP discontinuation and return to the clinic for a Safety Follow-Up Visit 30 days ±7 days after the ET visit.

[c] Vital signs 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.

[d] Brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical assessment as needed. A symptom-directed examination may be conducted at any time at the discretion of the investigator.

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

[f] Safety laboratory assessments will include blood samples for hematology, biochemistry, coagulation, and urine samples for urinalysis. On dosing days, samples will be collected ≤2 hours prior to dosing.

[g] Only applicable for female participants that are not postmenopausal or surgically sterile. For scheduled clinic visits, urine pregnancy tests will be conducted. For remote visits (Months 27, 33, 39, and 45), start and end dates of the last menses will be collected.

[redacted]

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

[q] Study staff will dispense sufficient IP for the participant to take daily at home until the next scheduled visit. IP will be shipped to the participant's home at remote visits (Months 27, 33, 39, and 45).

[r] At scheduled clinic visits, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing and all scheduled cognitive tests will be administered post dosing.

[s] At remote visits, site staff will check AiCure and query the participant about any missed doses or noncompliance.

Table 6: [redacted]

[redacted]

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 7: Abbreviations and Specialist Terms

Abbreviation	Definition
24(S)-HC	24(S)-hydroxycholesterol
718-CIH-301 v2 Completers	participants who have completed their Day 395 visit under Protocol Version 2 and wish to continue participation under Protocol Version 3 or higher
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AI	Apathy Inventory
[redacted]	[redacted]
CAG	cytosine-adenine-guanine
CAP	CAG-Age-Product
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CS	clinically significant
C-SSRS	Columbia–Suicide Severity Rating Scale
[redacted]	[redacted]
DILI	drug-induced liver injury
ECG	Electrocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

Abbreviation	Definition
[redacted]	[redacted]
HD	Huntington's Disease
HD-CAB	Huntington's Disease Cognitive Assessment Battery
[redacted]	[redacted]
[redacted]	[redacted]
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IP	investigational product
IRB	institutional review board
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
NCS	not clinically significant
NMDA	N-methyl-D-aspartate
PCS	physical component score
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TFC	Total Functional Capacity
THC	tetrahydrocannabinol
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
UP	unanticipated problem
US	United States
USM	urgent safety measure
[redacted]	[redacted]
[redacted]	[redacted]

5. INTRODUCTION

Huntington's disease (HD) is a rare, hereditary, neurodegenerative disease for which there is no approved pharmacologic therapy for the treatment of cognitive dysfunction. An estimated 18,600 to 30,000 adults (7.3 to 11.8 per 100,000) have been diagnosed with HD in the United States (NINDS 2022; Rawlins 2016). Based on population estimates, there are approximately 41,000 symptomatic Americans and more than 200,000 at-risk of inheriting HD (Huntington's Disease Society of America 2022), highlighting the unmet medical need in this population.

In the pre-motor stages of the disease, psychiatric and cognitive dysfunction predominate (Tabrizi 2012). Natural history studies have shown that cognitive decline begins to occur up to 15 years before motor symptoms manifest and the formal diagnosis occurs. Later stages of the disease are characterized by prominent motor symptoms, including chorea and rigidity, though cognitive impairment remains an ongoing concern and a significant driver of functional disability (Cardoso 2017; Duff 2010). Intervention at an early stage of the disease may help patients maintain cognitive capacities critical to everyday functioning.

Although the mechanisms underlying cognitive dysfunction in HD have not been fully elucidated, changes in glutamatergic neurotransmission have been implicated based on the results of nonclinical, postmortem, and clinical studies. Nonclinical studies have shown that moderate stimulation of N-methyl-D-aspartate (NMDA) receptors in an HD mouse model may impart neuroprotective effects (Okamoto 2009). Postmortem brain samples in a pre-symptomatic carrier of the HD allele reveal abnormalities of striatal NMDA receptors and projections to the globus pallidus and substantia nigra, suggesting core aspects of HD symptomatology may be consequential to reduction of NMDA signaling along these pathways (Albin 1990). Most important, reduction in plasma levels of 24(S)-hydroxycholesterol (24(S)-HC), an endogenous modulator of NMDA receptors, has been described in HD patients (Leoni 2013; Lewis 2019; Paul 2013). These data support proof of principle that lower 24(S)-HC levels in HD could reflect NMDA receptor dysfunction, as well as pathology relevant to in the etiology of associated cognitive deficits (Lewis 2019).

SAGE-718 is a novel, first-in-class, oxysterol-based positive allosteric modulator of NMDA receptors. SAGE-718 acts at the 24(S)-HC site that modulates the response of the receptor to glutamate but does not directly activate it. Glutamate, the most prevalent excitatory neurotransmitter in the brain, primarily signals through ionotropic ligand-gated receptors and metabotropic G-protein-coupled receptors. 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 and Zhou 2017).

SAGE-718 is being developed as a novel early intervention to treat cognitive dysfunction associated with HD, for which there is no approved pharmacologic therapy.

This is an open-label study to evaluate the long-term safety and tolerability of SAGE-718 in participants with premanifest or early manifest HD. Additional data on the effects of SAGE-718 in participants with HD will be collected throughout, including assessments of cognitive, neuropsychiatric, and motor symptoms.

5.1. Overall Risk/Benefit Assessment

The administration of SAGE-718 in premanifest and early manifest HD is expected to have moderate NMDA augmenting properties without impacting brain integrity, thereby improving cognition in HD patients and potentially alleviating one of the most significant and debilitating symptoms associated with the disease. This hypothesis is supported by the emerging clinical data revealing that the administration of SAGE-718, a novel and optimized analogue of 24(S)-HC, improves performance on tests of higher-order functioning in patients with pre-manifest or early manifest HD as well as in healthy participants with a ketamine-induced temporary state of relative NMDA receptor hypofunction (for details, refer to the investigator's brochure [IB]). In addition, SAGE-718 has been shown to improve cognition in other neurodegenerative disorders (for details refer to the IB). The potential benefit of SAGE-718 is coupled with low risk of NMDA receptor-associated excitotoxicity, as SAGE-718 does not directly activate the NMDA receptor and thus is not expected to cause NMDA receptor associated glutamatergic excitotoxicity.

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 (ADME), drug-drug interaction, and toxicology findings, including compound-related effects and the reversibility of these changes. In a radiolabeled rat ADME 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 the nonclinical studies conducted with rats and dogs, a C_{max} threshold for observation of convulsions occurred at exposures 20 to 40 times greater than clinically relevant exposures.

Two Good Laboratory Practice (GLP) chronic toxicology studies (6 and 9 months) were conducted in rats and dogs, respectively, in adherence to International Conference on Harmonization (ICH) M3(R2) guidance. The exposure levels following repeated oral dose administration of SAGE-718 at the no-observed-adverse-effect level represent approximately 15-fold to 45-fold higher (C_{max}) median exposures than would be expected in humans after 84 days of chronic dosing of 0.9 mg, as predicted by population PK models (for details, refer to the IB).

Two GLP embryo-fetal development studies in rats and rabbits were conducted in adherence to ICH S5(R3). There were no SAGE-718-related effects on maternal survival, clinical observations, mean maternal body weights, body weight gains, gravid uterine weights, food consumption, intrauterine growth, fetal survival, or fetal morphology (for details, refer to the IB).

In a GLP fertility study in female rats conducted in adherence to ICH S5(R3), there were no SAGE-718-related effects on estrous cyclicity, reproductive performance (including mating, fertility, and pregnancy indices), or precoital interval length at any dose level. There were no SAGE-718-related macroscopic findings or alterations in organ weights. In a GLP fertility study in male rats conducted in adherence to ICH S5(R3), body weight, body weight gains, food

consumption, reproductive performance (including mating, fertility, and pregnancy indices), macroscopic pathology, and organ weights were unaffected by SAGE-718 administration (for details, refer to the IB).

No deaths, serious adverse events (SAEs) or treatment-emergent adverse events (TEAEs) leading to discontinuation assessed as related to SAGE-718 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 TEAEs reported in patients with HD that were enrolled in the completed SAGE-718 studies.

There is no contraindication for use of the coronavirus disease 2019 (COVID-19) vaccination in the trial setting of SAGE-718. Vaccine status will be recorded as a concomitant therapy and COVID-19 safety protocols will be incorporated in all studies, data collection, and operating procedures.

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

5.2. Dose Justification

SAGE-718 has been well tolerated in both healthy participants and HD participants in previous and ongoing clinical studies. However, based on nonclinical findings, the United States Food and Drug Administration (FDA) imposed a median C_{max} cap of 45 ng/mL. To date, clinical studies have used doses that resulted in exposures within this cap; neither SAEs nor adverse events (AEs) leading to discontinuation have been reported. For additional information on exposure caps, see the IB.

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 patients with Parkinson's Disease, repeat doses of 3 mg when taken with a meal containing approximately 30 g of dietary fat showed beneficial effects on cognition assessments. The pharmacokinetic (PK) exposures in the above scenarios were similar, with individual maximum observed concentration (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 0.9 mg. The lipid formulation has improved bioavailability characteristics compared to solution and tablet forms. The dose is selected to provide 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 safety and tolerability of SAGE-718 softgel lipid capsule in participants with Huntington's Disease (HD)	• Proportion of participants experiencing treatment-emergent adverse events (TEAEs) and severity of TEAEs • Number of participants who withdraw due to adverse events (AEs) • Change from Baseline in vital signs, clinical laboratory parameters, electrocardiograms (ECGs), and Columbia Suicide Severity Rating Scale (CSSRS) responses.
Other	
[redacted]	

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a long-term, open-label study to evaluate the safety and tolerability of SAGE-718 in rollover participants from Phase 2 placebo-controlled studies and de novo participants with premanifest or early manifest HD.

Participants will be adults with genetically confirmed expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat within the huntingtin gene, who meet the eligibility criteria. An adult study partner is optional but highly recommended for each participant to support completion of study activities and answer questions about the participant's condition. For prospective participants and study partners, the study will begin with the informed consent process.

There will be 3 cohorts of participants:

- Cohort 1 (Direct rollover) includes rollover participants from the 718-CIH-201 and 718-CIH-202 studies for whom 718-CIH-301 informed consent date is ≤7 days after the last day of the corresponding parent study and who had previously met the corresponding parent studies' eligibility criteria.
- Cohort 2 (Gap rollover) includes rollover participants from the 718-CIH-201 and 718-CIH-202 studies who have experienced a gap of >7 days between completion of the corresponding parent study and signing of the 718-CIH-301 informed consent and who had previously met the corresponding parent studies' eligibility criteria.

Cohorts 1 and 2 include participants who exhibited a measurable functional impairment (6 < TFC < 13) and cognitive impairment (Montreal Cognitive Assessment [MoCA] < 26) at the time of screening for the parent study.

- Cohort 3 (De novo) includes de novo participants not previously included in a SAGE-718 clinical study. Enrollment of this cohort allows for assessment of the effect of SAGE-718 in a population that does not exhibit measurable functional impairment (TFC=13 [with MoCA ≤25]) or that meets the criteria of normal cognitive performance (MoCA >25 [with TFC ≤12]) (one or the other; not both). These participants must meet additional 718-CIH-301 study eligibility criteria for the de novo cohort outlined within this protocol.

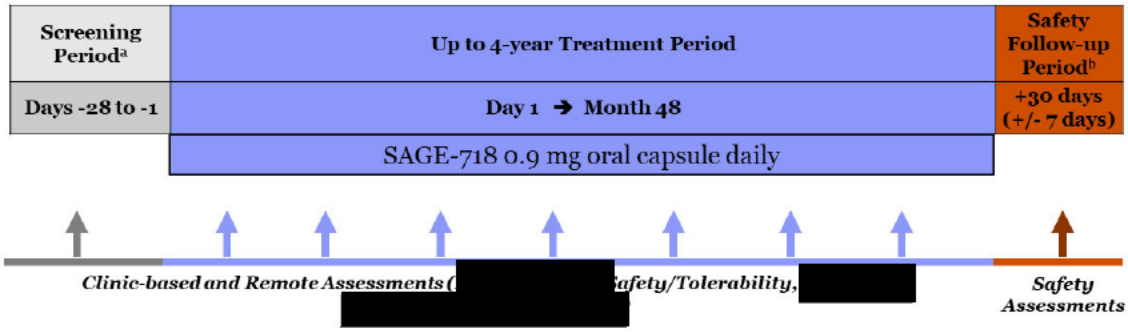
Data from these 3 cohorts will contribute to a comprehensive safety database in a broadly defined group of individuals affected by HD. Data in this study will be collected through the Safety Follow-up Visit.

[redacted]

7.1.1. Study Schematic

Screening (for Cohorts 2 and 3), safety, [redacted] will be performed according to the schedule presented in Table 2, Table 3, Table 4, Table 5, Table 6, Section 20.2, and Figure 1.

Figure 1: Study Schematics



Abbreviation: [redacted]
[a] De novo and gap (>7 days) rollover participants only. For direct (≤7 days) rollover participants, results of selected last parent study assessment to be used as Day 1 assessments when applicable.
[b] The Safety Follow-Up Visit will take place 30 days (±7 days) after the Month 48 or ET visit.

7.1.2. Screening Period

Screening assessments will be performed to determine eligibility for the de novo cohort with premanifest or early manifest HD, as specified in Table 2. The participants who rollover from the parent studies 718-CIH-201/202 with >7 days gap will confirm their eligibility and undergo selected screening/baseline assessments, as specified in Table 2. For the participants who rollover directly from the parent studies 718-CIH-201 and 718-CIH-202 (gap ≤7 days), the results of selected assessments will be carried over from the parent studies to 718-CIH-301 study, as specified in Table 3.

7.1.3. Treatment Period

Beginning on Day 1 and continuing through the Treatment Period, participants will self-administer investigational product (IP) once per day in the morning and will track IP intake in a participant diary. At clinic visits, participants will take the IP under staff supervision, followed by assessments [redacted]. Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by examination of the used packaging, counting any returned capsules, and reviewing the participant diary. Participants should continue to self-administer IP within the visit window up until the Month 48 Visit.

7.1.3.1. Additional visits related to the transition from Protocol Version 2 to Protocol Version 3

Participants who have completed Day 395 under Protocol Version 2 ("718-CIH-301 v2 Completers")

Participants who have completed their Day 395 visit under Protocol Version 2 and wish to continue participation under Protocol Version 3 or higher ("718-CIH-301 v2 Completers") will return to the site for a Re-Qualification Visit (Table 4) up to 28 days prior to resuming IP at their Next Scheduled Study Treatment Visit (relative to the date of their Day 1 visit, see Table 5). Participants must sign an ICF for Protocol Version 3 or higher prior to any further study procedures. Inclusion criteria #1-11 (Section 8.1) and exclusion criteria #1-17 and #20-22 (Section 8.2) will be re-confirmed at this visit and documented appropriately. Exclusion criteria #17 should be re-confirmed for both Cohort 1 and Cohort 2 participants. Exclusion criteria #2, #5, and #8 should be assessed at or relative to the time of the Re-Qualification Visit. Exclusion criteria #21 should be assessed relative to initial participation in 718-CIH-301 under Protocol Version 2 or prior.

718-CIH-301 v2 Completers will resume IP at their Next Scheduled Study Treatment Visit (see Table 5). The Next Scheduled Study Treatment Visit may be any visit within the Treatment Period and will depend on the participant's visit schedule, which will remain relative to the date of their Day 1 visit.

Thirty (30) days after resuming IP at their Next Scheduled Study Treatment Visit (Table 5), 718-CIH-301 v2 Completers will return to the site for a Post Re-Qualification Safety Check-in visit to evaluate safety (Table 4).

For 718-CIH-301 v2 Completers, interim medical history will be collected from the time of completion of Day 395 under 718-CIH-301 Protocol Version 2 through informed consent for 718-CIH-301 Protocol Version 3 or higher, AEs/SAEs will be collected from the time of informed consent for 718-CIH-301 Protocol Version 3 or higher through end of study participation, and prior and concomitant medications and procedures/therapies will be collected from the time of completion of Day 395 under 718-CIH-301 Protocol Version 2 through end of study participation. Documented ongoing AEs/SAEs and prior and concomitant medications and procedures/therapies from participation under 718-CIH-301 Protocol Version 2 or prior will be followed for resolution through end of study participation.

Participants who have completed Day 365 but not Day 395 under Protocol Version 2

Participants who have completed their Day 365 visit but not their Day 395 visit under Protocol Version 2 when Protocol Version 3 or higher is implemented will NOT be considered "718-CIH-301 v2 Completers". Instead, these participants will return to the site as soon as possible for a Study Continuation Visit (Appendix 2, Section 20.2) at which they will consent to Protocol Version 3 or higher, complete safety assessments, and be dispensed SAGE-718 to resume study treatment. They will continue study visits per Table 5 and will not have a Day 395 visit.

7.1.3.2. Remote Visits

After the second year of the Treatment Period (ie, after the Month 24 visit), participants will be contacted by site staff periodically for remote visits, as indicated in Table 5. Participants will

remotely complete selected safety and efficacy questionnaires, answer questions about any AEs and concomitant medications or procedures/therapies, and be asked the start and stop date of their last menses (FOCBP only). Site staff should check within AiCure for compliance issues. If the participant has missed any doses, site staff should question the participant during the phone visit. IP will be shipped to the homes of the participants (Section 10.5). Participants should return any unused packaging to the site at their next in-person study visit.

7.1.4. Follow-up Period

Participants who complete the Treatment Period (ie, through the Month 48 Visit) or who discontinue IP early and complete an early termination (ET) visit will be asked to return to the clinic for a Safety Follow-Up Visit 30 days ±7 days after the Month 48 or ET visit. The Safety Follow-Up Visit will be used to assess AEs and concomitant medications or procedures/therapies; participants will undergo a urine pregnancy test (females of childbearing potential [FOCBP] only), physical examination, vital signs, C-SSRS, [redacted]. For participants who discontinue IP early, see Section 8.4.

7.2. Number of Participants

There will be 3 cohorts in the study, including an estimated 128 rollover participants from the 718-CIH-201 study, an estimated 28 rollover participants from the 718-CIH-202 study and approximately 144 participants to be enrolled as a de novo cohort, comprising an estimated 300 participants total.

7.3. Treatment Assignment

In this open-label study, all participants will receive SAGE-718 oral softgel lipid capsules at 0.9 mg daily dose.

7.4. Dose Adjustment Criteria

Individual dose reductions will not be permitted.

7.4.1. [redacted]

[redacted]

7.4.1.1. [redacted]

[redacted]

[redacted]

7.4.2. Stopping Criteria

If clinical events suspicious for seizure occur after Screening, IP should be discontinued immediately with appropriate clinical follow-up, including EEG, repeat serum chemistry, urinalysis, and drug/alcohol tests. As close as possible to the timing of the event suspicious of seizure, [redacted] should be collected (Section 11.3.1.1).

During the treatment period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. At the discretion of the investigator, participants who cannot tolerate the 0.9 mg dose will be discontinued from IP. Treatment with SAGE-718 can be discontinued without down titration. See Section 8.4 for participants who discontinue IP early.

7.4.3. 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 liver 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.

7.4.4. Criteria for Study Termination

Sage Therapeutics (the Sponsor) 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 will provide written notification to the investigators. Investigational sites must promptly notify their institutional review board (IRB)/independent ethics committee (IEC), where required, and initiate withdrawal procedures for participants.

7.4.5. End of Study

End of study will be achieved when the last study participant completes the last study visit, as shown in Table 5. (See Appendix 2, Section 20.1 for country-specific requirements).

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

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

For all participants:

1. Completed 718-CIH-201 or 718-CIH-202 studies or meet eligibility criteria for the de novo cohort.
2. Be capable of providing informed consent in the opinion of the investigator (all cohorts) or be willing to have a legally authorized representative provide informed consent on their behalf (for 718-CIH-201 or 718-CIH-202 completers only).
3. Have signed (or a legally authorized representative has signed, if applicable) an informed consent form prior to any study-specific procedures being performed.
4. Agree to adhere to the study requirements.
5. Be capable of complying with study procedures, in the opinion of the investigator.
6. 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.
7. Be 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.
8. *[Revised in protocol version 3.0]*

8.A. 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 IP, unless she is postmenopausal (defined as no menses for 12 months without an alternative medical cause and confirmed by follicle-stimulating hormone > 40 mIU/mL), permanently sterile, or does not engage in sexual relations which carry a risk of pregnancy.

9. *[Revised in protocol version 3.0]*

9.A. 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 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.

10. *[Revised in protocol version 3.0]*

10.A. Agree, if male, to abstain from sperm donation during the treatment period and for **21** days after receiving the last dose of IP.

11. Agree to refrain from drugs of abuse for the duration of the study and from alcohol during the 48 hours preceding each study visit.

Additional inclusion criteria for the de novo cohort (Cohort 3)

12. Be at least 25 years old, but not older than 65 years of age at Screening.
13. Meet all of the following criteria for HD:
    a. Genetically confirmed disease with CAG expansion ≥40
    b. No features of juvenile HD
    c. CAG-Age-Product (CAP) score ≥90, as calculated using the CAP formula: AGE × (CAG – 30) / 6.49.
14. *[Revised in protocol version 3.0]*

14.A. At Screening, scores of EITHER

    a. UHDRS-TFC=13 and MoCA ≤25, OR
    b. UHDRS-TFC ≤12 and MoCA >25

15. Completion of HD-CAB Trail Making-B Test in <240 seconds at Screening (Days -28 to -1).

8.2. Participant Exclusion Criteria

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

For all participants

1. 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.
2. Have been diagnosed with and/or treated for any type of cancer (except successfully treated, locally excised basal cell carcinoma and melanoma in situ) within the past year prior to screening.
3. Had gastric bypass surgery, have a gastric sleeve or lap band, or have had any related procedures that interfere with gastrointestinal transit.
4. Plan to undergo elective surgery during participation in the study.
5. 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 amantadine, memantine, 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 they are prescribed.
6. 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.

7. 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.
8. Have supine vital signs outside of the following ranges at Screening or Baseline (vital sign measurements may be repeated once per visit 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.
9. 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.
10. Have a history of significant hand injury that would preclude either writing or rapid bimanual computerized responding.
11. Have a history of seizures or epilepsy, with the exception of a single episode of febrile seizures in childhood.
12. 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.
13. Have a history, presence, and/or current evidence of intracranial abnormality (eg, stroke, hemorrhage, space-occupying lesion).
14. Have a positive pregnancy test, be pregnant, be lactating, or intend to breast feed during the study.
15. Be investigative site personnel, sponsor personnel, or an immediate member of their family (spouse, parent, child, or sibling whether biological or legally adopted).
16. Is known to be allergic to any of SAGE-718 excipients, including soy lecithin.

Additional exclusion criteria for 718-CIH-201/202 completers who enroll after a gap of >7 days since completion of the parent study (Cohort 2) and for the de novo cohort (Cohort 3):

17. Have a history, presence, and/or current evidence of serologic positive results for human immunodeficiency virus (HIV)-1/HIV-2 or hepatitis B or hepatitis C.

Additional exclusion criteria for the de novo cohort (Cohort 3):

18. Have previous exposure to gene therapy, or have participated in any other 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). Participants with confirmation of enrollment in the placebo arm of these investigational trials would not be excluded. Additionally, participants who have received treatment with antisense oligonucleotides or an mRNA splicing modifier will be excluded.
19. 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 'suicidal ideation' items on the C-SSRS.

b. Suicidal behavior **within the past year**, as evidenced by a "Yes" on any of the C-SSRS Suicidal Behavior items on the C-SSRS.
c. Presenting a serious risk of suicide in the opinion of the investigator.

Additional exclusion criteria for 718-CIH-201/202 completers (Cohorts 1 and 2):

20. Have current or recent suicidality, defined as follows:
    a. Suicidal ideation **since last visit**, 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 **since last visit**, as evidenced by a "Yes" on any of the CSSRS Suicidal Behavior items on the C-SSRS.
    c. Presenting a serious risk of suicide in the opinion of the investigator.
21. Have one or more ongoing SAEs from the parent study that was assessed as related to IP.
22. Have ongoing, unresolved AE(s), which in the opinion of the investigator or sponsor, is likely to interfere with study conduct or compliance.

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, or due to pregnancy. Any necessary interruptions to dosing of IP (eg, surgery) will be handled on a case-by-case basis.

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

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

Participants who discontinue IP early will be invited by the investigator to complete an early termination (ET) visit within 7 days of IP discontinuation and will be asked to return to the clinic for a Safety Follow-Up Visit 30 days (±7 days) after the ET visit, if possible. The participant will be permanently discontinued from IP (if not previously discontinued) at the ET visit and from the study at the Safety Follow-Up Visit. If the participant does not complete a Safety Follow-Up Visit, they will be permanently discontinued from the study at the ET visit. The Safety Follow-Up Visit will be used to assess AEs and concomitant medications or procedures/therapies;

participants will undergo a urine pregnancy test (females of childbearing potential [FOCBP] only), physical examination, vital signs, C SSRS, [redacted].

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

8.4.1. Loss to Follow-up

A participant will be deemed lost to follow-up after at least 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.

8.4.2. Replacement of Participants

Participants who discontinue or withdraw from the study will not be replaced. However, additional participants may be enrolled in the de novo cohort 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 0.9 mg of SAGE-718 drug substance.

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

9.2.1. Prior and Concomitant Medications, Supplements, and Procedures/Therapies

All medications, supplements, procedures, and therapies taken within 8 weeks prior to obtaining 718-CIH-301 informed consent will be recorded through the end of the study.

All medications, supplements, procedures, and therapies used to treat Huntington's Disease or to treat or prevent COVID, regardless of timing will be recorded through the end of the 718-CIH-301 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:

- Exposure to gene therapy previously or anytime during the study
- Treatment with any other HD investigational drug, biologic, or device trial within 180 days prior to Screening and until the final visit
- Treatment with any non-HD investigational drug, biologic, or device trial within 30 days or 5 half-lives (whichever is longer) prior to Screening and until the final visit
- For the de novo cohort only: Treatment with antisense oligonucleotides or an mRNA splicing modifier previously or anytime during the study

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

- Medications that inhibit cholesterol absorption (eg, ezetimibe).
- Bile acid sequestrants (eg, colesevelam, colestipol, cholestyramine).
- 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. If possible, the PI should inform the

medical monitor about the use of any prohibited medications. 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, including antidepressants and anxiolytics, 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.

Adjustment and/or addition of medications that are known to affect cognitive performance (eg, stimulants, benzodiazepines, antipsychotics, anticholinergics) is to be avoided as much as possible.

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.

9.2.4. Acceptable Forms of Contraception

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

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

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

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

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

- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to screening);
- Vasectomized partner (performed at least 3 months prior to screening).
  (Note: vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the participants of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.)

Acceptable forms of contraception for male participants include:

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

9.3. Intervention After the End of the Study

Not applicable.

9.4. Treatment Adherence

Beginning on Day 1, participants will self-administer IP once per day in the morning. IP administration will be monitored via a medication adherence monitoring platform used on smartphones. At clinic visits, participants will take the IP under staff supervision, followed by assessments [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 capsules. This information will be documented in the source files, along with any deviations from the prescribed dosage regimen. Details about IP accountability are included in Section 10.6.

9.5. Randomization and Blinding

This is an open-label study in which all participants will receive SAGE-718.

Participants and study site staff will remain blinded to the participants' treatment assignment in the parent studies (718-CIH-201 and 718-CIH-202) for the duration of 718-CIH-301.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

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

Table 8: Investigational Product

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

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.

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 process.

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

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

Beginning at the Day 1 visit and continuing throughout the Treatment Period, an adequate supply of SAGE-718 0.9 mg will be provided as an oral softgel lipid capsule for self-administration once daily in the morning.

10.5. Investigational Product Administration

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

Participants are to swallow the capsule 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.

The SAGE-718 0.9 mg softgel lipid capsule will be self-administered by participants once daily in the morning. Sites will dispense a sufficient supply of IP to the participants to take at home with instructions for use until their next visit (refer to Table 2, Table 3, and Table 5).

This study will use a medication adherence monitoring platform for all participants in the study. 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). The AiCure platform is compliant with all applicable privacy and data security laws; data is captured, processed, and analyzed in a compliant manner as outlined in each local ICF.

In addition, the participant will be instructed to bring their dosing kit to the site as outlined in Table 2, Table 3, and Table 5. 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.

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

A third-party courier will ship IP from the site to the homes of the participants for Months 27, 33, 39, and 45, as specified in the Pharmacy Manual.

10.5.1. Medication Adherence and Reminder System

10.5.1.1. Registration in the AiCure platform

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 trial, 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, Table 3, and Table 5.

The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used, and returned/discarded.

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

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

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

10.7. Product Complaints

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

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

11. SCREENING, EFFICACY, AND CLINICAL PHARMACOLOGY ASSESSMENTS

A variety of measures will be employed in this study [redacted]. All assessments are to be completed according to the Schedules of Assessments (Table 2, Table 3, Table 4, and Table 5) [redacted] (Table 6).

For the participants who rollover directly from the parent studies 718-CIH-201/202 (that is 718-CIH-301 informed consent date ≤7 days after last day of the corresponding parent study), the results of the last assessments in the parent study will be carried over to the 718-CIH-301 study, as specified in Table 3.

The eligible participants in this study are expected to be able to independently care for themselves. However, some of these assessments include information provided by a study partner, if available.

11.1. Screening Assessments

11.1.1. Montreal Cognitive Assessment (MoCA)

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

The Montreal Cognitive Assessment Memory Total Score includes all cognitive domains measured and represent 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).

The MoCA will be audio recorded and a subset may be reviewed with the goal of minimizing the variability in assessment data. Protected health information 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 provides destruction authorization or other instructions.

Note: In addition to Screening, this assessment is also performed at other time points, as outlined in Table 2, Table 3, and Table 5.

11.1.2. Cigarette and(or) Tobacco Use Assessment

Data on cigarette and/or tobacco use will be collected, including the amount used over the past 7 days, at the time points specified for all participants.

11.2. [redacted]

[redacted]

[redacted]

11.2.1. [redacted]

[redacted]

11.2.1.1. [redacted]

[redacted]

11.2.1.2. [redacted]

[redacted]

11.2.1.3. [redacted]

[redacted]

11.2.1.4. [redacted]

[redacted]

[redacted]

11.2.1.5. [redacted]

[redacted]

11.2.1.6. [redacted]

[redacted]

11.2.1.7. [redacted]

[redacted]

11.2.2. [redacted]

[redacted]

11.2.2.1. [redacted]

[redacted]

11.2.2.2. [redacted]

[redacted]

11.2.2.3. [redacted]

[redacted]

11.2.3. [redacted]

11.2.3.1. [redacted]

[redacted]

11.2.3.2. [redacted]

11.2.3.3. [redacted]

11.2.3.4. [redacted]

11.2.3.5. [redacted]

[redacted]

11.2.3.6. [redacted]

[redacted]

11.2.3.7. [redacted]

[redacted]

11.2.3.8. [redacted]

[redacted]

11.2.3.9. [redacted]

[redacted]

11.2.4. [redacted]

11.2.4.1. [redacted]

[redacted]

[redacted]

11.2.5. [redacted]

[redacted]

11.2.5.1. [redacted]

[redacted]

11.2.5.2. [redacted]

[redacted]

11.2.6. [redacted]

[redacted]

[redacted]

[redacted]

[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]

[redacted]

11.3.2.2. [redacted]

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedules of Assessments (Table 2, Table 3, Table 4, and Table 5) [redacted].

Abnormalities in physical examinations, vital signs, ECG, 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.

AEs, or prior/concomitant medications and procedures/therapies from the parent studies will be collected in 718-CIH-301 according to the eCRF Completion Guidelines.

12.1.1. Demography and Medical History

Demographic characteristics (including age, race, sex, ethnicity, years of education, years of employment and current employment status) and a full medical history will be documented for all cohorts. Parent study demographic characteristics data will be carried over from the parent study for rollover participants, if not specifically collected in 718-CIH-301. Prior participation in 718-CIH-201 and 718-CIH-202 will be collected.

Medical history will be carried over from the corresponding parent studies 718-CIH-201/202 for all rollover participants. Any medical history from the end of the parent study through informed consent for 718-CIH-301 will also be collected via the medical history eCRF. Any resolved AEs from parent study will be included in the medical history eCRF if clinically relevant.

For 718-CIH-301 v2 Completers, interim medical history will be collected from the time of completion of Day 395 under 718-CIH-301 Protocol Version 2 through informed consent for 718-CIH-301 Protocol Version 3 or higher.

History of HD (for participant and family) will be collected separately.

12.1.2. Weight and Height

Height will be measured for de novo participants only. For the rollover participants, the preceding height measurement results will be carried over from the corresponding parent studies 718-CIH-201 and 718-CIH-202. Height will also be measured at the Re-Qualification Visit (Table 4) for 718-CIH-301 v2 Completers.

Weight will be measured in all participants and documented. Body mass index will be calculated.

12.1.3. Physical Examination

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

A full physical and neurological examination is to be conducted during Screening for de novo and gap rollover participants and carried over from the parent study for direct rollover participants, and Days 180 for all participants. A full physical and neurological examination will also be done at the Re-Qualification Visit (Table 4) for 718-CIH-301 v2 Completers. At other visits (refer to Table 2, Table 3, and Table 5), 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. An unscheduled, symptom-directed examination may be conducted at any time at the discretion of the investigator.

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

12.1.4. Vital Signs

Vital signs 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.

Any abnormality in vital signs will be interpreted by an investigator as abnormal, NCS; or abnormal, CS in source documents. Changes from baseline in vital signs are considered AEs if they result in discontinuation or interruption of IP, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be CS. Changes from baseline in vital signs that are clearly attributable to another AE do not require discrete reporting.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed at the time points described in Table 2, Table 3, Table 4, and Table 5. 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.

ECGs 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.

Any abnormality in ECG will be interpreted by an investigator as abnormal, NCS; or abnormal, CS in source documents. Changes from baseline in ECGs are considered AEs if they result in discontinuation or interruption of IP, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be CS. Changes from baseline in ECGs that are clearly attributable to another AE do not require discrete reporting.

12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 9.

Table 9: 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, urobilinogen, bilirubin, ketones, nitrite
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio
Serology (screening only for Cohort 2 and 3; re-qualification for 718-CIH-301 v2 Completers)	Hepatitis B and C screening tests, HIV-1 and -2 antibody
Genetic test (screening only)	CAG test[a]

[a] De novo participants only. Genetically confirmed disease with CAG expansion ≥36 (for de novo: ≥40) 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. Laboratory abnormalities are considered AEs if they result in discontinuation or interruption of IP, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be CS. Laboratory abnormalities that are clearly attributable to another AE do not require discrete reporting.

Serum FSH test will be conducted at Screening for the de novo female participants and rollover participants who are not surgically sterile and who have ≥12 months of spontaneous amenorrhea to confirm postmenopausal state as defined in this protocol. For the postmenopausal rollover participants (where postmenopausal state was confirmed in parent studies), the preceding FSH results will be carried over from the corresponding parent studies, 718-CIH-201/202, as applicable.

12.1.6.1. Drugs of Abuse, Alcohol

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

12.1.6.2. Pregnancy Testing

A serum pregnancy test will be conducted for de novo and gap rollover female participants at Screening. A serum pregnancy test will be done at the Re-Qualification Visit (Table 4) for 718-CIH-301 v2 Completers. For direct rollover participants, urine pregnancy related test results will be carried over from the parent study. Urine pregnancy tests will be conducted at other scheduled time points for all female participants that are not postmenopausal or surgically sterile. For direct rollover subjects, parent study urine pregnancy test results may be used to satisfy Exclusion Criterion #14 (Section 8.2).

12.1.7. Columbia-Suicide Severity Rating Scale

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

For de novo participants, the "Baseline/Screening" C-SSRS form will be completed at screening (1 month, 1 year, lifetime), and the "Since Last Visit" C-SSRS form will be completed at subsequent time points (Table 2 and Table 5). For rollover participants, the "Since Last Visit" C-SSRS form will be completed at the time points outlined in Table 2, Table 3, and Table 5. For 718-CIH-301 v2 Completers, the "Since Last Visit" C-SSRS form will be completed at the Re-Qualification Visit and the Post Re-Qualification Safety Check-in (Table 4).

12.1.8. COVID-19 Questions

Information regarding the history of diagnosis, hospitalization, vaccination, and treatment for COVID-19 will be collected at baseline and any changes collected throughout the study.

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 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 IP, 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.

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

12.2.2. Serious Adverse Event Definition

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

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

SAEs that occur in the period after the end of participation of the parent study and prior to the participant signing the ICF will be recorded as medical history (if the SAE is assessed as not related to IP). 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. 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 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 in order to protect the participants of a study against any immediate hazard to their health or safety. Examples of USMs include:

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

In accordance with FDA Guidance 21 Code of Federal Regulations (CFR) Part 312.66, some reported events may qualify as an unanticipated problem (UP), defined as any incident, experience, or outcome that meets all 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 ICF; and (ii) the characteristics of the population being studied; related or possibly related to an individual's participation in the study; and
- Suggests the study may place the participant or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the study than was previously known or recognized.

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

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

AEs spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness criteria (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 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 and designee.

Additional follow-up information, if required or available, should all be sent to Sage 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.

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

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

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 [(total bilirubin >2xULN) **AND** alkaline phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)] **AND** [(ALT or AST >3xULN) **AND** alkaline phosphatase <2xULN, any time post-baseline, measured at the same time point of assessment]. 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 7.4.3.

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 Sage and designee 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 and designee within 24 hours of awareness. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, pre-eclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death), the investigator should follow the procedures for reporting an SAE (Section 12.2.6).

The investigator will permanently withdraw the participant from IP if the participant becomes pregnant.

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 the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on the Special Considerations Form and sent to Sage and designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage and designee even if the overdose does not result in an AE. If an overdose results in an AE or 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, the AE must be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

13. STATISTICS

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

13.1. Data Analysis Sets

The Safety Set is defined as all participants who were administered IP during the study and will be used to describe the safety data.

The Full Analysis Set is defined as all participants who were administered IP during the study and have baseline and at least 1 post-baseline 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. No imputation process will be used to estimate missing data.

13.3. General Considerations

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

Continuous data will be summarized in terms of the number of participants, mean, standard deviation, minimum value, 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 and years of education, total years of employment, and current employment status) and baseline characteristics, such as height, weight, and body mass index will be summarized using the Safety Set.

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

Medical history will be summarized by cohort and listed by participant.

13.5. [redacted]

[redacted]

[redacted]

13.6. Safety Analyses

Safety and tolerability of SAGE-718 will be evaluated by the number and severity of TEAEs, the number of participants who withdraw due to AEs, and the change from baseline in vital signs, clinical laboratory analyses, ECGs, and responses on the C-SSRS. [redacted] Safety data will be listed by participant and summarized by cohort. All safety summaries will be performed on the Safety Set.

13.6.1. Adverse Events

AEs/SAEs will be collected beginning with completion of ICF through end of study participation. For gap and direct rollover participants, ongoing AE/SAE(s) from parent studies will be followed for resolution through the end of 718-CIH-301 participation.

For 718-CIH-301 v2 Completers, AEs/SAEs will be collected from the time of informed consent for 718-CIH-301 Protocol Version 3 or higher through end of study participation. Documented ongoing AEs/SAEs from participation under 718-CIH-301 Protocol Version 2 or prior will be followed for resolution through end of study participation.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA™) Version 25.0 or higher. A TEAE is defined as an AE with onset after the first dose of IP, either in the parent study or within this protocol and on or after the ICF sign off date. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by system organ class and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to discontinuation of IP 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.

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 post-baseline values in abnormality of results will be provided. Potentially CS values will be summarized by cohort. Clinical laboratory results will be listed by participant and timing of collection.

13.6.3. Physical Examinations

Physical examination dates and times will be collected and listed by participant. Any CS observation in physical examination will be reported as an AE.

13.6.4. Vital Signs

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

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for each participant: heart rate, PR, QRS, QT, and QTcF. ECG data will be summarized by visit. Potentially CS values of QTcF will be summarized by cohort. ECG findings will be listed by participant and visit.

13.6.6. Prior and Concomitant Medications

Medications will be coded using World Health Organization-Drug dictionary March 2021, or later.

All medications and supplements taken within 8 weeks prior to obtaining 718-CIH-301 ICF, all medications used to treat HD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD will be recorded through the end of the 718-CIH-301 study, according to the eCRF Completion Guidelines. All medications and supplements taken or changed after signing ICF through the end of the study (including start and end dates, route, dose/units, frequency, and indication) will be recorded.

For 718-CIH-301 v2 Completers, prior and concomitant medications and procedures/therapies will be collected from the time of completion of Day 395 under 718-CIH-301 Protocol Version 2 through end of study participation. Documented ongoing prior and concomitant medications and procedures/therapies from participation under 718-CIH-301 Protocol Version 2 or prior will be followed for resolution through end of study participation.

Medication 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.

13.6.7. Columbia Suicide Severity Rating Scale

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

13.6.8. [redacted]

13.7. [redacted]

[redacted]

13.8. Sample Size and Power

This is a long-term, open-label, safety study; there is no formal sample size calculation. The de novo cohort sample size of 144 or more was chosen to demonstrate the long-term safety for this de novo cohort. Approximately 156 participants are expected to rollover from the parent studies 718-CIH-201 and 718-CIH-202 assuming 10% dropout rate and 80% of completers from these 2 studies will be rolled over. If rollover rate is lower than 80%, more de novo participants will be enrolled to achieve the target enrollment of 300 participants.

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 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 or its representatives. Agreed upon site responsibilities will be documented in a Clinical Trial Agreement between Sage and the investigator.

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the 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.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage, 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 or authorized representatives of Sage, 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 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 immediately at InspectionNotification@sagerx.com if contacted by a regulatory agency or IRB/IEC about an inspection.

14.3. Institutional Review Board or Independent Ethics Committee

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

When the participant decides to participate in the study, the participant (or their legally authorized representative, if applicable, for 718-CIH-201/718-CIH-202 completers only) 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 and/or their legally authorized representative.

For all cohorts, participants who are capable of providing informed consent at Screening may be requested to identify a legally authorized representative who can provide consent on their behalf

should they lose the capacity to consent over the course of the study. If, in the opinion of the investigator, the participant's capacity to consent has been compromised at any point after signing the ICF, the legally authorized representative will be asked to provide consent on behalf of the participant. Procedures used to assess capacity to consent and identify legally authorized representatives must be in accordance with local practice and regulations.

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

16.4. Data Protection

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage 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 IP. The retention of records must be in accordance with local regulations (see Appendix 2, Section 20.1). and Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

All information concerning SAGE-718 is considered confidential and shall remain the sole property of Sage. 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. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage and the investigator.

19. LIST OF REFERENCES

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20. APPENDIX

20.1. Appendix 1: Country-Specific Changes

Country	Section Number	Original Language in Country-Specific Amendment	Updated Language for Country-Specific Amendment
United Kingdom (UK)	Section 7.4.5	End of study will be achieved when the last study participant completes the last study visit, as shown in Table 5.	End of study will be achieved when last study participant completes last study visit. 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 within 24 hours of awareness. 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. All samples intended [redacted] will be destroyed at the end of the study. [redacted]

Country	Section Number	Original Language in Country-Specific Amendment	Updated Language for Country-Specific Amendment
			[redacted]
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

20.2. Appendix 2: Study Continuation Visit for Participants Who Completed Day 365 But Not Day 395 Under Protocol Version 2

Participants who have completed their Day 365 visit but NOT their Day 395 visit under Protocol Version 2 and wish to continue participation under Protocol Version 3 or higher will return to the site for the assessments in the table below and then continue on to their Month 15 visit (see Table 5). The participant's visit schedule should remain relative to the date of their Day 1 visit.

Schedule of Assessments: Study Continuation Visit

Assessments	Study Continuation Visit
	Visit can occur anytime after the Day 365 visit up to Day 395 (±7 days)
Informed re-consent[a]	X
Body weight	X
Vital signs (including orthostatics)[b]	X
Physical examination[c]	X
Pregnancy test[d]	X
C-SSRS (Since Last Visit)	X
IP dispensation[e]	X
IP self-administration[f]	X
AEs/SAEs	X
Prior and concomitant medications and procedures/therapies	X

Abbreviations: AE = adverse event; C-SSRS = Columbia–Suicide Severity Rating Scale; IP = investigational product; SAE = serious adverse event.

[a] Both participants and study partners (if applicable) will be re-consented during at the Study Continuation visit. A legally authorized representative may consent on behalf of participants who are not capable of providing informed consent in the opinion of the investigator.

[b] Vital signs include body temperature, respiratory rate, heart rate, and blood pressure. 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. Vital signs can be repeated once if out of range.

[c] 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.

[d] Urine pregnancy tests will be conducted for female participants that are not postmenopausal or surgically sterile.

[e] Study staff will dispense sufficient IP for the participant to take daily at home until Month 15 visit.

[f] Participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing. Participants should continue to self-administer IP daily at home following the Study Continuation Visit.