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STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER: 718-CIH-301

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

Clinical Phase: 3

Author of SAP: [redacted]

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Sponsor:
Sage Therapeutics, Inc.
55 Cambridge Parkway,
Cambridge, Massachusetts 02142

AUTHORIZATION SIGNATURE PAGE

Author:

[redacted] Date

Approved by:

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

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1. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this Statistical Analysis Plan.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse Event
AI	Apathy Inventory
[redacted]	[redacted]
BMI	Body Mass Index
CAG	Cytosine-Adenine-Guanine
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	Coronavirus Disease 2019
CS	Clinically Significant
C-SSRS	Columbia–Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ET	Early Termination
FSH	Follicle-Stimulating Hormone
[redacted]	[redacted]
[redacted]	[redacted]
HD	Huntington's Disease
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ICF	Informed Consent Form
IP	Investigational Product
MoCA	Montreal Cognitive Assessment
NCS	Not Clinically Significant
PCS	Potentially Clinically Significant

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
TFC	Total Functional Capacity
[redacted]	[redacted]
UHDRS	Unified Huntington's Disease Rating Scale
[redacted]	[redacted]
[redacted]	[redacted]

2. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis for study protocol SAGE-718-CIH-301 and is based on the following approved study documents:

- Study Protocol v3.0, Amendment 2 (05 February 2024)
- electronic Case Report Form (eCRF), Version 7.0 (11 December 2024)

Due to results in Dimension (718-CIH-201) investigating SAGE-718, a decision was made on November 20, 2024, to prematurely terminate the 718-CIH-301 study. A synoptic clinical study report (CSR) will be produced. This SAP describes the analyses performed for the synoptic CSR, which will be purely descriptive and focused on primary endpoints only. All analyses and data presentations will be generated using SAS® Version 9.4 or higher Software (SAS Institute, Cary, North Carolina, USA). This SAP will be finalized and approved before the clinical database lock. Any changes made to the SAP after the clinical database lock will be documented and discussed in the CSR for this study.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the safety and tolerability of SAGE-718 softgel lipid capsule in participants with Huntington's Disease (HD)

3.2. Other Objectives

[redacted]

4. STUDY ENDPOINTS

4.1. Primary Endpoints

- Proportion of participants experiencing Treatment Emergent Adverse Events (TEAE)s and severity of TEAEs
- Number of participants who withdraw due to adverse events (AE)s
- Change from baseline in vital signs, clinical laboratory parameters, Electrocardiograms (ECG)s, and Columbia Suicide Severity Rating Scale (C-SSRS) responses.

4.2. Other Endpoints

[redacted]

5. STUDY DESIGN

5.1. Overall Design

This is a long-term, open-label study to evaluate the safety and tolerability of SAGE-718 in rollover or 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 to 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), that includes rollover participants from 718-CIH-201/202 studies, for which 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), that includes rollover participants from 718-CIH-201/202 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.

Cohort 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), that 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 who does not exhibit measurable functional impairment (TFC=13 [with MoCA ≤25]) or 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 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 Follow-up Visit.

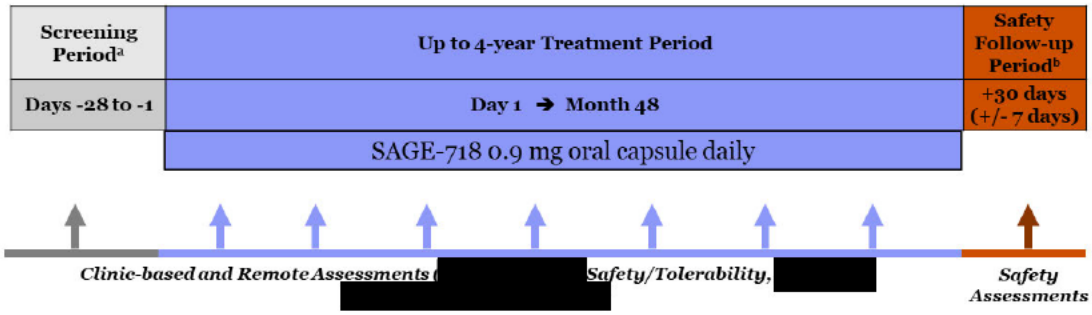
[redacted]

Protocol amendment 2 allowed the duration of participation to be extended from up to 1 year to up to 4 years and provided a path to resume treatment for participants who completed study (through Day 395 visit) under Protocol Version 2 ("718-CIH-301 v2 Completers") or

completed treatment (through Day 365 visit) but did not yet have a Day 395 visit. 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 up to 28 days prior to resuming IP at their Next Scheduled Study Treatment Visit (relative to the date of their Day 1 visit. Relevant inclusion and exclusion criteria 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, 718-CIH-301 v2 Completers will return to the site for a Post Re-Qualification Safety Check-in visit to evaluate safety.

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 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 in Table 3 and will not have a Day 395 visit.

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.

5.1.1. 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 5**. 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 5**. 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 6**.

5.2. Sample Size and Study Power

This is a long-term, open-label, safety study; there is no formal sample size calculation. The total target enrollment is 300 participants including rollover subjects and the de novo cohort.

5.3. Randomization

Study 718-CIH-301 is an open-label design, hence randomization does not apply.

5.4. Blinding and Unblinding

All participants who receive any IP in this study will receive SAGE-718 in an open-label manner; hence blinding/unblinding does not apply.

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

This SAP only details the statistical analyses necessary for the synoptic report, focusing on primary endpoints at visits Day 1, Day 90, Day 180, Day 365 and ET.

Cohort 3 (De novo) are not enrolled and therefore will not be included.

6.2. Modifications from the Approved Statistical Analysis Plan

This is the first version of the SAP for the final analysis.

6.3. Modifications from the Approved DMC Charter

Not applicable.

7. ANALYSIS SETS

7.1. Enrolled Set

The Enrolled Set is defined as all subjects who signed the informed consent form (ICF) and are not a screen failure.

7.2. Safety Set

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

8. STATISTICAL ANALYSIS

8.1. General Considerations

Continuous data will be summarized with the number of participants (n), mean, standard deviation (SD), minimum, and maximum. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place, and the SD (and the standard error [SE], if applicable) will be reported to two more decimal places, than the raw data recorded in the database. In general, the maximum number of decimal places reported will be four for any summary statistic. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

Categorical data will be summarized with the number of participants providing data at the relevant time point (n), frequency counts and percentages. Percentages will be reported to one decimal place unless otherwise specified. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will not be presented for zero counts. Percentages will be calculated using the number of participants (n) in the respective analysis set as the denominator. A missing category shall be included only for categorical variables where no data is available. The missing category will be omitted if there are no missing values for that variable.

For the laboratory results that are "≤ x" or "≥ x", where x is a number as collected in the data, the numeric part of the result will be used in the calculation in the summary tables. If a laboratory value contains 'y <' then y minus 0.1 for values measured to the first decimal place, 0.01 for values measured to the second place, 0.001 for values measured to the third decimal place, and so on, will be used for the analysis. If a laboratory value contains 'z >' then z plus 0.1 for values measured to the first decimal place, 0.01 for values measured to the second place, 0.001 for values measured to the third decimal place, and so on, will be used for the analysis. The same is true if the result is presented as below limit of quantification (BLQ) and a lower limit of quantification (LLOQ) value is provided – LLOQ value will be used for calculation in the summary tables. The actual results as collected will be displayed in the listings.

P-values greater than or equal to 0.0001, in general, will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001". P values greater than 0.9999 will be presented as ">0.9999".

Confidence intervals will be presented to one more decimal place than the raw data.

All analyses and summary outputs will be presented by cohort: Cohort 1 (Direct rollover), Cohort 2 (Gap rollover), and overall.

All participant data, including those derived, to support tables and figures will be presented in the participant data listings. In general, the participant data listings will be sorted by participant number and assessment visit and date (and time, if applicable).

General definitions are provided below:

- Baseline is defined as the last non-missing measurement prior to the first dose of IP in the current study, unless stated otherwise. If the time of an assessment is collected, baseline will be the latest assessment prior to first dose of IP administration time; if the time of an assessment is not collected, the assessment on Day 1 is assumed to be prior to dosing if the protocol mentions that this assessment needs to be before dosing or it is collected as "pre-dose".

For Cohort 1 (Direct Rollover), there is no screening period, instead carry-over results of the last assessments from parent studies (CIH-201/202) when applicable, which constitute the baseline or screening assessment for the cohort. For Cohort 2 (Gap Rollover), parent study data will be also carried over to comprise baseline or screening assessment for demographics and baseline characteristics as applicable.

8.1.1. Study Day Definition

- Study Day 1 is defined as the date of first dose for treated participants.
- Study Day will be calculated relative to the date of first dose for treated participants.

  If event is prior to the first dose, then study day is calculated as:

  Date of Event – Day 1

  If event is after the first dose, then study day is calculated as:

  Date of Event – Day 1 + 1

8.1.2. Missing Data

All subjects will be used in the analyses, as per the analysis sets, using all non-missing data available; Handling of missing or incomplete dates in AE is discussed in Appendix B.

8.2. Background Characteristics

8.2.1. Participant Disposition

A disposition of all participants who enter the study will be provided, from screening to study completion. A completer of the study is a participant with the study completion question answered 'Yes' on the End of Study CRF page. A completer of treatment is a participant with the treatment completion question answered 'Yes' on the IP Completion (End of Treatment) CRF page. The primary reason for discontinuing the study is provided in the respective CRF page.

The summaries of participant disposition of all participants will include:

- Number of participants screened,
- Number of participants screen-failed,

- Number of participants enrolled,
- Number of participants enrolled but not received any IP,
- Number and percentage of participants received at least one dose of IP
- Number and percentage of participants who had dose interrupted
- Number and percentage of participants completed one-year IP
- Number and percentage of participants discontinued IP and primary reason for IP discontinuation
- Number and percentage of participants completed the one-year study
- Number and percentage of participants withdrawal from the study and primary reason for withdrawal from the study

All percentages will be calculated based on the participants in the Safety Set. If a participant is rescreened because the participant has been a screen failure the first time, the status of the participant will be determined from the second screening. In the count of screened participants, this participant will be counted only once.

By-participant listings of disposition details will also be provided.

The number of participants in each analysis set will be provided. A separate listing will be provided for the participant who did not meet inclusion/exclusion criteria but have received IP using Enrolled set.

A separate data listing will be provided for all participants who prematurely discontinued IP or prematurely withdrew from the study with any reason, number of days on IP, date of withdrawal from the study using Safety Set.

8.2.2. Protocol Deviations

Protocol deviations will be classified as “major” or “minor” on ongoing basis by the clinical study team and sponsor and documented separately from the SAP.

A by-participant listing of all protocol deviations will also be provided.

8.2.3. Demographics and Baseline Characteristics

This analysis will be based on the Safety Set.

Demographic characteristics (including age, race, sex, ethnicity, childbearing status, years of education, current employment status, and total years of employment) and baseline characteristics, such as height, weight, body mass index (BMI), will be summarized.

Baseline subgroups will be summarized for the following categories:

- Age (≤50, >50)
- Sex (Male, Female, Unknown/Undifferentiated)

By-participant listing of demographic and other baseline characteristics will also be provided.

8.2.4. Physical Examination

This analysis will be based on the Safety Set.

Only clinically significant abnormalities are captured in the database – for post-baseline observations, these will be reported as adverse events, hence these will be included in AE displays; for pre-baseline observations will not be reported.

The dates of physical examination will be listed to confirm that the examination was done.

8.2.5. Investigational Product Exposure

This analysis will be based on the Safety Set.

Listing of first and last day of IP intake, total period of IP intake, and dates and duration of IP interruption will be provided by participant.

8.3. Safety Analysis

Safety and tolerability of SAGE-718 is the primary objective of this study. Proportion of participants experiencing treatment-emergent adverse events (TEAEs) and severity of TEAEs, number of participants who withdraw due to AEs, and change from baseline in vital signs, clinical laboratory analyses, electrocardiograms (ECGs), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS) are the primary endpoints.

The Safety Set will be used for all safety summary tables by cohort and overall.

The safety endpoints and variables considered in the summary tables for this study are summarized in Table 2.

Table 2: Safety Endpoints and Variables in the Summary Tables

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Normal Range Shift from Baseline	Potentially Clinically Significant	Abnormality/ Clinical Significance
Adverse Events	X					
Clinical Laboratory (Chemistry, Liver function, Hematology,		X*	X	X	X	

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Normal Range Shift from Baseline	Potentially Clinically Significant	Abnormality/ Clinical Significance
Coagulation, Urinalysis)						
Physical Exam		*				
Vital Signs		X	X		X	
ECG		X	X		X	*
C-SSRS	X	X		X		

ECG = Electrocardiograms; C-SSRS = Columbia–Suicide Severity Rating Scale
X = Safety Assessment will be summarized in tables
* = Safety Assessment will be listed in individual participant data listings

Anytime on treatment, last value on treatment and last value on study will be included in the summaries whenever indicated in the relevant sections as following: Anytime on treatment is defined as measurement on or after first dose, on or before the date of last dose. Last value on treatment is defined as the last post-baseline value between first dose of IP (exclusive) and up to the date of last dose of IP (inclusive). Last value on study is defined as the last post-baseline value on or after the first dose of IP and on or before the last date of the study.

The safety variables evaluated at scheduled visits are taken as done in nominal visit, without any windowing. If a value is available for a nominal scheduled visit, that value will be used in summary by visit. If scheduled visit value is not available, a value from the specific visit window will be included in summary.

For safety analysis, unscheduled measurements will be included only if a scheduled measurement is not available, and the unscheduled measurement falls within the visit window for the scheduled visit (Table 3). If there are two or more measurements in a visit window, the measurement taken closest to the study day target will be used in analysis. If the two have same distance from the target study day, the latter one will be used.

Table 3: Analysis Visit Window for Safety Analysis

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Baseline	1	≤1
Day 30 (±7 days)	30	2 to 44
Day 60 (±7 days)	60	45 to 74
Day 90 (±7 days)	90	75 to 130

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Day 180 (±14 days)	180	131 to 224
Day 270 (±14 days)	180	225 to 314
Day 365 (±14 days)	365	315 to 410
Month 15 (±14 days)	456	411 to 501
Month 18 (±14 days)	547	502 to 592
Month 21 (±14 days)	638	593 to 683
Month 24 (±14 days)	730	684 to 774
Month 27 (±14 days)	821	775 to 865
Month 30 (±14 days)	912	866 to 957
Month 33 (±14 days)	1003	958 to 1048
Month 36 (±14 days)	1094	1049 to 1139
Month 39 (±14 days)	1186	1140 to 1231
Month 42 (±14 days)	1277	1232 to 1321
Month 45 (±14 days)	1368	1322 to 1413
Month 48 (±14 days)	1459	≥1414

8.3.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation participant 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.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1.

A TEAE is defined as an AE with onset on or after the first dose of SAGE-718- - either in the parent study or within this protocol and on or after the ICF sign off date. For more clarification, a TEAE is defined as below:

- For Placebo rollover participants from parent study: TEAE is defined as an AE with onset on or after the first dose of SAGE-718 in this protocol.

- For SAGE-718 rollover participants from the parent study: TEAE is defined as an AE with onset on or after the ICF sign off in this protocol.

Pre-treatment AE is defined as below.

- For Placebo rollover participants from parent study: Pre-treatment AE is defined as an AE with onset before the first dose of SAGE-718 in this protocol and after ICF sign off date in this protocol or ongoing AE from parent study.
- For SAGE-718 rollover participants from the parent study: Pre-treatment AE is defined as an AE with onset after ICF sign off date in this protocol and before the first dose date of IP in the current protocol.

On-treatment TEAE:

- For Placebo rollover participants from parent study: On-treatment TEAE is defined as an AE with onset on or after the first dose of SAGE-718 in this protocol and on or before IP last dose date + 30 days (Note that time does not matter for the end of this period. i.e. if AE occurred after the last dose but on the same date of last dose, it is considered as on-treatment TEAE).
- For SAGE-718 rollover participants from the parent study: On-treatment TEAE is defined as an AE with onset on or after first IP dose date/time and on or before IP last dose date + 30 days.

Post-treatment TEAE: AE onset date on or after IP last dose date + 31 days.

The analysis of AEs will be based on the concept of TEAEs. If the date of an adverse event is incomplete and an unambiguous determination could not be made with respect to its onset time versus the first dose of study drug and/or last dose of study drug, the adverse event will be assumed to be a TEAE. For imputation of missing AE dates, please refer to Appendix B.

An overall summary of TEAEs will include the number and percentage of participants in the following categories:

- Any TEAEs
- Any TEAEs (Pre-treatment, On-treatment, Post-treatment)
- TEAEs by maximum Severity (severe>moderate>mild)
- Any TEAEs related to IP
- Any TEAEs leading to death
- Any TEAEs leading to IP discontinuation
- Any TEAEs leading to withdrawal from the study
- Any TEAEs leading to IP interruption
- Any serious TEAEs
- Any serious TEAE related to IP

- Any serious TEAE leading to IP discontinuation
- Any serious TEAE leading to withdrawal from the study

Incidence of TEAEs in following categories will be provided by System Organ Class (SOC) and Preferred Term (PT). A participant is counted only once under each SOC and PT in case of multiple occurrences of the same AE. These tables will be sorted by decreasing frequency of SOC in overall group, then alphabetically first within SOC then within PT.

- Any TEAE
- TEAEs by maximum severity
- TEAEs by relationship
- Serious TEAEs
- TEAEs leading to IP discontinuation
- TEAEs leading to withdrawal from the study
- TEAEs leading to IP interruption

Additionally, incidence of TEAEs will be summarized by PT. Most common TEAEs reported >5% in any cohort will also be summarized by PT.

For maximum severity, participants will be counted only once within each SOC and PT at the maximum severity in the following order: severe> moderate> mild; an AE with missing severity will be omitted from severity presentation and will not be imputed. For relationship to IP, participant will be counted only once within each SOC and PT at the strongest relationship to IP in the following order: related > not related; an AE with relationship missing is treated as related. For seriousness, an AE with missing seriousness will not be included in the summary tables. The incidences will be sorted by descending frequency of SOC and then, within a SOC, by descending frequency of PT based on overall group, and in alphabetical order of PT if the incidence within a PT is a tie.

All TEAEs through the end of the study will be listed by participant. Separate listings of pre-treatment AE, treatment-emergent serious adverse event (SAE), TEAEs leading to IP discontinuation, TEAEs leading to withdrawal from the study, TEAEs leading to IP interruption, and death will be provided.

8.3.2. Clinical Laboratory

Clinical laboratory assessments will include blood samples for hematology, clinical chemistry, coagulation, and urinalysis. Analytes to be evaluated are summarized in Table 4.

All laboratory values will be summarized for the Safety Set by cohort and overall. Results of continuous hematology, clinical chemistry parameters, coagulation, and urinalysis parameters (quantitative) at each scheduled visit and mean changes from baseline will be summarized using standard international (SI) units. In addition, it will also include the summary of anytime on treatment, last values on treatment and last value on study.

All laboratory results will be listed in individual participant data listings.

Results from Hepatitis B and C screening tests, HIV-1 and -2 antibody, CAG test, FSH test at Screening will be listed separately by participant.

Results from urine drug test pregnancy test will be listed separately by participant.

[redacted]

Normal ranges for each parameter will be provided by the laboratory.

Table 4: 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)	Hepatitis B and C screening tests, HIV-1 and -2 antibody

Liver function tests will be monitored closely for potentially clinically significant PCS values, and will be summarized for occurrence anytime post-baseline for the following parameters for these PCS threshold (for condition involving more than one parameter, the results need to be from the same timepoint):

- Alanine Aminotransferase: >3xULN, >5xULN, >10xULN
- Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN

- Alanine Aminotransferase or Aspartate Aminotransferase: >3xULN, >5xULN, >10xULN
- Alkaline Phosphatase: >1.5xULN, >2xULN
- Total Bilirubin: >1.5xULN, >2xULN
- Total Bilirubin >2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN) [any time post-baseline, does not need to be measured at the same time point of assessment]
- 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]

  Note: The conditions in the first pair of brackets do not need to occur at the same timepoint as the conditions in the second pair of brackets.

8.3.3. 12-Lead Electrocardiogram

A single ECG will be measured after the participant has been in the supine position for at least 5 minutes. A summary of raw values and change from baseline values using the derived mean will be summarized by each scheduled visit for the following ECG parameters: heart rate, PR, QRS, QT, and QTcF interval. This summary will also include any value on treatment, last values on treatment and on study. A by-participant listing of 12-lead ECG will also be provided for each of the ECG measurements.

Each ECG is evaluated as 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant'. The number and percentage of participants with the categories of 'abnormal, clinically significant' and 'abnormal, not clinically significant' from the latest ECG value will be provided at baseline and each post-baseline scheduled assessment time point.

8.3.4. Vital Signs

Vital signs will include oral temperature(°C), respiratory rate (breaths per minute), heart rate (beats per minute [bpm]), and blood pressures (mmHg). Heart rate and blood pressure were collected in supine position and standing position at all scheduled time points.

Vital sign results and mean changes from baseline will be summarized by scheduled visit. It will also include the summary of last values on treatment and on study assessments.

8.3.5. Physical Examination

Only the physical examination dates and times are collected. These will be presented in individual participant data listings only. After screening, any clinically significant abnormal findings in physical examinations will be reported as AEs.

8.3.6. Columbia Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS is collected during the study. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

The participant's non-suicidal self-injurious behaviors is also assessed separately as part of C-SSRS.

The "Baseline/Screening" C-SSRS form will be completed at screening (lifetime history). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.

The assessments for suicidal ideation are ranked as follows with 5 being the worst:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods
4. Active suicidal ideation with some intent
5. Active suicidal ideation with specific plan

The assessments for suicidal behavior are ranked as follows with 5 being the worst:

1. Preparatory acts or behavior
2. Aborted attempt
3. Interrupted attempt
4. Actual attempt (non-fatal)
5. Completed suicide

Suicidal behavior is considered worse than suicidal ideation.

Baseline for each question is defined as the worst of the assessments done before the first dose of IP, excluding the lifetime version. This will typically include the 'past 12-month' version from screening and 'since last visit version' from Day 1, as well as any unscheduled visits done before the first dose of IP; any Yes will make the baseline value as Yes.

The number and percentage of participants with at least one response of 'Yes' to any C-SSRS suicidal ideation or suicidal behavior item, as well as for Participant's non-suicidal self-injurious behavior, will be summarized first by visit, then separately for baseline and anytime post-baseline.

Summary of shift from baseline in C-SSRS suicidal ideation and suicidal behavior will be presented for the following categories (no suicidal ideation/behavior, suicidal ideation, and suicidal behavior) for each scheduled assessment time point. If the answer to the first and second assessments in suicidal ideation and all non-missing assessments in suicidal behavior is 'No', then the category for the table is considered as 'No suicidal ideation/behavior'. If any of the assessments in suicidal behavior is Yes, the category is considered as 'Suicidal behavior'. If any of the assessments in suicidal ideation is Yes but all assessments in suicidal

behavior is No, the category is considered as 'Suicidal ideation'. If the participant has both suicidal ideation as well as suicidal behavior, the participant will be counted under suicidal behavior only.

In addition, a summary of shift in suicidal ideation from baseline maximum rank score for any time post-baseline maximum rank score will be presented. Maximum score 0 refers to all 'No' for all assessments in the desired period for all 5 questions on suicidal ideation.

A bar graph for percentage of participants with suicidal ideation and suicidal attempt over time will be provided.

A listing of suicidal ideation and suicidal behavior will be provided.

8.4. Other Analysis

Not applicable

9. SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable

10. REFERENCES

[redacted]

11. LIST OF APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS

Table 5: Schedule of Assessments: 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

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]
[redacted]								
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]						
[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]
[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] 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 7) 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 8).

[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.

[redacted]

[o] Only applicable for gap rollover participants that did not provide a genetic research sample 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]

[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 6: Schedule of Assessments: 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]

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]
C-SSRS (Since Last Visit)	X		X	X	X	X	X	X
UHDRS[p]	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	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]
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] erity; 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 7) 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 8).

[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 needed 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 [redacted] 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 7: 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 8)[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 7) 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 8).

[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 (Study Protocol, Appendix 2, Section 20.2) and then continue on to their Month 15 visit (see Table 8). 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 8). 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 the Protocol (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 8: 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]													
UHDRS[j]													
[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 8) 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 [redacted] 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 9: [redacted]

[redacted]

APPENDIX B. HANDLING OF MISSING DATES

Dates missing the day, or both the day and month of the year will adhere to the following conventions in order to classify TEAEs and to classify prior and concomitant medications.

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in derivation. In instances where imputed values will be presented, imputed values will be flagged.

Adverse Events

If the AE start date is completely missing, do not impute a date but consider it as TEAE, unless the AE end date is before the initiation of treatment, in which case the AE will be considered prior.

For partial AE start dates:

- When the year is known, but the month and day is unknown, then:
  - If the year matches the year of first dose date and the end date (if present) is after first dose date, or AE is ongoing, then impute as the month and day of the first dose date.
  - If the year of AE onset < year of initiation of the treatment, then the month and day will be set to December 31st.
  - If the year of AE onset > the year of initiation of treatment, then the month and day will be set to January 1st.
- If the year and month are known, but the day is unknown, then:
  - If the year of AE onset = the year of initiation of the treatment and:
    - the month of AE onset = the month of initiation of the treatment, then the day will be set to the day of initiation of the treatment.
    - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of month.
    - if the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1^{st} day of month.
  - If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of month.
  - If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1^{st} day of month.

If the imputed AE onset date is after the AE stop date, then the onset date will be set to the stop date.

- When the year and day are present and the month is missing, treat it as if the day is missing, and only year is present. Follow the imputation rules for "year is known, but the month and day is unknown".
- When the year is missing, but the month and/or day is known, treat this date as missing; do not impute.