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

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STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER: 718-CIH-201

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

Short Title: A Study to Evaluate the Effect of Sage-718 on Cognitive Function in Participants with Huntington's Disease

Clinical Phase: 2

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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
[redacted]	[redacted]
AIC	Akaike's Information Criterion
AR1	First-order Autoregressive
ASO	Antisense oligonucleotide
[redacted]	[redacted]
ECG	Electrocardiogram
BMI	Body Mass Index
[redacted]	[redacted]
CAG	Cytosine, adenine, guanine
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CAP	CAG-Age-Product
CGI	Clinical Global Impression
[redacted]	[redacted]
CGI-S	Clinical Global Impression – Severity
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CS	Clinically Significant
CSR	Clinical Study Report
C-SSRS	Columbia–Suicide Severity Rating Scale
eCRF	electronic Case Report Form
[redacted]	[redacted]
DEC	Dose Evaluation Committee
ECGs	Electrocardiograms
[redacted]	[redacted]
ET	Early Termination

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GEE	Generalized Estimating Equation
[redacted]	[redacted]
HD	Huntington's Disease
HD-CAB	Huntington's Disease Cognitive Assessment Battery
Hi-DEF	Huntington's Disease Everyday Functioning
HIV	Human immunodeficiency virus
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
IRT	Interactive Response Technology
IS	Independent Scale
MAR	Missing at random
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed-effects model for repeated measures
MNAR	Missing Not at Random
MoCA	Montreal Cognitive Assessment
[redacted]	[redacted]
[redacted]	[redacted]
NCS	Not Clinically Significant
NMDA	N-methyl-D-aspartate
[redacted]	[redacted]
OTS	One Touch Stockings of Cambridge
OTS - MLC	One Touch Stockings of Cambridge Mean Latency until Correct response

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PAM	Positive Allosteric Modulator
[redacted]	[redacted]
PCS	Potentially Clinically Significant
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PMM-MI	Pattern Mixture Model Multiple Imputation
[redacted]	[redacted]
PT	Preferred Term
PTAP	Paced Tapping
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
[redacted]	[redacted]
SE	Standard Error
SOC	System Organ Class
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
TFC	Total Functional Capacity
THC	tetrahydrocannabinol
[redacted]	[redacted]
[redacted]	[redacted]
TMT B	Trail Making Test: Part B
UHDRS	Unified Huntington's Disease Rating Scale

Abbreviation	Definition
US	United States
VAS	Visual Analogue Scale
WHO-DD	World Health Organization-Drug dictionary
[redacted]	[redacted]

2. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis for study protocol SAGE-718-CIH-201 and is based on the following approved study documents:

- Study Protocol v6.0, Amendment 5 (19 August 2024)
- electronic Case Report Form (eCRF), Version 12.0 (09 July 2024)

This SAP addresses the objectives of the study and describes the planned statistical analyses and data presentations. 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 and treatment unblinding. Any changes made to the SAP after the clinical database lock will be documented and discussed in the clinical study report for this study.

[redacted]

3. STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the effect of SAGE-718 on cognitive performance in participants with Huntington's Disease (HD).

3.2. Secondary Objectives

- To evaluate the effect of SAGE-718 on cognition and daily function in participants with HD.
- To evaluate the safety and tolerability of SAGE-718 in participants with HD.

3.3. [redacted]

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

4. STUDY ENDPOINTS

4.1. Primary Endpoint

Change from Baseline (CFB) to Day 84 on the Symbol Digit Modalities Test (SDMT). The estimand for the primary efficacy analysis is defined in Section 8.3.3.1.

4.2. Secondary Endpoints

4.2.1. Key Secondary Endpoint

1. CFB to Day 84 on the Unified Huntington's Disease Rating Scale (UHDRS) - Independence Scale.
2. CFB to Day 84 on the Trail Making Part B (TMT-B) in the subgroup of participants who completed Trail Making Test Part B (TMT-B) at Baseline within the allowable time limit (240 sec)
3. CFB to Day 84 on the One Touch Stockings of Cambridge (OTS-Mean Latency until Correct response [OTS-MLC])
4. CFB to Day 84 on the Paced Tapping Test (PTAP)
5. CFB to Day 84 in Huntington's Disease Everyday Functioning (Hi-DEF) – at home subdomain score
6. CFB to Day 84 in Clinical Global Impression – Severity (CGI-S) – cognitive status subdomain score

4.2.2. Safety Endpoints

- A Proportion of participants experiencing treatment-emergent adverse events (TEAEs).

4.3. [redacted]

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

- [redacted]
  - [redacted]
  - [redacted]
  - Change from baseline in vital signs, clinical laboratory analyses, electrocardiograms (ECGs), [redacted]
  - [redacted]

5. STUDY DESIGN

5.1. Overall Design

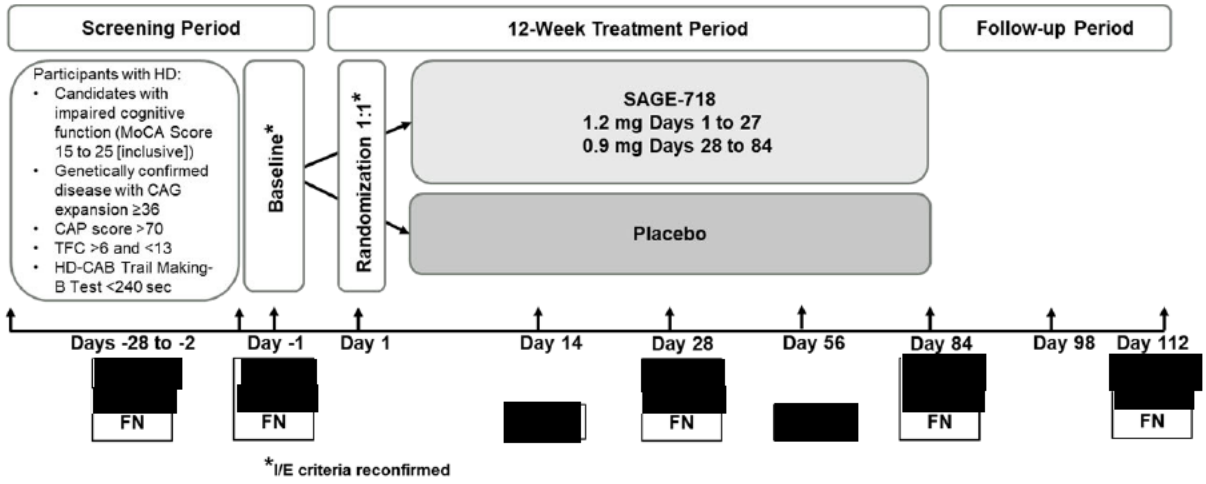
This is a randomized, placebo-controlled, double-blind study to evaluate the cognitive effects, safety, tolerability, [redacted] of SAGE-718 in participants with premanifest or early manifest HD. Participants will be adults with genetically confirmed expansion of the Huntingtin (HTT) gene cytosine, adenine, and guanine (CAG) trinucleotide repeat at Screening who meet diagnostic criteria detailed in the inclusion criteria (including UHDRS scores and CAG-Age-Product [CAP] scores within specific ranges). An adult study partner is optional but highly recommended for each participant to support completion of study activities and to answer questions about the participant's condition.

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

During the Treatment Period, eligible participants will be randomized 1:1 to receive either SAGE-718 (1.2 mg at Day 1 visit through the day prior to Day 28 visit and 0.9 mg from Day 28 visit until End of Treatment) or placebo for 84 days. Participants who cannot tolerate 1.2 mg will receive 0.9 mg for the remainder of the treatment period. Beginning on Day 1 and continuing through Day 84, participants will self-administer blinded investigational product (IP) once per day in the morning. IP administration will be monitored via [redacted], which is a medication adherence monitoring platform used on smartphones to visually confirm IP ingestion. At clinic visits, participants will take the IP under staff supervision, followed by assessments of cognitive function, [redacted]. Study staff will dispense sufficient IP for daily administration until the next scheduled study visit. Adherence to the dosing regimen will be assessed at each in-clinic visit by review of the medication adherence monitoring platform, examination of the used packaging, and counting any returned tablets. During the treatment period, participants will be able to receive IP as long as there are no dose limiting safety/tolerability concerns. At the discretion of the investigator, participants who cannot tolerate the 0.9 mg dose will be discontinued from IP. Participants who discontinue IP early should complete the remaining study visits as scheduled unless the participant withdraws consent or loses the capacity to grant consent. If a participant withdraws from the study/stops study participation early, an early termination visit should be conducted. Treatment with SAGE-718 can be ended without down titration.

After completing the treatment period, participants will return to the clinic for follow-up visits at on Day 98 and Day 112 (Early Termination [ET] Visit) to collect continued safety and efficacy data.

Figure 1. Study Design



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

5.2. Sample Size and Study Power

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

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

5.3. Randomization

This is a randomized, placebo-controlled, double-blind study. Eligible participants will be randomized 1:1 with block size of 4 to receive either SAGE-718 or placebo for 84 days.

Randomization will be performed centrally via [redacted] interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to treatment group will be based on the randomization schedule. The randomization schedules will be kept in a secure place, accessible only to authorized personnel until the time of study unblinding.

5.4. Blinding and Unblinding

This is a randomized, placebo-controlled, double-blind study. Participants, clinicians, and the study team will be blinded to treatment allocation during the study. The randomization schedules will be accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

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

The database lock will be conducted after the last participant's last visit (Day 112 or ET) and the database will be locked in two parts (Part 1 and Part 2). Part 1 will include all visits of participants up to the last patient last Day 84 visit to enable change from baseline to Day 84 analyses. A restricted team of Sponsor personnel will be unblinded after Part 1 of database lock. Site personnel, participants, and other Sponsor personnel will remain blinded until Part 2 of database lock. The final database lock (Part 2) will include all remaining visits (the Follow-Up Visit at Day 112 or ET) of participants who were enrolled after April 15, 2024, and had ongoing status or end of study on or after September 5, 2024.

The data collected in Part 1 will be analyzed and reported in the Topline results. The study data, collected in both Parts 1 and 2, will be analyzed together after the final database lock (Part 2).

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

Protocol Amendment 5 - change the primary endpoint from CFB Day 84 on HD-CAB composite score to CFB Day 84 SDMT, upgraded some secondary endpoints to key secondary endpoints, [redacted] and clarify the plan to conduct database lock in two parts.
The SAP was adjusted to incorporate the changes described above.

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. Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized participants who initiate IP and have baseline and at least 1 post-baseline efficacy evaluation. FAS will be used to analyze the efficacy data (participants will be analyzed according to the treatment group randomized to).

7.2. [redacted]

[redacted]

7.3. Safety Set

The Safety Set (SS) is defined as all participants who were administered IP (participants will be analyzed according to the treatment they received). The SS will be used to describe the safety data.

7.4. Other Analysis Sets

The Randomized Set is defined as all participants who have been randomized.

[redacted]

8. STATISTICAL ANALYSIS

8.1. General Considerations

Continuous data will be summarized in terms of the number of participants, 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 in terms of 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 and/or in specific treatment group 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 summaries and figures will be provided by treatment group – either by randomized treatment or actual treatment received depending on the analysis set being used. Treatment groups are presented as: SAGE-718 or Placebo.

Participants who are randomized to 1.2 mg treatment and received 0.9 mg dose due to dose reduction will be summarized under one treatment group. For efficacy data analysis, participants' data are analyzed by randomized treatment. For safety data analysis, participants' data are analyzed per the actual treatment received, and this is determined as

follows: if a participant received any dose of SAGE-718 at any point of time, the participant is assigned to actual treatment of SAGE-718.

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). The treatment will be identified for each participant.

General definitions are provided below:

- Baseline is defined as the last non-missing measurement prior to the first dose of IP, 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".
- Study day 1 is defined as the date of randomization for untreated randomized participants or the date of first dose for treated participants.
- Study Day will be calculated relative to the date of randomization for untreated randomized participants and relative to the date of first dose for treated participants.

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

  Date of Event – Date of Randomization or First Dose

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

  Date of Event – Date of Randomization or First Dose + 1

8.2. Background Characteristics

8.2.1. Participant Disposition

This analysis will be based on all screened participants (i.e., all participants who have signed an informed consent).

A disposition of all participants who enter the study will be provided, from screening to study completion. The summaries of participant disposition of all participants will include:

- Number of participants screened
- Number of participants screen-failed
- Number of participants randomized
- Number of participants randomized but not treated
- Number and percentage of participants received at least one dose of IP
- Number and percentage of participants completed full treatment period of IP
- Number and percentage of participants discontinued from IP and primary reason for premature IP discontinuation

- Number and percentage of participants completed the study (completed Day 112 visit)
- Number and percentage of participants who had dose reduction before Day 28
- Number and percentage of participants discontinued from the study and primary reason for premature study discontinuation
- Number and percentage of subjects who were randomized to placebo but received SAGE-718

All percentages will be calculated based on the participants from the Safety Set. Treatment arm assignment will be according to the randomized treatment. In addition, a summary of analysis sets including Safety Set, FAS, [redacted] will be provided for participants randomized.

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.

Listings by treatment group will be provided for disposition of participants: screen failures, inclusion/exclusion criteria, completion and discontinuation from study treatment and study participation, and inclusion in analysis sets.

Summary of analysis sets including Safety Set, FAS, [redacted] will be provided for participants from Randomized 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.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the participant's right, safety, well-being, and/or the validity of the data for analysis. Minor protocol deviations include all deviations from the protocol excluding the major protocol deviations.

Major protocol deviations and any action to be taken regarding the exclusion of participants or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

The study team will identify the major protocol deviations related to efficacy or that may have impact on efficacy to determine the participants in the FAS to be excluded from the [redacted] prior to the first database lock in a blinded fashion. (Some major protocol deviations may not lead to participants' data being excluded from the [redacted].) The [redacted] will be updated before the final database lock if needed.

The number and percentage of participants with a major protocol deviation in the FAS will be summarized by randomized treatment group. A by-participant listing of all protocol deviations will also be provided.

In addition, COVID-19 related protocol deviations such as remote telephone/video visit/assessment, home healthcare visit, missed visit/assessment, out of window

visit/assessment, safety reporting, IP administration, and other will be documented and provided as a separate listing.

8.2.3. Demographics and Baseline Characteristics

This analysis will be based on the Safety Set and FAS.

Demographic characteristics (age, race, sex, ethnicity, childbearing status, civil/marital status, highest level of education, years of education, current employment status, and total years of employment [employment history]) and baseline characteristics, such as height (cm), weight (kg), body mass index (BMI, kg/m^2), SDMT score, UHDRS – IS/ [redacted] CAG expansion, CAP (CAG-Age-Product, truncation of Trail Making Test B value, (complete within 240 sec: yes/no), previous ASO use and use of Antidopaminergic Medications (ADM, see Appendix D for details) will be summarized by treatment group (randomized for FAS and actual for Safety Set) and overall.

Baseline subgroups will be summarized for the following categories:

- Age (≤50, >50)
- Race (Black or African American, White, Other)
- Sex (Male, Female, Unknown/Undifferentiated)
- BMI (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2)
- Country (US, Rest of World)
- Baseline MoCA score (<18, ≥18)
- Baseline UHDRS – Independent scale (<80, ≥80)
- CAP (<100, ≥100)
- [redacted]
- [redacted]
- [redacted]
- Baseline Symbol Digit Modalities Test (SDMT) (<M,>=M, where M-Mean value at Baseline in FAS)
- Baseline Trail Making Test B (complete within 240 sec: yes/no)
- Previous use of ASO drug (Yes / No)
- Use of ADM (Yes/No)
- Use of Anti-Chorea Medication (Yes / No)
- Use of Anti-Psychotic Medication (Yes / No)

If height was collected in inches the following formula will be used to convert it to cm: Cm = Inch * 2.54. If the value for CAP is missing at baseline, it should be calculated as CAP=AGE × (CAG – 30) / 6.49). BMI will be calculated as weight (kg)/height (m^2).

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

8.2.4. Medical History

This analysis will be based on the Safety Set.

Medical history at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1 and summarized using system organ class (SOC) and preferred term (PT) on Safety Set by actual treatment group.

In addition, participant's COVID-19 history will be collected via medical history eCRF page and will be coded by MedDRA.

By-participant listing of medical history will also be provided.

8.2.5. Prior and Concomitant Medications/Procedure

This analysis will be based on the Safety Set.

Medications/procedures will be recorded at each study visit during the study and will be coded using World Health Organization-Drug dictionary (WHODrug-Global-B3) September 2022 B3. All medications/procedures taken within 60 days prior to informed consent through the duration of the study will be recorded. Those medications/procedures started and stopped prior to the initiation of the start of IP will be denoted "Prior". Those medications/procedures taken prior to the initiation of the IP and continuing beyond the initiation of the IP, or those medications/procedures started at the same time or after the initiation of the IP will be denoted "Concomitant".

Medications/procedures will be presented according to whether they are "Prior" or "Concomitant" as defined above. If medication/procedures dates are incomplete and it is not clear whether the medication/procedures are concomitant, it will be assumed to be concomitant.

Missing or partial dates will be imputed for medication/procedures. Algorithm for missing or partial start /end date is documented in Appendix C.

Concomitant medications/procedures are further categorized as on-treatment and post-treatment as follows:

1. On-treatment concomitant medications/procedures are those that have been used between first and last dose of IP (both inclusive) as well as medications started prior to first dose of IP and continue beyond the initiation of IP.
2. Post-treatment concomitant medications/procedures are those that have been started after the last dose of IP.

Concomitant medications and concomitant procedures will be summarized on Safety Set using ATC level 1 and preferred term by actual treatment group. By-participant listings of prior and concomitant (on-treatment and post-treatment) medications, and concomitant procedure will also be provided.

8.2.6. Physical Examination

This analysis will be based on the Safety Set.

Full physical examinations will be performed at Screening and Day 112 (or ET), and include assessment of body system (e.g., head, eye, ear, nose, and throat [HEENT], heart, lungs, abdomen, and extremities) as well as cognitive and neurological examination, and mental status examination. Unscheduled physical examinations may also be conducted per the Investigator's discretion. At other visits, brief physical examination will be performed including general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems. Any abnormality in physical examinations will be interpreted by an Investigator as abnormal, not clinically significant (NCS); or abnormal and clinically significant (CS) which will be reported as an AE.

By-participant listing of physical examination will be provided.

8.2.7. Investigational Product Exposure

This analysis will be based on the Safety Set.

Total drug exposure (in mg), total exposure duration to IP (in days), and percent of planned exposure received (in %) will be summarized for the Safety Set by actual treatment group.

Total drug exposure (in mg) is defined as the total IP in mg for SAGE-718 that was taken during the study. Total drug exposure for participants randomized to placebo is zero unless the participant has taken SAGE-718 by mistake, in which case the total exposure comes from SAGE-718 exposure and is summarized under SAGE-718 as eth actual treatment. If a participant skips a dose on any of the days, the dose taken is 0 mg.

Total exposure duration to IP (in days) is defined as the date of the last dose minus the date of first dose plus 1. Note that this does not exclude days when the dose has been missed.

Percent of the planned exposure received is defined as the total drug exposure, divided by planned exposure, times 100.

1) For participants randomized to SAGE-718 who complete the treatment period, planned exposure is (Date of Day 28 visit – First Dose Date of 1.2 mg) times 1.2 mg plus
    a. (Date of Day 84 visit – Date of Day 28 visit+1) times 0.9 mg if Study Day of Day 84 visit is >81 and <87.
    b. (First Dose Date of 1.2 mg + 86 – Date of Day 28 visit) times 0.9 mg if Study Day of Day 84 Visit > 86.
    c. (First Dose Date of 1.2 mg +82 – Date of Day 28 visit) times 0.9 mg if Study Day of Day 84 Visit <82.
2) For participants who discontinue the treatment earlier than Day 28, the planned exposure is (Last Dose Date – First Dose Date + 1) times 1.2 mg for participants randomized to SAGE-718.

3) For participants who discontinue the treatment on or after Day 28 but prior to Day 84, the planned exposure is (Date of Day 28 visit – First Dose Date of 1.2 mg) times 1.2 mg plus (Last Dose Date of 0.9 mg – First Dose Date of 0.9 mg +1) times 0.9 mg
4) For participants who cannot tolerate 1.2 mg prior to Day 28 therefore received 0.9 mg for the remainder of the treatment period, the planned exposure is (Last Dose Date of 1.2 mg – First Dose Date of 1.2 mg + 1), times 1.2 mg plus
    a. (Date of Day 84 visit – First Dose Date of 0.9 mg +1) times 0.9 mg if Study Day of Day 84 visit is >81 and <87.
    b. (First Dose Date of 1.2 mg + 86 – First Dose Date of 0.9 mg) times 0.9 mg if Study Day of Day 84 Visit > 86.
    c. (First Dose Date of 1.2 mg +82 – First Dose Date of 0.9 mg) times 0.9 mg if Study Day of Day 84 Visit <82.
5) For participants who never received SAGE-718, this measure is not applicable.

By-participant listing of extent of exposure will also be provided.

8.2.8. Investigational Product Adherence

This analysis will be based on the FAS.

IP adherence (%) is defined as the number of capsules taken, divided by the number of capsules planned to be taken, times 100%. The planned number of capsules taken is defined as similar way as planned exposure, with consideration of the Day 84 visit windows (+/- 2 days).

1) For participants who complete the treatment period, the planned number of capsules taken is defined as follows:
    a. 82 if Study Day of Day 84 Visit < 82
    b. (Date of Day 84 visit – First Dose Date + 1) if Study Day of Day 84 Visit is between 82 and 86 (inclusive)
    c. 86 if Study Day of Day 84 Visit > 86
2) For participants who discontinue the treatment earlier than Day 84 Visit, the planned exposure is (Last Dose Date – First Dose Date + 1).

Number and percentage of participants with IP adherence in categories (<80%, 80-100%, >100%) will be provided. By-participant listing of IP adherence will be provided.

8.3. Efficacy Analysis

8.3.1. Definition of Efficacy Variable(s)

8.3.1.1. Primary Efficacy Assessment

The Symbol Digit Modalities Test is widely used to monitor changes in cognitive function over time and for early detection of cognitive dysfunction. The task requires participants to

use a reference key to pair specific numbers with geometric figures. The number of correct pairings (out of 110 possible) achieved within 90 seconds is summed to generate a total score.

The SDMT will be assessed on Screening Period (Day -28 to -2 and Day -1), Day 14, Day 28, Day 84, and Day 112.

8.3.1.2. Key Secondary Efficacy Assessments

Key secondary outcomes are Change from Baseline to Day 84 in 1) UHDRS-Independence Scale; 2) Trail Making B (TMT-B) in a subgroup of participants who were able to complete the test within 240 seconds (yes/no) at Baseline; 3) One Touch Stockings of Cambridge (OTS) ; 4) Paced Tapping Test (PTAP); 5) Huntington's Disease Everyday Functioning (Hi-DEF) – at home subdomain score; 6) Clinical Global Impression – Severity (CGI-S) – cognitive status subdomain score.

8.3.1.2.1.1. UHDRS – Independence Scale

The Independence Scale (Part V) is a part of the Unified Huntington's Disease Rating Scale (UHDRS) described in detail in Section 8.3.1.3.7. It is intended to assess the ability of the participant to function independently in activities of daily living across the full spectrum of the disease. A single independence rating is provided on a scale ranging from 10 to 100, with higher scores reflecting better functioning.

The UHDRS – Independence Scale will be assessed on Screening Period (Day -28 to -2 and Day -1), Day 28, Day 84, and Day 112.

8.3.1.2.1.2. Trail Making B (TMT-B)

The Trail Making test is a timed graphomotor test of visual attention and task switching, administered in two parts. Only part B will be used for the key secondary analysis. Part B -requires the examinee to connect a series of alternating numbers and letters in order from lowest to highest, as in 1-A-2-B-3-C..., in the shortest time possible. The primary measure for analysis is time to completion. Standard administration of the TMT-B uses a 300 second time limit, at which point the test is stopped and scored using the maximum allowable time if not yet completed. The developers of the HD-CAB have adopted a briefer limit of 240 seconds to reduce overall duration of testing, fatigue, and frustration. However, a floor effect is an acknowledged concern that reduces the TMT-B's ability to distinguish impairment levels among individuals unable to complete within the standard time limit (Abreu et al., 2021). This shorter time limit used by the HD-CAB may further compromise the test's sensitivity to measure drug effects when scored using the maximum allowable time. For this reason, an inclusion criterion was added to the study protocol in amendment 4 version 5. Accordingly, scores of 240 are considered unevaluable for purposes of this study and the key secondary

analysis in this study will be done within a subgroup of participants who were able to complete the test within the allowable time.
The TMT-B test will be assessed on Screening Period (Day -28 to -2 and Day -1), Day 14, Day 28, Day 84, and Day 112.

8.3.1.2.1.3. One Touch Stockings of Cambridge (OTS - MLC)

One Touch Stockings of Cambridge is a computerized test of executive function. For this task, participants must stack a set of colored balls to match an example by moving 1 ball at a time into 1 of 2 possible locations. The goal is to perform the task using the smallest number of moves possible. The primary measure for analysis is time to 1st correct response.
The OTS test will be assessed on Screening Period (Day -28 to -2 and Day -1), Day 14, Day 28, Day 84, and Day 112.

8.3.1.2.1.4. Paced Tapping Test (PTAP)

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

The PTAP test will be assessed on Screening Period (Day -28 to -2 and Day -1), Day 14, Day 28, Day 84, and Day 112.

8.3.1.2.1.5. Huntington's Disease Everyday Functioning (Hi-DEF) – at Home Subdomain Score

The Hi-DEF Scale is a self-reported measure to capture difficulties experienced in daily life due to HD across four different areas of functioning. The key secondary outcome will consider Home subdomain assessment. More detail about Hi-DEF and how these scores should be calculated are presented in Section 8.3.1.3.10.1.

The Hi-DEF will be assessed on Screening Day -1, [redacted] Day 84, [redacted].

8.3.1.2.1.6. Clinical Global Impression – Severity (CGI-S) – Cognitive Status Subdomain score

The CGI-S scale is a validated instrument developed by the National Institute of Mental Health specifically for use in clinical studies. Cognitive Status Subdomain is one of clinical global impression severity scales domains, for which clinicians generate ratings of the severity of the participant's condition over the past 7 days (including the day of the clinic visit) (Guy 1976, Busner 2007). Please see Section 8.3.1.3.12 for more details.

The CGI-S test will be assessed on Screening Period (Day -28 to -2 and Day -1), [redacted] Day 84, [redacted].

8.3.1.3. [redacted]

[redacted]

[redacted]

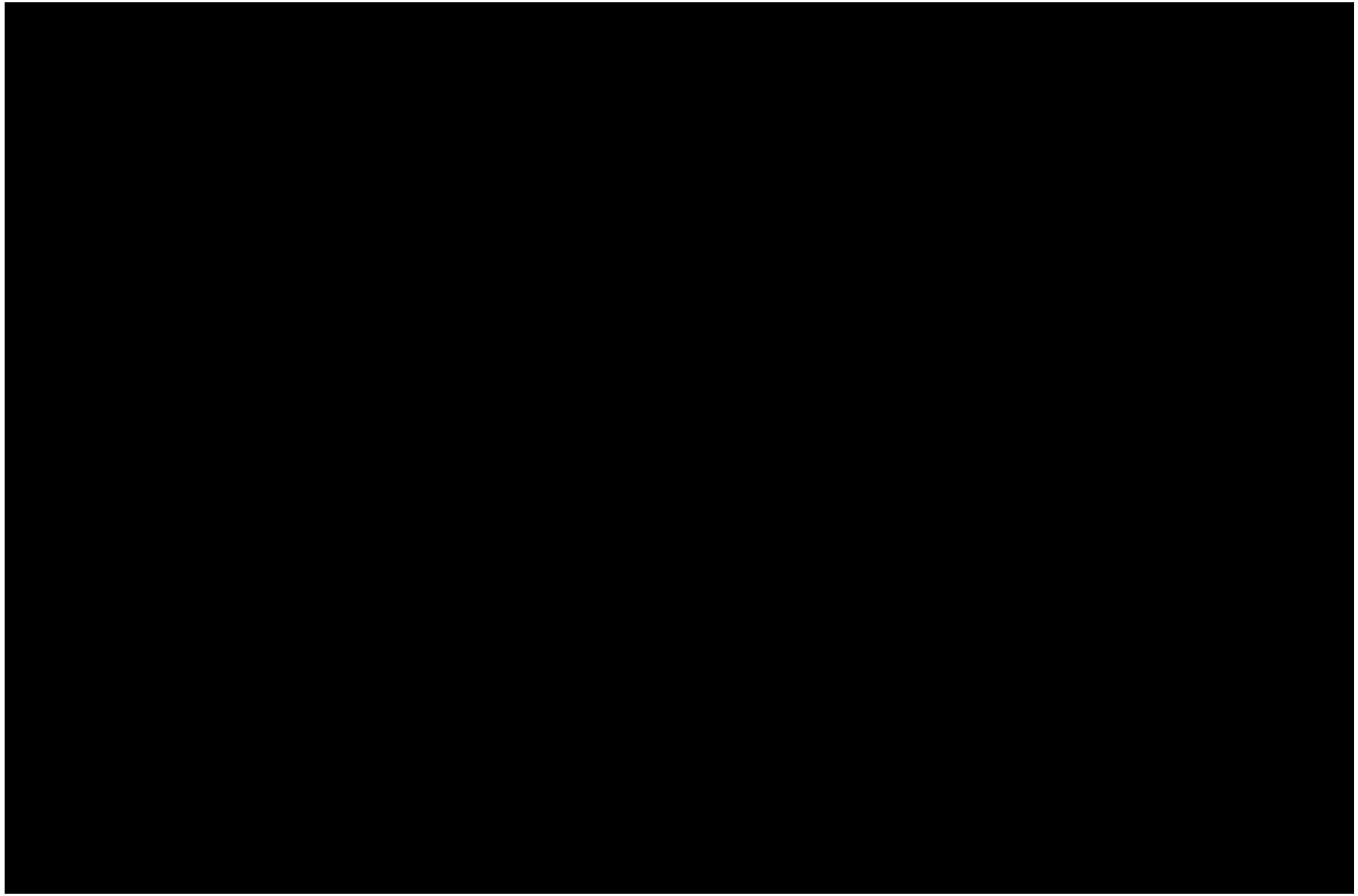
[redacted]

[redacted]

[redacted]

Table 2. [redacted]

[redacted]



8.3.1.3.1. [redacted]

[redacted]

8.3.1.3.2. [redacted]

[redacted]

8.3.1.3.3. [redacted]

[redacted]

8.3.1.3.4. [redacted]

[redacted]

8.3.1.3.5. [redacted]

[redacted]

8.3.1.3.6. [redacted]

[redacted]

8.3.1.3.7. The Unified Huntington's Disease Rating Scale UHDRS

The Unified Huntington's Disease Rating Scale (UHDRS) was developed as a multi-domain clinical rating scale for assessment of functional capacity in HD. Select scales of UHDRS Part V (Independence Examination) will be administered in this study as described above. Note that the Independence Examination constitutes a Key Secondary Endpoint assessment.

[redacted]

8.3.1.3.7.1. [redacted]

[redacted]

8.3.1.3.7.2. [redacted]

[redacted]

8.3.1.3.8. [redacted]

8.3.1.3.8.1. [redacted]

[redacted]

8.3.1.3.8.2. [redacted]

8.3.1.3.8.2.1. [redacted]

[redacted]

8.3.1.3.8.2.2. [redacted]

[redacted]

[redacted]

8.3.1.3.8.2.3. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
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[redacted]

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8.3.1.3.8.2.4. [redacted]

[redacted]

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[redacted]

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

8.3.1.3.8.2.5. [redacted]

[redacted]

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8.3.1.3.9. [redacted]

8.3.1.3.9.1. [redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

8.3.1.3.9.2. [redacted]

[redacted]

[redacted]

8.3.1.3.9.3. [redacted]

[redacted]

8.3.1.3.9.4. [redacted]

[redacted]

[redacted]

8.3.1.3.9.5. [redacted]

[redacted]

8.3.1.3.9.6. [redacted]

[redacted]

[redacted]

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

8.3.1.3.10. [redacted]

8.3.1.3.10.1. [redacted]

[redacted]

[redacted]

[redacted]

8.3.1.3.10.2. [redacted]

[redacted]

[redacted]

[redacted]

8.3.1.3.10.3. [redacted]

[redacted]

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

[redacted]

8.3.1.3.11. [redacted]

8.3.1.3.11.1. [redacted]

[redacted]

[redacted]

8.3.1.3.11.2. [redacted]

[redacted]

8.3.1.3.11.3. [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

8.3.1.3.11.4. [redacted]

[redacted]

8.3.1.3.12. Clinician-Rated Outcomes of Symptomatology

8.3.1.3.12.1. Clinical Global Impression Severity (CGI-S) [redacted]

The CGI-S [redacted] scales are validated instruments developed by the National Institute of Mental Health specifically for use in clinical studies. For clinical global impression severity scales, clinicians generate ratings of the severity of the participant's condition over the past 7 days (including the day of the clinic visit) (Guy 1976, Busner 2007). These scales will be administered at Baseline and at the end of treatment. [redacted]

The CGI-S will be assessed on Screening Period (Day -28 to -2 and Day -1), [redacted] Day 84, [redacted]

The key outcome measure is a single score of:

- [redacted]
- [redacted]
- CGI-S: Cognitive Status
- [redacted]
- [redacted]

[redacted]

8.3.1.3.13. [redacted]

[redacted]

8.3.2. Analysis Visit Windows for Efficacy Analyses

In the analysis of efficacy endpoints data from multiple visits will be used. The scheduled visits will not be windowed and will be used at nominal visit value for treatment period (Days 14, 28, 56 and 84). Unscheduled and early termination (ET) visit will be mapped to a scheduled visit for analysis. Unscheduled measurements and early termination visit will be included only if a scheduled measurement is not available, and if the unscheduled measurement falls within the visit window for the scheduled visit. 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. [redacted]

[redacted]

Table 4. Analysis Visit Windows for UHDRS – Independence Scale, Hi-DEF, [redacted] CGI-S, [redacted]

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Baseline	1	≤1
[redacted]		
Day 84 (±2 days)	84	57 to 98
[redacted]		

Table 5. [redacted]

[redacted]

Table 6. [redacted]

[redacted]

Table 7. Analysis Visit Windows for MoCA

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Baseline	Day -28 to -2	≤1
[redacted]		

8.3.3. Analysis of Primary Efficacy Variable

The FAS will be used for all efficacy summary tables. Participants will be analyzed according to randomized treatment.

8.3.3.1. Primary Analysis and Estimand

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

1) The treatment regimen for participants is placebo or SAGE-718 for 84 days.

2) The target population is adult participants with premanifest or early manifest HD.
3) The variable of interest is the change from baseline to Day 84 in Symbol Digit Modalities Test (SDMT)
4) The intercurrent events could be:
    a) The premature discontinuation of treatment for any reason. The treatment policy strategy will be used.
    b) Taking certain medications including, but not limited to, medications with potent effects at the NMDA receptor, including memantine, amantadine, ketamine, or related compounds or other medications, given at doses, frequencies, or in combinations that are likely, in the opinion of the investigator, to have a deleterious effect on cognitive performance, or prescribed cannabis or other THC-containing substances. The treatment policy strategy will be used.
5) The population summary level deals with the difference between SAGE-718 and placebo treatments in mean change from baseline to Day 84 in Symbol Digit Modalities Test (SDMT) The primary efficacy endpoint is the change from baseline to Day 84 on the SDMT score. This primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include baseline SDMT score as a continuous explanatory variable, treatment, assessment time point, and time point-by-treatment as categorical explanatory variables. The Kenward-Roger correction to degrees of freedom will be applied. All explanatory variables will be treated as fixed effects in the model. All post-baseline time points will be included in the model. An unstructured (UN) covariance matrix with the default Newton-Raphson optimization algorithm as implemented in the SAS procedure PROC MIXED will be used to estimate the within-subject correlation. If this model fails to converge, the Fisher Scoring algorithm (via the SCORING option of the PROC MIXED statement), the no-diagonal factor analytic structure (via the TYPE=FA0(*T*) option of the REPEATED statement, where *T* is the total number of time points), Toeplitz, Autoregressive (1) [AR (1)], Compound symmetry (CS) covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with CS structure, the Glimmix procedure with option of parametrizing UN to Cholesky root matrix will be used and in the case it also does not converge no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance-covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS. The primary comparison will be between SAGE-718 and placebo at the Day 84. Least squares means and 95% confidence interval will be summarized, and the p-value from the hypothesis test of no difference between the treatment groups will be also presented.

A plot showing the LS means of SDMT score ± SE bar over time within each treatment group will be provided.

8.3.3.2. Sensitivity Analysis of Primary Endpoint

Sensitivity analysis is planned if >5% of participants in any treatment group have missing data in the primary endpoint or the values could not be used due to the use of prohibited medications.

If any of the sensitivity analyses yields a result that is in a different direction from the result of the primary analysis, the nature of the discrepancy will be examined to clearly explain the discrepancy based on statistical principles and the discrepancy will be discussed in the CSR.

8.3.3.2.1. Complete Data Analysis

A sensitivity analysis using only participants who have at least baseline and Day 84 values will be performed. The MMRM analyses proposed for the analysis of the primary outcome will be provided for change from baseline to Day 84. A plot showing the LS mean ± SE bar over time within each treatment group will be provided.

8.3.3.2.2. Control-Based Pattern Mixture Model Multiple Imputation (PMM-MI)

- A sensitivity analysis using control-based Pattern Mixture Model Multiple Imputation (PMM-MI) under the missing not at random (MNAR) assumption will be used to investigate the impact of missing data (Lingling 2019, SAS Institute Inc.). MNAR assumes the missingness depends on the unobserved study data and cannot be predicted solely based on participant's observed data.

Control-based PMM-MI under MNAR involves four steps as described below.

Step 1. Assessing the pattern of missing data

To investigate the pattern of missing data, 'ods output misspattern' will be used in the MI procedure of the SAS system (PROC MI). The imputation method will be based on the observed pattern of missing data and amount of missing data. The pattern of missing data will be assessed as monotone or arbitrary.

Step 2. Turning the arbitrary missing patterns to monotone missing patterns under MAR assumption

If a mixture of non-monotone and monotone missing patterns exist in the data with majority of monotone missing patterns, then the arbitrary missing patterns will be converted to monotone missing patterns under MAR assumption.

Step 3. Generation of imputed datasets for AVAL using control-based pattern imputation under MNAR

PROC MI will be used to generate *m* complete datasets. The selection of *m* depends on the required computing time and will be determined based on the amount of missing information prior to the last patient last visit but has been recommended varying from 5 to 100.

Step 4. Convert datasets into long format in which CHG variable represents all change from baseline with different values of avisit.

Step 5. Conducting model-based analysis using each imputed dataset

The *m* complete datasets are analyzed using MMRM.

Step 6. Pooling the results from the imputed *m* datasets for inference

The results from the m complete datasets are combined to produce inferential results.

8.3.3.2.3. Tipping Point Analysis

Another sensitivity analysis – tipping point analysis will be considered to investigate the robustness of the result to departures from the missing at random (MAR) assumption of the MMRM model and to identify the tipping point where the treatment effect in participants with missing data overturns the treatment effect from statistically significant to statistically non-significant.

Hence the tipping point analysis will only be performed if the primary efficacy analysis is statistically significant in treatment effect.

Implementing the tipping point approach includes the following steps (Yuan 2014, SAS Institute Inc.):

1) Under the MNAR assumption, missing SDMT scores up to Day 84 will be imputed using PROC MI under MNAR.
2) The imputed values for observations in SAGE-718 treatment group will be adjusted directly using the shift parameter (δ).
3) The imputed datasets with the shift parameter applied will be anlyzed using PROC MIXED.
4) The results will be combined for the inference using PROC MIANALYZE.
5) Step 1-4 will be repeated until the result is not statistically significant.
6) If needed, step 1-5 will be repeated with more stringent shift parameter applied until the result is not statistically significant.

The shift parameter (δ) value will start from 0 and decrease by 0.2 decrements until non-significant p-value is achieved. One hundred datasets will be generated.

The tipping point summary for each pairwise comparison will include LSmeans difference, the 95% CI, and p-value for each of δ value. From δ = (-3, 0), iterations including the tipping point will be summarized.

8.3.3.3. Supportive Analysis of Primary Endpoint

The primary analysis will be repeated based on the [redacted]. No sensitivity analysis will be performed based on the [redacted].

A forest plot of the difference in LS means and 95% CI bar for the changes from baseline to Day 84 on SDMT score using primary analysis, sensitivity analyses (excluding tipping point analysis) and supportive analysis will be provided.

8.3.3.4. Subgroup Analyses of Primary Analysis

Primary endpoint will be analyzed for the following subgroups:

- Age (≤50, >50)
- Sex (Male, Female, Unknown/Undifferentiated)
- BMI (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2)
- Country (US, Rest of World)
- Baseline MoCA score (<18, ≥18)
- Baseline UHDRS – Independent scale (<80, ≥80)
- CAP (<100, ≥100)
- [redacted]
- [redacted]
- [redacted]
- Baseline Symbol Digit Modalities Test (SDMT) (<M,>=M, where M-Mean value at Baseline in FAS)
- Baseline Trail Making Test B (completed within 240 sec: yes/no)
- Use of ADM (Yes / No)
- Use of Anti-Chorea Medication (Yes / No)
- Use of Anti-Psychotic Medication (Yes / No)

The MMRM analyses will also be provided for change from baseline in primary endpoint within each baseline subgroup level. If any treatment group for any level of subgroup has ≤10 participants with available CFB at Day 84, the subgroup level will not be used in the analysis.

A forest plot of the difference in LS means and 95% CI bar for the changes from baseline to Day 84 on SDMT score overall and in each subgroup will be provided.

8.3.4. Analysis of Key Secondary Efficacy Variable

The key secondary efficacy endpoints are the change from baseline to Day 84 on 1) UHDRS-Independence Scale; 2) Trail Making B (TMT-B) in a subgroup of participants who were able to complete the test within 240 seconds at Baseline; 3) One Touch Stockings of Cambridge (OTS-MLC) ; 4) Paced Tapping Test (PTAP); 5) Huntington's Disease Everyday Functioning (Hi-DEF) – at home subdomain score; 6) Clinical Global Impression – Severity (CGI-S) – cognitive status subdomain score. These key secondary endpoints will be analyzed similarly to the analysis of primary endpoint.

Plot showing the LS means of key secondary endpoints ± SE bar over time within each treatment group will be provided.

8.3.5. Multiplicity Adjustment

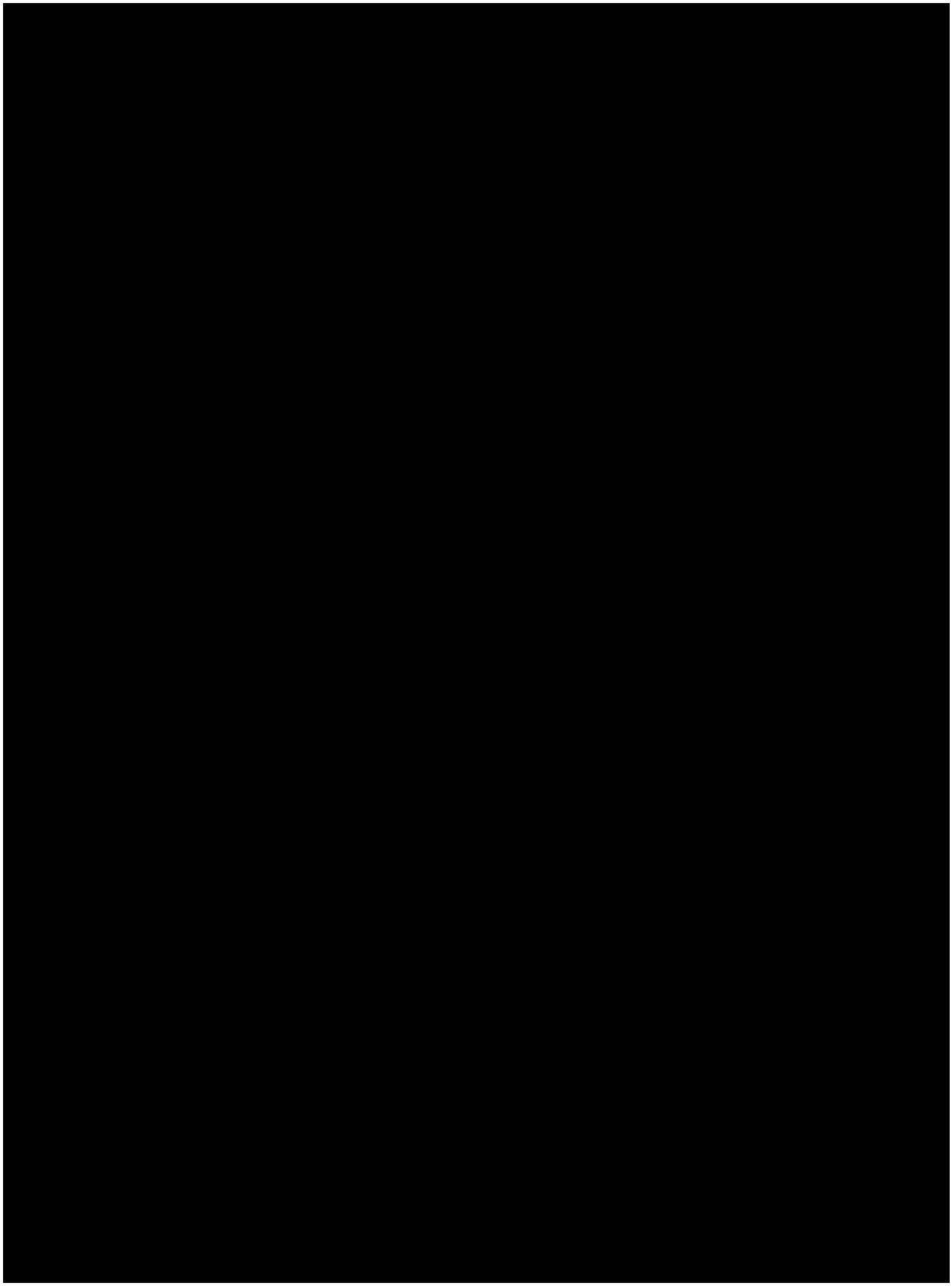
The statistical comparisons for the primary efficacy endpoint and the key secondary endpoint will be carried out in the fixed-sequence procedure which tests hypotheses in a hierarchical order to control the familywise type I error rate. This means that statistically significant results for the comparison in the higher rank (primary) for no difference between SAGE-718 versus placebo is required to initiate the testing of the next comparison in the lower rank (key secondaries) for no difference between SAGE-718 versus placebo. Since a hierarchical procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved. The hierarchical order for the key secondary outcomes is as follows: 1) UHDRS-Independence Scale; 2) Trail Making B (TMT-B) in a subgroup of participants who were able to complete the test within 240 seconds at Baseline; 3) One Touch Stockings of Cambridge (OTS-MLC) ; 4) Paced Tapping Test (PTAP); 5) Huntington's Disease Everyday Functioning (Hi-DEF) – at home subdomain score; 6) Clinical Global Impression – Severity (CGI-S) – cognitive status subdomain score.

8.3.6. [redacted]

[redacted]

Table 7. [redacted]

[redacted]



[redacted]

[redacted]

Table 8. [redacted]

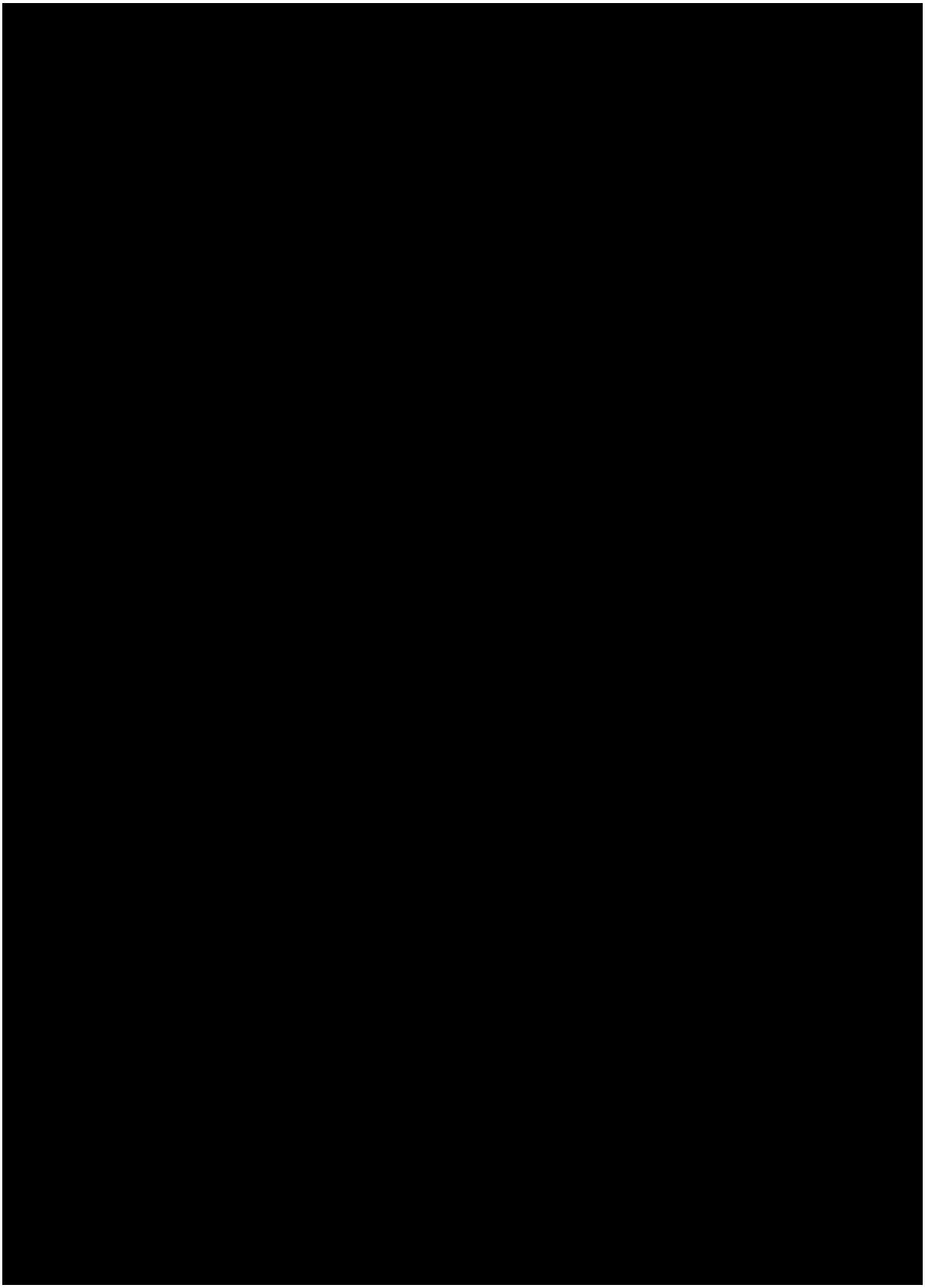
[redacted]

[redacted]

[redacted]

Table 9: [redacted]

[redacted]



[redacted]

For clinician-rated outcomes of symptomatology, analysis will be performed as described in Table 10.

Table 10. Clinician-Rated Outcomes of Symptomatology

Assessments	Description	Variable	Analysis
Clinical Global Impression – Severity (CGI-S)	[redacted] Cognitive Status, [redacted]	Continuous and categorical	Key outcome measures: - MMRM - LS mean/SE plot Other outcome measures: - Descriptive statistics

[redacted]

Generalized estimating equation (GEE) methods will also be used [redacted] GEE models will include baseline severity score, treatment, visit, and visit-by-treatment as categorical explanatory variables. An average of CGI-S severity scores [redacted] will be considered as a baseline severity score for CGI. The comparison of interest will be the difference between SAGE-718 and matching placebo at the Day 84 time point. Odds ratios and 95% confidence interval will be summarized, and the p-value from the hypothesis test of no difference between the treatment groups will be also presented.

8.4. Safety Analysis

Safety and tolerability of SAGE-718 is a secondary objective of this study. Proportion of participants experienced treatment-emergent adverse events (TEAEs) is one of the secondary endpoints, and change from baseline in vital signs, clinical laboratory analyses, electrocardiograms (ECGs), [redacted] (Table 11). All safety analysis will be performed on the Safety Set using actual treatment received.

The safety endpoints evaluated at scheduled visits within treatment period 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 Post-treatment period visits, the choice of the visit will follow the same rule as described inTable 12 and Table 13.

Anytime on treatment, last value on treatment and last value on study will be included in the summaries whenever indicated in the relevant sections below. 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.

No statistical hypothesis testing will be conducted on the safety analyses.

Table 11: Summary of Safety Analysis

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Normal Range Shift from Baseline	Potentially Clinically Significant	Abnormality/ Clinical Significance
Adverse Events	X					
Clinical Laboratory		X	X	X	X	*
Physical Exam		*				
Vital Signs		X	X		X	
ECG		X	X		X	*
[redacted]						

ECG = electrocardiogram; [redacted]
X = Safety Assessment will be summarized in tables
* = Safety Assessment will be listed in individual participant data listings

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 12 and Table 13). 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 12: Analysis Visit Windows for Safety Analysis – Vital Signs and [redacted]

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Baseline	1	≤1
Day 14 (±2 days)	14	2 to 20
Day 28 (±2 days)	28	21 to 42
Day 56 (±2 days)	56	43 to 70
Day 84 (±2 days)	84	71 to 91
Day 98 (±2 days)	98	92 to 105
Day 112 (±2 days)	112	≥105

Table 13. Analysis Visit Windows for Safety Analysis – Clinical Laboratory and ECG

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Baseline	1	≤1
Day 28 (±2 days)	28	2 to 56
Day 84 (±2 days)	84	57 to 98
Day 112 (±2 days)	112	≥99

Table 14. [redacted]

[redacted]

8.4.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1. Intensity/severity and relationship of AE will be evaluated by the investigator.

A TEAE is defined as an AE with onset on or after the first dose of IP or any worsening of a pre-existing medical condition/AE with onset after the start of IP and throughout the study. The analysis of AEs will be based on the concept of TEAEs. Where the AE start date is missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior

to the first dose of study treatment. Missing or partial dates will be imputed for AE. The algorithm for missing or partial start /end date is documented in Appendix C.

Adverse events are assigned an AE period based on the onset date/time. AE periods are defined as follows:

- Pre-treatment AE: AE onset date before first IP dosing date/time
- TEAE: AE onset date/time on or after the first IP dose date/time (If an AE start date same as IP first dose date, but no time either in AE start or treatment start, then consider this AE to be in treatment period TEAE.)
- On-treatment TEAE: AE onset date/time on or after first IP dose date/time 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)
- Post-treatment TEAE: AE onset date on or after IP last dose date + 31 days

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

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

Incidence of TEAEs in following categories will be provided by SOC and 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 System Organ Class (SOC) in SAGE-718 group, then in placebo group, then alphabetically first within SOC then within preferred term.

- TEAEs
  - On-treatment TEAEs
  - Post-treatment TEAEs

- TEAEs by maximum Severity
  - On-treatment TEAEs
  - Post-treatment TEAEs
- TEAEs by relationship (related, not related) to IP
  - On-treatment TEAE
  - Post-treatment TEAE
- TEAEs by maximum Severity and relationship (related, not related) to IP
  - On-treatment TEAE
  - Post-treatment TEAE
- Serious TEAEs
- TEAEs leading to IP dose reduction
- TEAEs leading to IP withdrawal
- 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 either treatment group 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 imputed. The incidences will be presented by descending frequency of SOC and then, within a SOC, by descending frequency of PT based on the participant count, and in alphabetical order of PT if the incidence within a PT is a tie.

In addition, TEAE summary by SOC and PT will also be presented by the following subgroups:

- Age group: ≤50, >50 years
- Race (Black or African American, White, Other)
- Sex (Male, Female, Unknown/Undifferentiated)
- BMI (≤18.4, 18.5-24.9, 25-29.9, ≥30 kg/m^2)
- Country (US, Rest of World)

A by-participant listing of each TEAE category will also be provided. All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study, and most frequent (5%) TEAE will be listed.

8.4.2. Clinical Laboratory

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

Any lab results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

All laboratory values will be summarized for the Safety Set using actual treatment received. 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 last post-baseline values on treatment (on or after first dose, on or before last dose) and on study (on or after first dose, on or before last day of the study).

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

Normal ranges for each parameter will be provided by the laboratory. Shift from baseline to worst post-baseline values in abnormality of results at anytime on treatment, the last value on treatment (on or after first dose, on or before last dose and the last value on study (on or after first dose, on or before last day of the study) in abnormality of results will be summarized. If a participant has both low and high post-baseline records, the participant will be counted twice for each low and high cell.

The number and percentage of participants with potentially clinically significant (PCS) values will be provided in separate displays in hematology, clinical chemistry and liver function tests provided for such occurrence for anytime on treatment, last value on treatment, within 28 Days after the last dose of treatment (follow-up period). PCS values will be identified for specific laboratory parameters as outlined in the table below.

Liver function tests will be monitored closely for 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.

Any lab results considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays.

Table 15: Potentially Clinically Significant Values for Specific Laboratory Parameters

Laboratory Parameter	**Sex**	**Units**	**Criteria for PCS Values (Observed values)**	
			High	**Low**
Hematology				
Hemoglobin	Male	g/L	>185	<115
	Female	g/L	>170	<100
Hematocrit	Male	Fraction of 1	>0.55	<0.385
	Female	Fraction of 1	>0.49	<0.345
Platelet count		10^9/L	>600	<125
White blood cell		10^9/L	>15	<2.5
Basophils		10^9/L	>0.5	NA
Eosinophils		10^9/L	>1.5	NA
Neutrophils		10^9/L	NA	<1.5
Lymphocytes		10^9/L	>6.0	<0.5
Monocytes		10^9/L	>1.4	NA
Coagulation				
Prothrombin time (PT)		Sec	>=1.11 x ULN	Not Specified
Partial thromboplastin time (PTT)		Sec	>1.5 x ULN	Not Specified
Serum Chemistry				
Albumin		g/L	>70	<28

Blood urea nitrogen		mmol/L	>10.71	NA
Calcium		mmol/L	>2.75	<2.0
Chloride		mmol/L	>120	<90
Creatinine		mmol/L	>3xULN or >3x Baseline	
Gamma Glutamyl Transferase			>3xULN	
Glucose		mmol/L	>13.9	<2.8
Sodium		mmol/L	>150	<132
Potassium		mmol/L	>5.4	<3.3
Protein		g/L		<45
Bicarbonate		mmol/L	>34	<18
Phosphorus		mmol/L	>1.94	<0.61
Liver Function Tests (LFT)				
Bilirubin		µmol/L	>2xULN	NA
Aspartate Aminotransferase		U/L	>3xULN	NA
Alanine Aminotransferase		U/L	>3xULN	NA
Alkaline Phosphatase		U/L	>1.5xULN	NA

8.4.3. 12-Lead Electrocardiogram

A single 12-lead ECG under Protocol Amendment 2 and triplicate 12-lead ECG under Original Protocol and Protocol Amendment 1 will be performed after the participant has been resting in the supine position for at least 5 minutes. If the multiple 12-lead ECG are performed, the average of all values on the same date will be used in the summary. If there are both scheduled visit and unscheduled visit on the same date, all the assessments on that date are considered as the scheduled visit for the summary. A summary of the observed values (raw values for the single ECG; average values for the multiple ECG on the same date) and change from baseline values 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 the 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 triplicated ECG value will be provided at baseline and each post-baseline scheduled assessment time point.

Potentially clinically significant values of QTcF as outlined in the table below will be summarized by treatment for anytime on treatment, last value on treatment, within 28 Days after the last dose of treatment (follow-up period). This analysis includes triplicate values individually and is not based on average value. Electrocardiogram findings will be listed by participant and visit.

Table 16. Potentially Clinically Significant Values for 12-Lead ECG Parameters

12-Lead ECG	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline)	
		High	Low	Increase	Decrease
QTcF	msec	>450 but ≤480 >480 but ≤500 >500	NA	≥30 to 60 >60	NA

8.4.4. 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. Potentially clinically significant values as outlined in the table below will be summarized by treatment and for anytime on treatment, last value on treatment, within 28 Days after the last dose of treatment (follow-up period). By-participant listing of vital signs will also be provided.

Table 17. Potentially Clinically Significant Values for Vital Sign Parameters

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCS values (Change from Baseline values)	
		High	Low	Increase	Decrease
Heart rate (supine and standing)	Beats/min	>120	<40	NA	NA
Respiratory Rate	Breaths/min	>20	<8	NA	NA
Systolic blood pressure (supine and standing)	mmHg	>180	<90	≥30	≥30

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCS values (Change from Baseline values)	
		High	Low	Increase	Decrease
Diastolic blood pressure (supine and standing)	mmHg	>110	<50	≥20	≥20
Supine – Standing Systolic Blood Pressure	mmHg	≥20			
Supine – Standing Diastolic Blood Pressure	mmHg	≥10			
Orthostatic hypotension: supine – standing SBP and DBP	mmHg	SBP ≥20 and DBP ≥10			
Possible orthostatic hypotension: supine – standing SBP and DBP	mmHg	SBP ≥20 or DBP ≥10			

8.4.5. Physical Examination

A full physical examination is to be conducted during Screening and at Day 112. At other visits, physical examinations will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems and followed by a targeted physical assessment as needed. A by-participant listing of physical examination findings will also be provided.

8.4.6. [redacted]

[redacted]

[redacted]

8.4.7. [redacted]

[redacted]

[redacted]

8.4.8. Other Safety Analysis

Not applicable.

8.5. [redacted]

[redacted]

9. SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable.

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11. LIST OF APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS

Assessments	Screening Period		Treatment Period					Follow-Up	
	Days -28 to -2	Day -1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (±2 days)	Day 98 (±2 days)	Day 112 (±2 days) or ET
Informed consent[a]	X								
Inclusion/exclusion criteria	X	X	X						
Family/Medical history and demographics[b]	X	X							
Participant training[c]	X	X							
Body weight	X		X		X	X	X		X
Body height	X								
Vital signs (including orthostatics)[d]	X		X	X	X	X	X	X	X
Physical examination[e]	X				X		X		X
CAG test[f] (if not collected as part of medical history)	X								
FSH test[g]	X								
Serology test[h]	X								
12-lead ECG[i]	X				X		X		X
Clinical laboratory assessments[j]	X		X		X		X		X
Urine drug test	X		X	X	X	X	X	X	X
Alcohol test[k]	X		X	X	X	X	X	X	X
Cigarette/tobacco use assessment[l]	X		X	X	X	X	X	X	X
Pregnancy test[m]	X		X		X		X		X

Assessments	Screening Period		Treatment Period					Follow-Up	
	Days -28 to -2	Day -1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (±2 days)	Day 98 (±2 days)	Day 112 (±2 days) or ET
[redacted]									
C-SSRS (Screening/Baseline)	X								
[redacted]									
UHDRS[p]	X	[redacted]					X	[redacted]	
Montreal Cognitive Assessment	X								
Global Impression – Severity[q]	X						X		
[redacted]									
Cognitive battery[r]	X								
[redacted]									
Hi-DEF Scale							X		
[redacted]									

Assessments	Screening Period		Treatment Period					Follow-Up	
	Days -28 to -2	Day -1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (±2 days)	Day 98 (±2 days)	Day 112 (±2 days) or ET
[redacted]									
Randomization			X						
IP self-administration[v]			X (once daily in the morning)						
IP dispensation[w]			X	X	X	X			
IP Adherence[x]			X						
IP Accountability/Return[y]			X	X	X	X	X		
AEs/SAEs	X (from time of ICF throughout the duration of participation)								
Prior and concomitant medications	X								

Abbreviations: AE = adverse event, COVID-19 = coronavirus disease 2019; C-SSRS = Columbia–Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HD = Huntington's Disease; Hi-DEF = Huntington's Disease Everyday Functioning Scale; HIV = human immunodeficiency virus; ICF = informed consent form; IP = investigational product; [redacted]; SAE = serious adverse event; UHDRS = Unified Huntington's Disease Rating Scale.

Note: [redacted]

a. Both participants and study partners (if applicable) will be consented during the Screening Period. [redacted]
b. In addition to full medical history, all medications and supplements taken within 8 weeks prior to Screening, all medications used to treat HD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD are to be recorded. Information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at screening and throughout the study. Confirmed (genetically tested) or suspected family history of HD will be collected.
c. Participants and study partners (if applicable) will be trained by study staff on the use of software applications and devices necessary for the conduct of the study.

d. Vital signs to include body temperature, respiratory rate, heart rate, and blood pressure. On dosing days, vital signs will be measured prior to dosing. Blood pressure and heart rate will be measured after the participant has been in the supine position for at least 5 minutes and then repeated approximately 1 and 3 minutes after standing at all scheduled time points. Vital signs can be repeated once per visit if out of range.
e. A full physical examination is to be conducted during Screening and at Day 112. At other visits, physical examinations will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems and followed by a targeted physical assessment as needed. A symptom-directed examination may be conducted at any time at the discretion of the investigator.
f. Test results of genetically confirmed disease with CAG expansion ≥36 collected as part of medical history is acceptable in lieu of central laboratory confirmation. For any genetic counseling, the study sites should follow the local practice.
g. Serum FSH test will be conducted at Screening for the female participants to confirm whether a female participants with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal.
h. To include hepatitis B and C screening tests, HIV-1 and -2 antibody.
i. Single ECG will be measured after the participant has been in the supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, blood draws should be carried out after ECG and vital signs.
j. Clinical laboratory assessments will include blood samples for hematology, clinical chemistry, biochemistry, coagulation, serology, genetic testing, and urinalysis. Samples will be collected ≤2 hours prior to dosing on dosing days. On non-dosing days, collection may occur at any time.
k. A breath test for alcohol will be performed.
l. Data on cigarette use will be collected using the question: “How many packs of cigarettes did you smoke over the past 7 days?” at the time points specified.
m. Serum pregnancy tests will be conducted for all female participants at Screening; urine pregnancy tests will be conducted at other scheduled time points for female participants that are not postmenopausal or permanently sterile.
[redacted]
p. [redacted]. Independence Scale will be conducted at Screening, and on Days -1, 28, 84 and 112.
[redacted]
r. Cognitive tests at all time points are to be performed at the same time of day (±2 hours) and postdose on dosing days. [redacted]

[redacted]

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

APPENDIX B. DETAILS OF STATISTICAL METHODOLOGY

Sample SAS Code for MMRM

```
proc mixed data=data method=ml;
    class trtp(ref="Placebo") avisit usubjid ;
    model chg = trtp avisit trtp*avisit base  /ddfm=kr;
    repeated avisit / subject= usubjid type=UN r;
    lsmeans trtp*avisit / diff=all cl alpha=0.05;
    ods output diffs=lsdiffs lsmeans=lsmeans ConvergenceStatus=cs;
run;
```

Sample SAS Code for GEE

```
proc gee data=data;
    class trtp(ref="Placebo") avisit usubjid;
    model avalc = trtp avisit trtp*avisit base  / dist=binomial link=logit;
    repeated subject= usubjid / corrb corrw covb type=UN;
    lsmeans trtp*avisit / diff oddsratio cl;
    ods output diffs=diffs responseprofile=proportion;
run;
```

Sample SAS Code for PMM-MI under MNAR

Step 1. Assessing the pattern of missing data

```
proc mi data=non_mono seed=xxx nimpute=0;
    var trtp base y1-y3; *y1=Day 14, y2=Day 28, y3=Day 84;
    ods output misspattern=pattern;
run;
```

Step 2. Turning the arbitrary missing patterns to monotone missing patterns under MAR assumption

```
proc mi data=non_mono out=mono seed=xxx nimpute=m;
    min=. . x x x; *period (.) means no imputation needed;
    max=. . y y y;
    var trtp base y1 y2 y3;
    mcmc chain=multiple impute=monotone;
run;
```

Step 3. Generation of imputed datasets for AVAL using control-based pattern imputation under MNAR

```
proc mi data=mono seed=xxx nimpute=m outs=imputed;
    min=. . x x x;
    max=. . y y y;
```

```
    by _imputation_;
    class trtp;
    var y1 y2 y3;
    monotone reg(/details);
    mnar model(y1 y2 y3/ modelobs=(trtp='Placebo')); *only control group is used to
derive the imputation model;
run;
```

Step 4-1. Calculate CHG14, CHG28, and CHG84.

Step 4-2. Convert datasets into long format in which CHG variable represents all change from baseline with different values of avisit.

Step 5. Conducting model-based analysis using each imputed dataset

```
proc mixed data= imputed;
    by _imputation_;
    class subjid trtp(ref='Placebo') avisitn;
    model chg = trtp base avisitn trtp*avisitn / ddfm=kenwardroger;
    repeated avisitn / subject=usubjid type=UN;
    lsmeans trtp*avisitn / diff=all cl alpha=0.05;
    ods output lsmeans=lsmeans diffs=diffs;
run;
```

Step 6. Pooling the results from the imputed *m* datasets for inference

```
proc sort data=lsmeans;
by trtp avisitn _imputatoin_;
run;

proc mianalyze parms=lsmeans;
modeleffects estimate;
ods output ParameterEstimates=lms;
by treatment avisit;
run;

proc sort data=diffs;
by avisit _imputatoin_;
run;

proc mianalyze parms=diffs;
modeleffects estimate;
ods output ParameterEstimates=dif;
by avisit;
run;
```

Sample SAS Code for Tipping Point Analysis

```
/*-------------------------------------------------------------*/
```

```
/*--- Generate imputed data set for specified shift parameters ---*/
 /*--- data= input data set ---*/
 /*--- smin= min shift parameter ---*/
 /*--- smax= max shift parameter ---*/
/*--- sinc= increment of the shift parameter ---*/
 /*--- out= output imputed data set ---*/
/*-----------------------------------------------------------------*/
%macro midata( data=, smin=, smax=, sinc=, out=);
     data &out;
      set _null_;
run;

/*------------ # of shift values ------------*/
     %let ncase= %sysevalf( (&smax-&smin)/&sinc, ceil );
/*------- Imputed data for each shift -------*/
%do jc=0 %to &ncase;
     %let sj= %sysevalf( &smin + &jc * &sinc);
     proc mi data=&data seed=xxx nimpute=m out=outmi;
          class trtp;
          monotone reg(y1 y2 y3);
          mnar adjust( y1 y2 y3 / shift=&sj adjustobs=(trtp='Placebo') ); *active treatment is
          used;
          var trtp y1 y2 y3;
     run;

     data outmi;
          set outmi;
          Shift= &sj;
     run;

     data &out;
          set &out outmi;
     run;
%end;
%mend midata;
```

APPENDIX C. 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.

Prior and Concomitant Medications

For the partial start date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.
- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

For the partial end date of medication:

- If the year is present and the month and day are missing, then the month and day will be set to December 31.
- If the year and day are present and the month is missing, then the month will be set to December.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month.
- If the year and day are present and the month is missing, then treat it as if the day is also missing. Set the month and day to be December 31.

APPENDIX D. ANTIDOPAMINERGIC MEDICATIONS

A list of neuroleptics and anti-chorea medications which are commonly referred collectively as Antidopaminergic Medications (ADM) in the HD community.

Anti-Psychotic Medications:

1. ARIPIPRAZOLE
2. CHLORPROMAZINE
3. FLUPHENAZINE
4. HALOPERIDOL
5. LUMATEPERONE TOSYLATE
6. OLANZAPINE
7. QUETIAPINE FUMARATE
8. QUETIAPINE
9. RISPERIDONE

Anti-Chorea Medications:

1. DEUTETRABENAZINE
2. TETRABENAZINE
3. VALBENAZINE

APPENDIX E. HI-DEF SCORING INSTRUCTIONS

The scoring algorithm of the Hi-DEF scales includes four steps: 1) rescoring the item responses; 2) assigning scores for participants who do not work or drive due to HD; 3) calculation of the raw sum score; and 4) linking the raw scale scores to the Rasch-based interval level 0-100 score.

Step 1: Rescoring the item responses

Before the scores can be calculated, the data from item responses should be rescored so as: (i) the lowest item-level score is zero, and (ii) the highest item-level score is four.

Table 14. Item Rescoring | At home, At work, and Driving items

	No difficulty	A little difficulty	Some difficulty	A lot of difficulty	Cannot do this anymore
Original scoring	1	2	3	4	5
Revised scoring	0	1	2	3	4

Table 15. Item Rescoring | Communicating items

	Never	Sometimes	Often	Almost always
Original scoring	1	2	3	4
Revised scoring	0	1	2	3

Step 2: Assigning scores for participants who do not work or drive due to HD

If a participant indicates that they do not work or drive due to their HD, this implies the same principle as the highest response option on the Hi-DEF scale (i.e., they "Cannot do this anymore" due to their HD).
Participants who indicate that they i) do not work due to their HD or ii) do not drive due to their HD should therefore be rescored with the highest score (i.e., the score indicating the lowest level of functioning) for all items within the corresponding subscale (i.e., Driving or At work), as illustrated in the table below.

Table 20 Assigned scoring – Participants who do not work or drive due to HD

	Does not work due to HD	**Does not drive due to HD**
Original scoring	Missing on all Work scale items	Missing on all Driving scale items
Assigned scoring	Score of 4 ("Cannot do this anymore") will be assigned for all Work items and Total score 44 for Total Work score	Score of 4 ("Cannot do this anymore") will be assigned for all Driving items and Total score 32 for Total Driving score

Step 3: Calculation of the raw score

The data to be used for the calculation of the Hi-DEF full scale scores are presented in the table below. with the number of items included in the scale, the minimum number of items needed for score calculation, and the range of the raw score (raw score is the simple sum of the item scores). The table also presents the corresponding item numbers as presented in the updated version of the scales.

Table 21. Description of the Hi-DEF Scale Scores

	Number of items	Number of items needed for score calculation	Raw score range	Corresponding item numbers from original 47-item version of the scale
Home	15	8	0–60	02, 03, 04, 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 17
Work†	11	6	0–44	19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30
Driving‡	8	4	0–32	32, 33, 34, 35, 36, 37, 38, 39
Communicating	6	3	0–18	41, 42, 43, 44, 46, 47
Hi-DEF total score	40	21*	0–154	02, 03, 04, 05, 06, 07, 08, 09, 10, 11, 12, 13, 14, 15, 17, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39, 41, 42, 43, 44, 46, 47
Hi-DEF Short form	7	4	0–26	02, 04, 07, 09, 10, 41, 42

**Except for Work and Driving scales if the participant indicates they do not work or drive due to HD, in which case all items for the relevant scale (Work or Driving) are assigned a score of 4 ("Cannot do at all"), as explained in Step 2 above; †Assigned Work scale score = 44 for participants who indicated they do not work due to HD; ‡Assigned Driving scale score = 32 for participants who indicated they do not drive due to HD; ^As 21items are needed to calculate the Hi-DEF total score, this score cannot be calculated if both Work and Driving scales are missing, unless both are missing as the participant does not work and drive due to HD, in which case the assigned scores explained in Step 2 are used to calculate the Hi-DEF total score*

Hi-DEF subscales and short form

Complete data
For complete data, for each participant, the responses for each subscale are added up (once rescored according toError! Reference source not found. Table 14 and Table 15) to produce a total raw score for each scale. Use the applicable conversion table, provided under Step 4.

Missing data
If there is missing data as the participant does not work or drive due to HD, assign scores for the Work and Driving scales as explained in Step 2.
For data missing for other reasons, if there is more than 50% missing data, the data from the individual should be set to missing. If there is less than 50% missing data, the data can be imputed. For example, for the home scale (15 items), ≥8 items need to be completed and in the driving scale (8 items), ≥4 items need to be completed.
Use the following steps to produce a complete within-person response pattern (subscale total raw score):

1. Substitute the average raw score of the non-missing items for the missing item(s) value.
2. Calculate a sum total score for the domain and round to the nearest whole integer.

Following this you can move to Step 4 (score transformation).

Hi-DEF Total score

To calculate a total score, the instructions above need to be followed for each subscale and then the 4 scores should be summed. Therefore, a total score can only be calculated for those participants who have completed at least half of the items in each of the four scales. If the participant does not work and does not drive for reasons other than due to their HD, a total score cannot be summed.

Step 4: Score transformation

The conversion table transforms total raw scores to Rasch logit measure scores, which are subsequently mapped to a 0–100 scale for convenience. This conversion is a simple linear

transformation that changes the logit mean of the minimum to maximum scores and converts the most extreme measures to 0 and 100, respectively.
The applicable conversion tables below should be used to derive the corresponding measure score. The tables also show the crosswalk between the Hi-DEF short form and total score.

Raw score (complete data)	0-100 transformed score	Raw score (complete data)	0-100 transformed score
0	0	31	49
2	13	33	51
4	19	35	53
6	24	37	55
8	27	39	57
10	30	41	59
12	32	43	61
14	34	45	64
16	36	47	66
18	38	49	69
20	40	51	73
22	42	53	77
24	43	55	82
26	45	57	88

27	46	**58**	93
28	47	**59**	99
29	48	**60**	100
30	49		

Table 23 Work scale raw score to transformed score

Raw score (complete data)	0-100 transformed	Raw score (complete data)	0-100 transformed
0	0	**23**	51
1	8	**24**	52
2	13	**25**	53
3	17	**26**	54
4	20	**27**	55
5	23	**28**	57
6	25	**29**	58
7	28	**30**	59
8	30	**31**	61
9	31	**32**	62
10	33	**33**	64
11	35	**34**	66
12	36	**35**	67
13	38	**36**	69
14	39	**37**	72
15	41	**38**	74
16	42	**39**	78
17	43	**40**	81
18	44	**41**	86
19	46	**42**	91
20	47	**43**	98
21	48	**44**	100

22	49		

Table 24 Driving scale raw score to transformed score

Raw score (complete data)	0-100 transformed	Raw score (complete data)	0-100 transformed
0	0	**17**	49
1	10	**18**	50
2	17	**19**	52
3	22	**20**	53
4	27	**21**	55
5	30	**22**	56
6	33	**23**	59
7	35	**24**	62
8	37	**25**	65
9	39	**26**	70
10	40	**27**	75
11	42	**28**	80
12	43	**29**	84
13	44	**30**	89
14	45	**31**	94
15	47	**32**	100
16	48		

Table 25 Communicating scale raw score to transformed score

Raw score (complete data)	0-100 transformed
0	0
1	12
2	21
3	28
4	34
5	39
6	43
7	47
8	50
9	53
10	56
11	58
12	61
13	64
14	67
15	70
16	74
17	81
18	100

Table 26 Crosswalk between Hi-DEF total score and short-form score raw score

Total		Short form		Total				Total		Short form		Total		Short form	
Raw score	0-100	Raw score	0-100	Raw score	0-100	Raw score	0-100	Raw score	0-100	Raw score	0-100	Raw score	0-100	Raw score	0-100
0	0			39	39			78	50			117	61	20	60
1	7			40	40	8	40	79	51			118	61		
2	11	0	11	41	40			80	51			119	62		
3	14			42	40			81	51	15	51	120	62	21	62
4	16			43	41			82	51			121	63		
5	18			44	41			83	52			122	63		
6	19	1	19	45	41			84	52			123	63		
7	21			46	42	9	42	85	52			124	64		
8	22			47	42			86	52			125	64		
9	23			48	42			87	53			126	65	22	65
10	24			49	43			88	53	16	53	127	65		
11	25	2	25	50	43			89	53			128	66		
12	26			51	43	10	43	90	53			129	66		
13	27			52	43			91	54			130	67		
14	27			53	44			92	54			131	67	23	67
15	28	3	28	54	44			93	54			132	68		
16	29			55	44			94	54	17	54	133	69		
17	29			56	45			95	55			134	69		
18	30			57	45	11	45	96	55			135	70		
19	31			58	45			97	55			136	71		
20	31	4	31	59	45			98	55			137	71	24	71
21	32			60	46			99	56			138	72		
22	32			61	46			100	56			139	73		
23	33			62	46			101	56	18	56	140	74		
24	33			63	46	12	46	102	56			141	75		
25	34	5	34	64	47			103	57			142	76		
26	34			65	47			104	57			143	77		
27	35			66	47			105	57			144	78	25	78
29	36			68	48			107	58	19	58	146	80		
30	36	6	36	69	48	13	48	108	58			147	82		
31	36			70	48			109	58			148	83		
32	37			71	49			110	59			149	85	26	86
33	37			72	49			111	59			150	87		
34	37			73	49			112	59			151	89		
35	38			74	49			113	60			152	92		
36	38	7	38	75	50	14	50	114	60			153	96		

37	39			**76**	50			**115**	60			**154**	100		
38	39			**77**	50			**116**	61						

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