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

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STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER 718-CIH-202

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

Short Title: 28-Day Placebo-Controlled Study of SAGE-718 on Functioning Capacity in Participants with Huntington's Disease

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
ADM	Antidopaminergic Medications
AE	Adverse event
[redacted]	[redacted]
ASO	Antisense oligonucleotide
ATC	Anatomical therapeutic chemical
[redacted]	[redacted]
BLQ	Below limit of quantification
BMI	Body mass index
[redacted]	[redacted]
CAG	Cytosine, adenine, guanine
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CAP	CAG-Age-Product
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence Interval
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
[redacted]	[redacted]
eCRF	Electronic case report form
ECGs	Electrocardiograms
[redacted]	[redacted]
ERT	Emotion Recognition Test
ET	Early Termination
FAS	Full analysis set

Abbreviation	Definition
FDA	Food and Drug Administration
[redacted]	[redacted]
HD	Huntington's Disease
HD-CAB	Huntington's Disease Cognitive Assessment Battery
[redacted]	[redacted]
HEENT	Head, eye, ear, nose, and throat
[redacted]	[redacted]
HP	Healthy participant(s)
HPS	Healthy Participant Set
[redacted]	[redacted]
HTT	Huntingtin gene
HVLT	Hopkins Verbal Learning Test-Revised
[redacted]	[redacted]
ID	A participant identification
IP	Investigational product
IRT	Interactive response technology
[redacted]	[redacted]
LFT	Liver function test
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MoCA	Montreal Cognitive Assessment
[redacted]	[redacted]
[redacted]	[redacted]
NCS	Not clinically significant
[redacted]	[redacted]
NIH	National Institute of Health
[redacted]	[redacted]
OTS	One Touch Stockings of Cambridge
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
RMIB	Reduced Motor Impact Battery
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SE	Standard error
SEM	Standard error of the mean
SOC	Standard Organ Class
SS	Safety set
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
TMT A	Trial Making Test: Trial A
TMT B	Trial Making Test: Trial B
UHDRS	Unified Huntington's Disease Rating Scale
[redacted]	[redacted]

2. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis and is based on the following approved study documents:

- Study Protocol Version 3.0, Amendment 2 (26 May 2023)
- Electronic Case Report Form (eCRF), Version 8.0 (05 February 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 version (SAS Institute, Cary, North Carolina, USA). This SAP has been finalized and approved before the clinical database lock. Any changes made to the SAP after the clinical database lock has occurred will be documented and discussed in the clinical study report for this study.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To assess the magnitude of the baseline difference between participants with early Huntington's Disease (HD) and healthy participants (HP) with respect to measures of cognitive performance.

3.2. Secondary Objectives

- To evaluate safety and tolerability of SAGE-718 in participants with HD.

[redacted]

- To evaluate additional safety and tolerability parameters of SAGE-718 in participants with HD.

[redacted]

4. STUDY ENDPOINTS

4.1. Primary Endpoint

- Difference in baseline measures of the Huntington's Disease Cognitive Assessment Battery (HD-CAB) cognitive composite score in participants with HD and HP.

4.2. Secondary Endpoints

- Safety and tolerability of SAGE-718 in HD participants as assessed by the incidence of adverse events (AEs)/serious AEs (SAEs), and by changes in vital signs, and clinical laboratory parameters.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Change from Baseline and between-group effects (SAGE-718 and placebo) for [redacted] electrocardiograms (ECGs), and responses on the Columbia-Suicide Severity Rating Scale (C-SSRS).
- [redacted]
- [redacted]
- [redacted]

5. STUDY DESIGN

5.1. Overall Design

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

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

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

Screening, safety, and efficacy assessments will be performed according to the schedule presented in Appendix A (HD) and Appendix B (HP). [redacted]

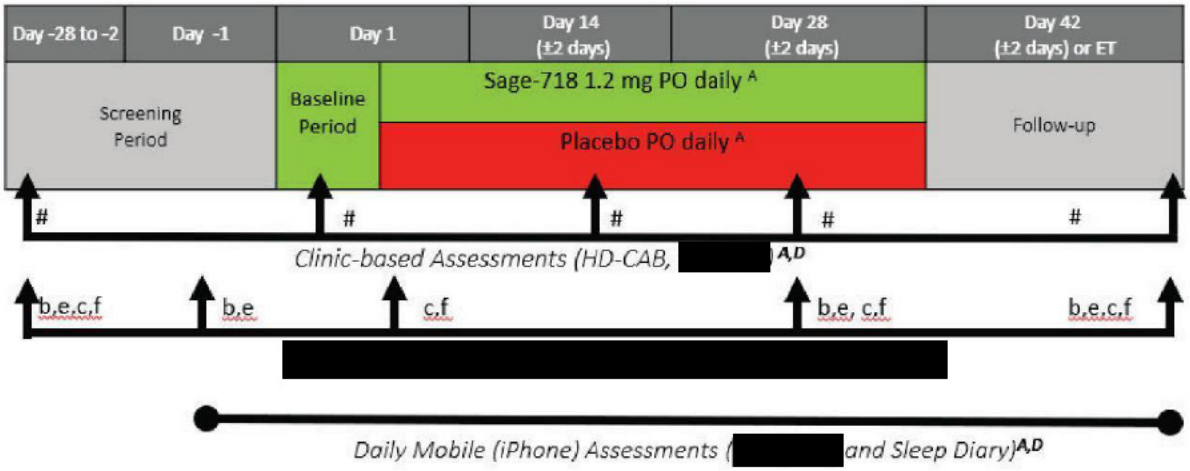
Screening assessments will be performed to determine eligibility. Participants and study partners (if applicable) will receive training on the study procedures and devices.

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

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

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

Figure 1. Study Design



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

A Participants with HD:

b [redacted]

c [redacted]

D HP: (Assessments Only)

e [redacted]

f [redacted]

[redacted]

5.2. Sample Size and Power

The study is designed to detect a difference between participants with HD and HP on HD-CAB composite score as the primary endpoint. Using a two-sided alpha level of 0.05, a sample size of at least 80 participants (40 HP and 40 participants with HD) would provide at least 80% power to detect a baseline difference in HD-CAB composite score assuming Cohen's D effect size equal to 0.63, which is in the range of effect sizes reported in the literature (Stout et al., 2014).

Using a CI approach for sample size estimation, and assuming a common SD of 1.51 in HD-CAB, a sample size of 32 evaluable participants with HD (16 per treatment arm) will provide 80% confidence level for estimating the population mean with 0.50 precision or margin of error.

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

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

5.3. Randomization

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

Randomization will be performed centrally via an interactive response technology (IRT) system. Randomization schedules will be generated by an independent statistician. The allocation to treatment group will be based on the randomization schedule.

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

5.4. Blinding and Unblinding

Participants, clinicians, and the study team will be blinded to treatment allocation during the study. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

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

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

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

- Adding stratification factor of previous intake of antisense oligonucleotide drugs (yes/no) to all analyses done with [redacted].
- Change from baseline in concomitant medications will not be analyzed. Concomitant medications will be summarized.
- Full Analysis Set definition was updated to clarify HP and HD participants inclusion.
- All Randomized Set was replaced by All Enrolled to better describe the study participants.
- Two exploratory cognitive batteries were created to separately examine SAGE-718 effects on (1) tests of the executive function domain, referred to as the Executive Function Focus battery (EFFB) and (2) tests utilizing response formats that minimize demands on psychomotor speed and coordination, referred to as the Reduced Motor Impact battery (RMIB). The latter battery is intended to inform the utility of the HD-CAB in participants where motor symptoms may impede or otherwise confound performance of certain tests. The EFFB consists of Symbol Digit Modalities Test (SDMT), Trail Making Test: Trail B (TMT B) and One Touch Stockings of Cambridge (OTS). The RMIB consists of OTS, Hopkins Verbal Learning Test-Revised (HVLT) and Emotion Recognition (ERT).

[redacted]

6.2. Modifications from the Approved Statistical Analysis Plan

This is the first version of the statistical analysis plan for final analysis.

6.3. Modifications from the Approved DMC Charter

Not applicable.

7. ANALYSIS SETS

7.1. Efficacy Analysis Sets

Full Analysis Set: The Full Analysis set (FAS) will include all randomized HD participants and all HP who meet the eligibility criteria and have at least one baseline assessment of HD-CAB (participants with HD and HP) and will be used in the analysis of primary endpoint.

Full Analysis Set 1: The Full Analysis Set 1 (FAS1) will include all participants who initiate IP and have baseline and at least one postbaseline efficacy evaluation (participants with HD only). For participants with HD the efficacy endpoints will be analyzed according to the treatment the participant is randomized to.

Full Analysis Set 2: The Full Analysis Set 2 (FAS2) will include all participants with HD who initiate IP or HP who meet eligibility criteria and have baseline and at least one postbaseline efficacy evaluation (participants with HD and HP). For participants with HD the efficacy endpoints will be analyzed according to the treatment the participant is randomized to.

Healthy Participants Set: The Healthy Participant Set (HPS) will include all HP who meet eligibility criteria and have at least one baseline assessment and one postbaseline assessment of at least one of the following tests: HD-CAB [redacted]

7.2. Safety Analysis Sets

Safety Set: The Safety Set (SS) will include all participants with HD who were administered IP or HP who met eligibility criteria and will be used to describe the safety data. The Safety Set will be further subdivided to describe participants with HD and HP separately.

Safety Set 1: The Safety Set 1 (SS1) will include all participants with HD in the safety analysis set.

Safety Set 2: The Safety Set 2 (SS2) will include all healthy participants in the safety analysis set.

7.3. Other Analysis Sets

All Enrolled Set: All Enrolled Set will include all randomized HD participants and all HP who meet the eligibility criteria and will be used to describe participant disposition and protocol deviations.

[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 shall 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) 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. Actual treatment is defined as: SAGE-718 or Placebo.

Participants who are randomized to 1.2 mg treatment will be summarized under SAGE-718 group. For efficacy data analysis, participants' data are analyzed by randomization assignment. 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 defined as below:

- Baseline for participants with HD 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".
- Baseline for HP is defined as the last non-missing measurement on or prior to Day 1.
- Study day 1 is defined as the date of randomization for untreated randomized HD participants or the date of first dose for treated HD participants.
- Study day 1 is defined as the date of completion of the baseline assessments for HP.
- Study day will be calculated relative to Study day 1.

  If event is prior to Study day 1, then study day is calculated as:

  Date of Event – Date of Study day 1

  If event is after Study day 1, then study day is calculated as:

  Date of Event – Date of Study day 1 + 1

8.2. Background Characteristics

8.2.1. Participant Disposition

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion. This analysis will be based on All Enrolled Set.

The summaries of participant disposition on all participants will include:

- Number of participants screened (HD and HP)
- Number of participants screen-failed (HD and HP)
- Number of participants enrolled (HD and HP)
- Number of healthy participants (HP) enrolled
- Number of participants randomized (HD)
- Number of HD participants randomized but not treated
- Number and percentage of HD participants received at least one dose of IP

- Number and percentage of HD participants completed full treatment period of IP
- Number and percentage of HD participants discontinued from IP and primary reason for premature IP discontinuation
- Number and percentage of participants (HD and HP) completed the study (completed Day 42 visit)
- Number and percentage of participants (HD and HP) discontinued from the study and primary reason for premature study discontinuation

Percentages will be calculated based on the participants that were randomized and received IP for HD participants, and percentages will be calculated based on all eligible participants for HP, accordingly. Treatment arm assignment of HD participants will be according to the randomized treatment. If a participant is rescreened because the participant has been a screen failure the first time, the status of the participant will be determined from the second screening. In the count of screened participants, this participant will be counted only once.

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

8.2.2. Protocol Deviations

This analysis will be based on the All Enrolled Set.

Protocol deviations will be classified as "major" or "minor" on an ongoing basis by the clinical study team and sponsor.

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.

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

8.2.3. Demographics and Baseline Characteristics

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

Demographic characteristics (age, race, sex, ethnicity, childbearing status, civil/marital status, years of education, highest level of education, current employment status, and total years of employment) and baseline characteristics, such as height (cm), weight (kg), body mass index (BMI) (kg/m^2), and HD-CAB composite score, [redacted] and HD-CAB Trail making test B will be summarized by treatment group, overall and HP.

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, Canada)
- [redacted]
- [redacted]
- CAG expansion (<40, ≥40)
- [redacted]
- Previous use of ASO drug (Yes / No)
- [redacted]
- [redacted]
- Baseline Trail Making Test B (<240, =240)
- Use of Antidopaminergic Medications (ADM see Appendix F for details) (Yes / No)

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 1 and Safety Set 2.

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

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

8.2.5. Prior and Concomitant Medications

This analysis will be based on the Safety Set 1 and Safety Set 2.

Medications 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 taken within 60 days prior to informed consent through the duration of the study will be recorded. Those medications started and stopped prior to the initiation of the start of IP for HD and day 1 for HP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP, or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant” for HD.

Those medications taken prior to day 1 and continuing beyond day 1, or those medications started at the same time or after day 1 will be denoted "Concomitant" for HP.

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

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

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

On-treatment concomitant medications 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.

Post-treatment concomitant medications are those that have been started after the last dose of IP.

Concomitant medications will be summarized on Safety Set using Anatomical Therapeutic Chemical (ATC) level 1 and preferred term by actual treatment group.

By-participant listings of prior and concomitant medications, and concomitant procedures will also be provided.

8.2.6. Physical Examination

This analysis will be based on the Safety Set 1 and Safety Set 2.

Full physical examinations will be performed at Screening and Day 42 (±2 days)/ET, and include assessment of body system (eg, head, eye, ear, nose, and throat [HEENT], heart, lungs, abdomen, and extremities) [redacted] At other visits (eg, Day 28 for participants with HD), 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 1.

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. 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.

Planned drug exposure (in mg) for completers is defined as

a) 1.2·(Study Day of Day 28 visit – Day of the first dose +1) mg, if Study Day of Day 28 visit is in 28±2 window;

b) 1.2·26 mg, if Study Day of Day 28 visit < 26;

c) 1.2·30 mg, if Study Day of Day 28 visit > 30.

Planned drug exposure (in mg) for non-completers is 1.2 mg times date of the last dose minus the date of first dose plus 1.

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

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

8.2.8. Investigational Product Adherence

This analysis will be based on the FAS1.

IP adherence (%) is monitored using the medication adherence monitoring platform for all participants in the study. The IP adherence is defined as the number of capsules taken, divided by the number of capsules planned to be taken, times 100. For participants that complete the treatment period the planned number of capsules taken is

a) (Study Day of Day 28 visit – Day of the first dose +1), if Study Day of Day 28 visit is in 28±2 window;

b) 26, if Study Day of Day 28 visit < 26;

c) 30, if Study Day of Day 28 visit > 30.

For participants that discontinue the treatment early, the planned number of capsules is (Last Dose Date – First Dose Date + 1).

IP adherence will be summarized on Safety Set by treatment group. Number and percentage of participants with IP adherence in categories (<80%, 80-100%, >100%) will be provided. IP adherence will be listed.

8.3. Efficacy Analysis

8.3.1. Definition of Efficacy Variables

8.3.1.1. Primary Efficacy Assessment and Estimand

The main interest of the primary analysis in this trial is to estimate the baseline differences between participants with HD and HP in HD-CAB composite outcome. This is a comparison between two populations without establishing a treatment effect and without potential intercurrent events. Therefore, we will not present an explicit definition of an estimand in this analysis.

The HD-CAB is a cognitive assessment battery developed for HD patients by Stout et al. (2014). The HD-CAB will be assessed on Screening Period (Day -28 to -2), pre-dose on Day 1, post-dose on Day 14 and Day 28, and during follow-up on Day 42.

HD-CAB consists of 6 subtests and each variable will be used to calculate HD-CAB composite score as outlined in Table 2. If at least 1 out of 6 HD-CAB subtests are missing, the HD-CAB composite score will be set to missing.

Table 2. HD-CAB Test Variables

Subtest Name (Assessment Type)	Cognitive Function Assessed	Variables	Score Range		Interpretation of Raw value	Recode
			Min.	Max.		
Symbol Digit Modalities Test (Paper)	Visuospatial attention, processing speed, working memory	Number of correctly coded items	0	110	High score indicates better performance	Not Needed; Use raw score
One Touch Stockings of Cambridge (Computer)	Planning, working memory	Mean time to reach a correct response (sec), averaged across all 10 trials	Not defined	Not defined	High score indicates worse performance	Part 1: Divide scores by 1000 to convert scores from milliseconds to seconds Part 2: Multiply scores by -1 so that higher values represent

Subtest Name (Assessment Type)	Cognitive Function Assessed	Variables	Score Range		Interpretation of Raw value	Recode
			Min.	Max.		
						better performance
Trail Making Test: Trail B (Paper)	Flexibility, visuospatial attention, psychomotor speed	Time (seconds) to complete the task	0 sec	240 sec	Higher value indicates worse performance	Multiply raw values by -1 so that higher values represent better performance
Hopkins Verbal Learning Test-Revised (Paper)	Verbal memory	Total correct recall trials over the 3 learning and 1 delayed recall trials	0	48	High score indicates better performance	Not Needed; Use raw score
Paced Tapping (Computer)	Timing, psychomotor coordination	The reciprocal of the standard deviation of the intertap intervals that occurred following cessation of the	Not defined	Not defined	Higher value indicates better performance	Not Needed; Use raw score

Subtest Name (Assessment Type)	Cognitive Function Assessed	Variables	Score Range		Interpretation of Raw value	Recode
			Min.	Max.		
		pacing tones over all trials taken (ms^{-1})				
Emotion Recognition (Computer)	Emotion recognition	Number of negative emotions correctly identified	0	24	High score indicates better performance	Not Needed; Use raw score

Computing HD-CAB composite scores involves following three steps. HD-CAB composite scores will be calculated per each visit per each baseline population sample mean as defined in the step 2.

Step 1: For Trail Making Test B and One Touch Stockings, reverse the score by multiplying by -1 to make higher scores indicate better performance across all the 6 subtests (See Recode column of Table 2)

Step 2: For each subtest, compute two z-scores for each participant using the formula:

$$z = \frac{\chi - \mu}{\sigma}$$

where χ is a participant's score, μ is a mean and σ is a standard deviation at baseline of

(i) HD population sample when it is used for efficacy assessment between Sage-718 vs. placebo (if not otherwise is stated);

(ii) Healthy population sample when it is used for the comparison of HP vs. participants with HD.

Step 3: To compute each participant's composite score, by calculating the average of six z-scores for each population sample mean.

The computation of exploratory cognitive batteries will be done as following:

(i) Executive Function Focus Battery (EFFB) composite score will be calculated as an average of three z-scores of Symbol Digit Modalities Test (SDMT), Trail Making Test: Trail B (TMT B) and One Touch Stockings of Cambridge (OTS) for each population; If any individual subtest score is missing, the EFFB composite score will be set to missing.

(ii) Reduced Motor Impact Battery (RMIB) composite score will be calculated as an average of three z-scores of OTS, Hopkins Verbal Learning Test-Revised (HVLT) and Emotion Recognition (ERT); If any individual subtest score is missing, the RMIB composite score will be set to missing.

Because the HD cohort in the study is relatively more progressed compared to the HD cohort in Stout et al. (2014), some participants may not be able to complete the TMT B test in the allotted 240 seconds (see more details in Appendix G). As such, we will explore the following approaches:

(i) Calculate the outcome of TMT B test as

$$25 \cdot \frac{Time}{L},$$

where L is an order number of the last symbol reached in TMT B test and $Time$ is the observed time of completion of TMT B.

The rational for this approach is to estimate the time to completion using the time needed to complete one symbol multiplied by the total number of symbols, which

is equal to 25. This calculated outcome of TMT B test will be recorded by multiplying by -1 so that higher values represent better performance.

(ii) Calculate the outcome of TMT B test as a speed of completion, which is the number of symbols done in 1 second as an outcome of TMT B test, and calculate it as

$$\frac{L}{Time},$$

where L is an order number of the last symbol reached in TMT B test and $Time$ is the observed time of completion of TMT B in seconds.

(iii) Consider only participants with baseline TMT B values < 240 seconds.

For all sensitivity analyses the calculation of HD-CAB and exploratory composite scores will be done accordingly.

8.3.1.1.1. HD-CAB Symbol Digit Modalities Test

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

8.3.1.1.2. HD-CAB One Touch Stockings of Cambridge

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

8.3.1.1.3. HD-CAB Trail Making B

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

8.3.1.1.4. HD-CAB Hopkins Verbal Learning Test

The Hopkins Verbal Learning Test assessed is used to assess verbal learning and memory. The test consists of three learning trials over which a 12-item semantically categorized list is read aloud by an examiner. The examinee is asked to recall as many items as possible from memory immediately following each trial (immediate recall) and again following a delay (delayed recall). The learning list items are then presented among additional items that were not previously presented, and examinee is asked to identify which items were on the original list by responding yes/no to each item (recognition). The primary measure for analysis is the total

words correctly recalled over 4 trials (3 immediate and 1 delayed) with a maximum of 48 correct.

8.3.1.1.5. HD-CAB Paced Tapping Test

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

8.3.1.1.6. HD-CAB Emotion Recognition Task

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

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8.3.1.2.5.3. National Sleep Foundation Sleep Diary

Once daily in the morning, participants will briefly answer 5 questions about sleep length, sleep latency, night awakenings, and sleep quality. These questions have been modified from version 6 of the National Sleep Foundation Sleep Diary (National Sleep Foundation). This diary will be completed each morning during the Treatment Period using a mobile device. At scheduled clinic visits, the task will be performed in the clinic under observation by study staff, otherwise the participant will perform this task remotely (at home). Sleep length will be calculated in minutes as a difference between participant get out of bed this morning and time participant went to bed last night if the participant went to sleep before the midnight, otherwise the difference will be before the out of bed time and the time when participant went to bed in this day. Mean sleep diary assessments will be derived based on study days for clinic visit days using the mean of non-missing assessments between the previous visit day (exclusive) and the current visit day (inclusive). The baseline sleep diary measurement will be calculated as the mean of days immediately preceding the first dose day time. The precision level of averages to keep one decimal place. Refer to Table 3 above for the visit derivation.

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8.3.2. Visit Windows for Efficacy Analyses

The scheduled visits will not be windowed and will be used at nominal visit value for treatment period (Days 14, 28, and 42). Unscheduled and 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 or 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 4. Analysis Visit Windows for HD-CAB

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 35
Day 42 (±2 days)	42	≥36

8.3.3. Analysis of Primary Outcome

The FAS will be used for primary summary tables. All participants who have baseline measures will be analyzed.

8.3.3.1. Primary Analysis

The primary efficacy endpoint is the difference between participants with HD and HP in baseline measures of the HD-CAB composite z-score standardized using mean and standard deviation from healthy participants. This primary endpoint will be analyzed using T-test. The mean difference, its standard error (SE) and 95% confidence interval (CI) and corresponding p-value will be reported.

A scatterplot showing the composite scores in two cohorts with mean ± standard error of the mean (SEM) bars and a boxplot comparing the distribution in two groups will be provided.

8.3.3.2. Sensitivity Analyses for the Primary Outcome

Sensitivity analyses of the primary endpoint will be done similarly to the primary analysis while the values of TMT B test truncated at 240 seconds will be calculated or eliminated as described in Section 8.3.1.1. Namely, to investigate the influence of stopping patients at 240 seconds on TMT B test, we will run the following:

1) Sensitivity Analysis 1 in which we will calculate the value of TMT B outcome as $25 \cdot \frac{240}{L}$, where L is the order number of the last symbol reached in the TMT B test and $Time$ is the observed outcome of TMT B; For the HD-CAB and EFFB calculations the outcome of the adjusted TMT B test will be multiplied by -1 so that higher values represent better performance.
2) Sensitivity Analysis 2 in which the outcome of TMT B is a speed of completion calculated as $\frac{L}{Time}$, where L is an order number of the last symbol reached in the TMT B test and $Time$ is the observed outcome of TMT B;
3) Sensitivity Analysis 3 in which we will run the analysis only among participants with baseline values of TMT B <240 seconds.

In both analyses the rest of HD-CAB calculations will remain the same.

Scatterplots showing the composite scores in two cohorts with mean ± standard error of the mean (SEM) bars will be provided for sensitivity analyses.

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8.3.4.4. Sleep Diary

A summary of sleep diary and sleep length will be presented using descriptive statistics.

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8.4. Safety Analysis

Safety and tolerability of SAGE-718 is a secondary objective of this study. The incidence of adverse events/serious adverse events, and changes in vital signs and clinical laboratory parameters are secondary endpoints, change from baseline in electrocardiograms and responses on the Columbia-Suicide Severity Rating Scale are the other endpoints (Table 8). 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 in Table 9, Table 10 and Table 11.

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 last dose. Last value on treatment is defined as the last post-baseline value between first dose of IP (exclusive) and up to last dose of IP (inclusive). Last value on study is defined as the last post-baseline value after the first dose of IP.

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

Table 8. Summary of Safety Endpoints

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	*
C-SSRS		X*		X		

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Normal Range Shift from Baseline	Potentially Clinically Significant	Abnormality/ Clinical Significance
ECG = Electrocardiograms; C-SSRS = Columbia–Suicide Severity Rating Scale X = value will be summarized in tables * = value 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 9, Table 10 and Table 11). 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 9. Analysis Visit Windows for C-SSRS

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 35
Day 42 (±2 days)	42	≥36

Table 10. Analysis Visit Windows for Vital Signs

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 35
Day 42 (±2 days)	42	≥36

Table 11. Analysis Visit Windows for 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 35
Day 42 (±2 days)	42	≥36

8.4.1. Adverse Events

Adverse events will be coded MedDRA Version 25.1 Intensity/severity and relationship of AE will be evaluated by the investigator.

A TEAE will be assessed among HD patients and 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 D.

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 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.

- TEAE

- On-treatment TEAE
- Post-treatment TEAE
- TEAEs by maximum Severity
- TEAEs by relationship
- Serious TEAEs
- 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/PT will also be presented by the following subgroups:

- 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)
- Age group: ≤50, >50 years

A by-participant listing of all AEs, SAEs (including those with onset or worsening before the start of IP), TEAEs leading to death, TEAEs leading to IP withdrawal through the end of the study, TEAEs leading to withdrawal from the study, and most frequent (5%) TEAEs will be provided.

8.4.2. Clinical Lab

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

The actual results as collected will be displayed in the listings.

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 value 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 central laboratory. Shift from baseline to worst post-baseline values at any time on treatment, and shift from baseline to 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, after the last dose of treatment (follow-up period). PCS values will be identified for specific laboratory parameters as outlined in Table 12.

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 [(Alanine Aminotransferase or Aspartate Aminotransferase >3xULN) AND Alkaline Phosphatase <2xULN (any time post-baseline, measured at the same time point of assessment)]

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

Table 12. 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

Laboratory Parameter	Sex	Units	Criteria for PCS Values (Observed values)	
			High	Low
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 1 and 2 and triplicate 12-lead ECG under Original Protocol 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 QT corrected according to Fridericia's formula (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 Table 13 will be summarized by treatment for anytime on treatment, last value on treatment, after the last dose of treatment (follow-up period). Electrocardiogram findings will be listed by participant and visit.

Table 13. 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. This will also include the summary of last values on treatment and on study assessments. Potentially clinically significant values as outlined in Table 14 will be summarized by treatment and for anytime on treatment, last value on treatment, after the last dose of treatment (follow-up period). By-participant listing of vital signs will also be provided.

Table 14. 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
Diastolic blood pressure (supine and standing)	mmHg	>110	<50	≥20	≥20
Supine – Standing Systolic Blood Pressure	mmHg	≥20			

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCS values (Change from Baseline values)	
		High	Low	Increase	Decrease
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 42 (±2 days). 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. Columbia Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS is collected during the clinical visits at Screening, Days 1, 14, 28, and 42. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe).

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

The "Baseline/Screening" C-SSRS form will be completed at screening (lifetime history and in the past 1 month or past 1 year). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points.

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

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

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

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

Suicidal behavior is considered worse than suicidal ideation.

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

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

Summary of shift from baseline in C-SSRS suicidal ideation and suicidal behavior will be presented for the following categories (no suicidal ideation/behavior, suicidal ideation, and suicidal behavior) for each scheduled assessment time point. If there is no 'Yes' response to all assessments in suicidal ideation and behavior, then the category for the table is considered as 'No suicidal ideation/behavior'. If any of the assessments in suicidal behavior is Yes, the category is considered as 'Suicidal behavior'. If any of the assessments in suicidal ideation is Yes but all assessments in suicidal behavior is No, the category is considered as 'Suicidal ideation'. If the participant has both suicidal ideation as well as suicidal behavior, the participant will be counted under suicidal behavior only.

In addition, a summary of shift in suicidal ideation from baseline maximum rank score for anytime post-baseline maximum rank score will be presented. Maximum score 0 refers to all 'No' for all assessments in the desired period for all 5 questions on suicidal ideation. A graph of distribution of participants with suicide-related events based on the C-SSRS scores over time by treatment group will be generated. A listing of suicidal ideation and suicidal behavior will be provided.

8.4.7. Other Safety Analysis

Not applicable.

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9. SUMMARY OF INTERIM AND DMC ANALYSES

Not applicable.

10. REFERENCES

SAS® Version 9.4 of the SAS System for Personal Computers. Copyright ©2013. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

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11. LIST OF APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS – HUNTINGTON'S DISEASE

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

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

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

a. Both participants and study partners (if applicable) will be consented during the Screening Period.

b. Randomization will take place on Day 1, following all safety assessments (vital signs, physical examinations, 12-lead ECGs and clinical laboratory), eligibility requirements (C-SSRS, urine drug, alcohol and pregnancy testing) and confirmation of inclusion/exclusion criteria.
c. In addition to full medical history, all medications and supplements taken within 8 weeks prior to Screening, all medications used to treat HD regardless of timing, and all nonpharmacological methods (eg, psychosocial, psychotherapeutic) used to treat or prevent neuropsychiatric, functional, and cognitive manifestations of HD will be recorded. Information regarding diagnosis and/or hospitalization due to COVID-19 will be documented as part of medical history regardless of timing. The following demographics will be collected: age, race, sex, ethnicity, years of education, employment history, and current employment status.
d. Participants and study partners (if applicable) will be trained by study staff on the use of software applications and devices necessary for the conduct of the study.
e. Vital signs will include temperature, respiratory rate, heart rate, and blood pressure. Heart rate and blood pressure to be collected in supine position and standing position at all scheduled time points.
f. A full physical examination is to be conducted during Screening (Days -28 to -2) and at Day 42 (±2 days)/ET. At other visits [eg, Day 28 (±2 days) for participants with HD], physical examinations will include a brief assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems and followed by a targeted physical assessment as needed. A symptom-directed examination may be conducted at any time at the discretion of the investigator.
g. Test results of genetically confirmed disease with CAG expansion ≥36 collected as part of medical history is acceptable in lieu of central laboratory confirmation. For any genetic counseling, the study sites should follow their local practice.
h. Serum FSH test will be conducted at Screening for the female participants who are not surgically sterile to confirm whether a female participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal.
i. To include hepatitis B and C screening tests, HIV-1 and -2 antibody.
j. A single ECG will be measured after the participant has been in the supine position for at least 5 minutes. When ECG measurements coincide with vital signs assessment or blood draws, blood draws should be carried out after ECG and vital signs.
k. Clinical laboratory assessments will include blood samples for hematology, clinical chemistry, biochemistry, coagulation, genetic testing, and urinalysis. Samples will be collected ≤2 hours prior to dosing on Days 1 to 28. On nondosing days, collection may occur at any time.

[redacted]

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

[redacted]

t. Cognitive tests at all time points will be performed at the same time of day (±2 hours) and will be conducted predose on Day 1 only, and postdose on Day 14 (±2 days) [redacted]. The cognitive tests include the Huntington's Disease Cognitive Assessment Battery (HD-CAB; Symbol Digit Modalities Test, One Touch Stockings of Cambridge, Trail Making A and Trail Making B, Hopkins Verbal Learning Test_Revised, Paced Tapping Test, and Emotion Recognition Test) [redacted]

x. Daily reminders will be sent to participants via a mobile device to complete assessments on remote device. Daily assessments include [redacted] the National Sleep Foundation Sleep Diary. It is recommended that these assessments are completed at approximately the same time each day, within 1 hour following IP administration. Daily mobile assessments should be completed in a quiet area of participant's home. If in conflict with clinic visit schedule, remote assessment may be completed in the clinic under observation by the study staff.

y. On Days 1, 14, and 28 study visits, participants will self-administer IP in the clinic under the supervision of study staff. All scheduled safety assessments will be conducted prior to dosing. All scheduled cognitive tests will be administered predose on Day 1 Visit only and postdose on Day 14 Visit (±2 days) and Day 28 Visit (±2 days). Participants will record the date and time of each dose taken at home and in-clinic using an application.

z. Study staff will dispense enough IP for the participant to take daily at home until the next scheduled visit.

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

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

APPENDIX B. SCHEDULE OF ASSESSMENTS – HEALTHY PARTICIPANTS

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

Assessments	Screening Period		Reliability Assessment Period			Follow-up
	Days -28 to -2	Day -1	Day 1	Day 14 (±2 days)	Day 28 (±2 days)	Day 42 (±2 days) or ET
Prior and concomitant medications	X----------					----------X

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

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

p. Daily reminders will be sent to participants via a mobile device to complete assessments on remote device. Daily assessments include [redacted] the National Sleep Foundation Sleep Diary. It is recommended that assessments are completed at approximately the same time each day. Daily mobile assessments should be completed in a quiet area of participant's home. If in conflict with clinic visit schedule, remote assessment may be completed in the clinic under observation by the study staff.

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

APPENDIX C. DETAILS OF STATISTICAL METHODOLOGY

Sample SAS Code for T-test

```
proc ttest data=data sides=2 alpha=0.05 h0=0 test=diff;
    class subjgrp;
    var aval;
    ods output statistics=statistics ttests=ttests equality=equality;
run; *Note: if probf > 0.05 reading results from pooled method, if probf > 0.05 reading
results from satterthwaite method;
```

APPENDIX D. 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 + 1 day.
  - 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

If the medication start date is completely missing, do not impute a date but consider it as concomitant, unless the medication end date is before the initiation of IP for HD or day 1 for HP, in which case the medication will be considered prior.

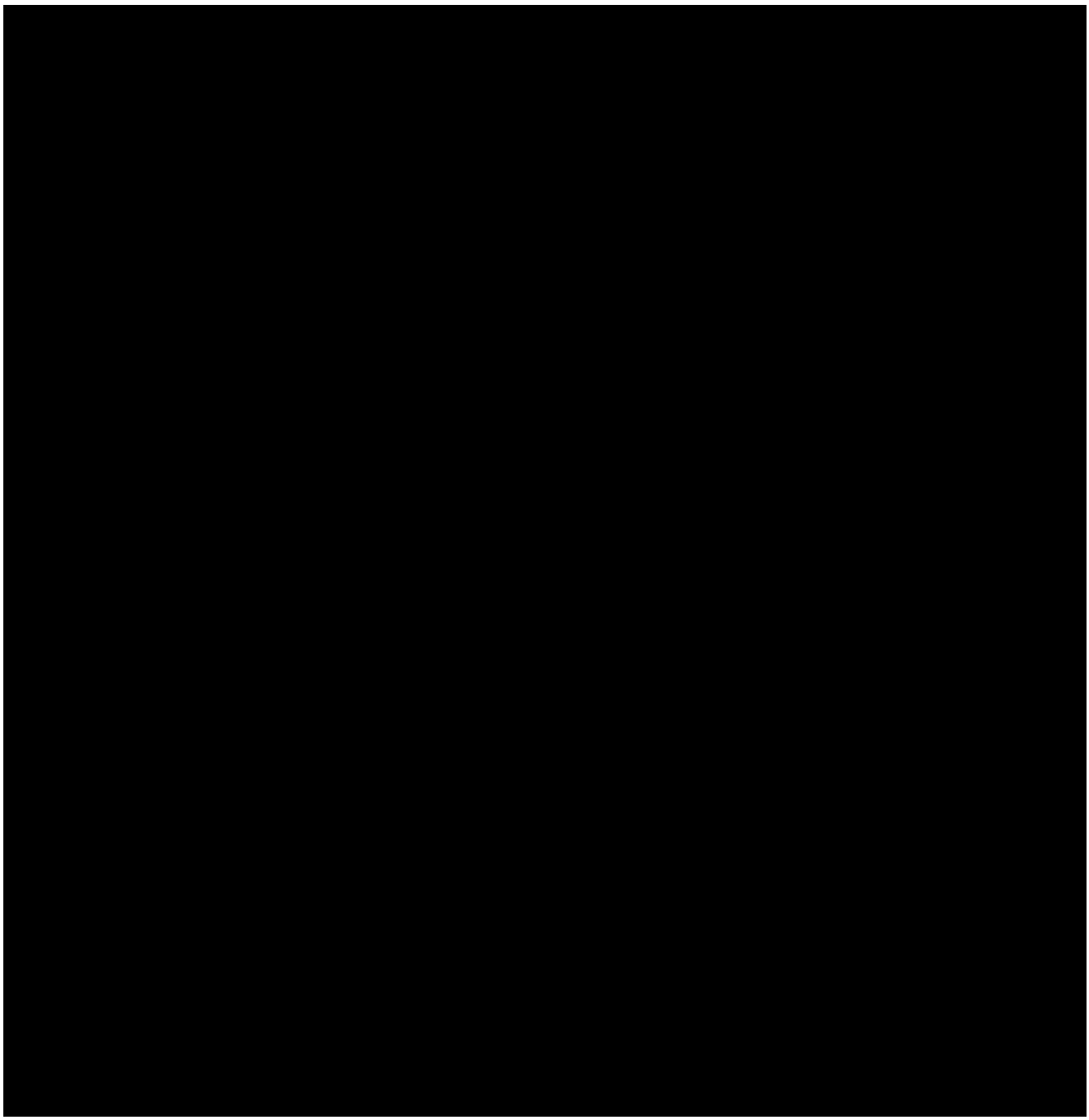
For the partial start date of medication:

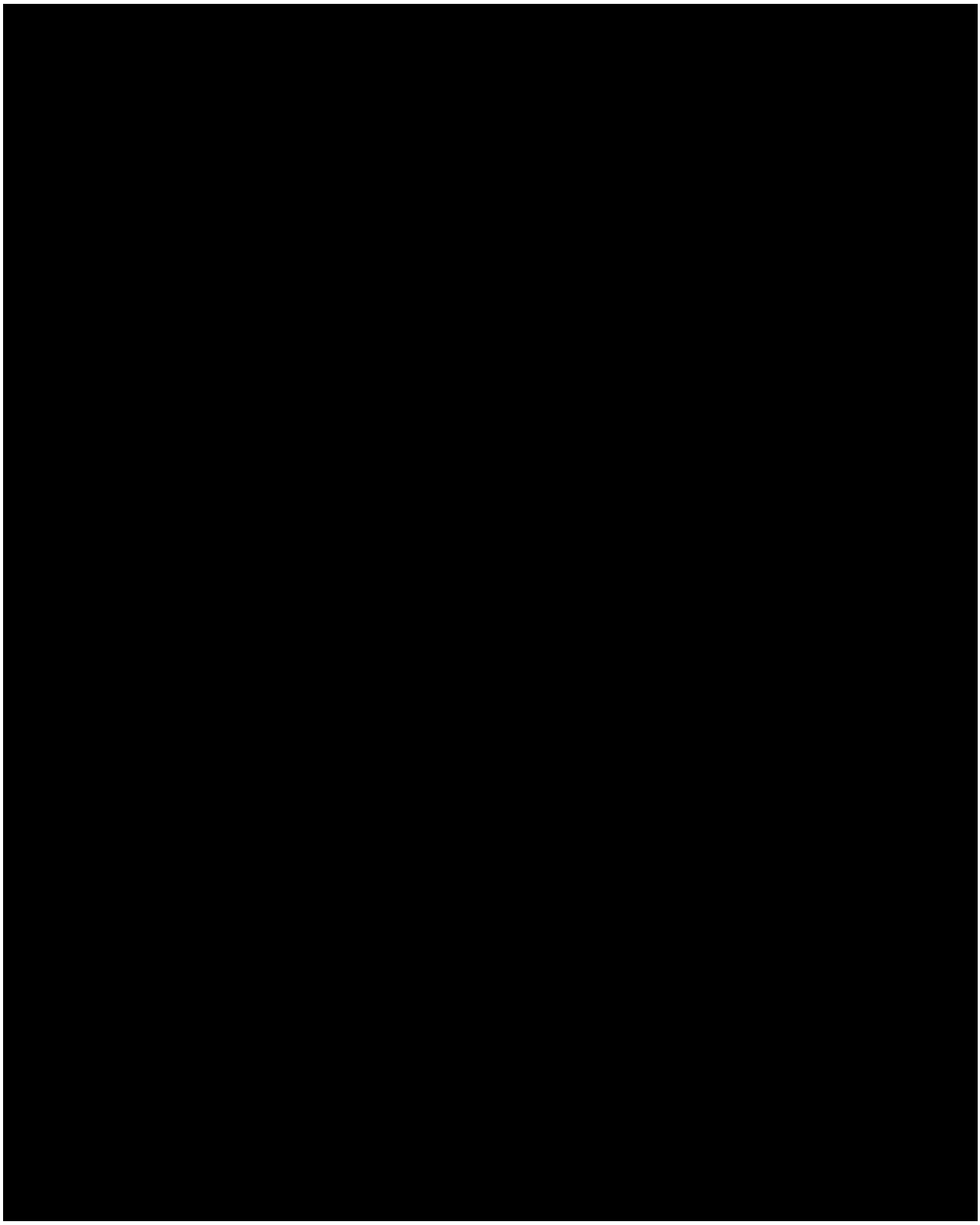
- If the year is present and the month and day are missing, then the month and day will be set to January 1 unless the year is the same as the first dose date then impute the first dose date.
- If the year and day are present and the month is missing, then t treat it as if the day is missing and only year is present. Follow the imputation rules for "year is known, but the month and day is unknown".
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month unless the month is the same as the date of the first dose then impute as the date of the first dose.
- 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.

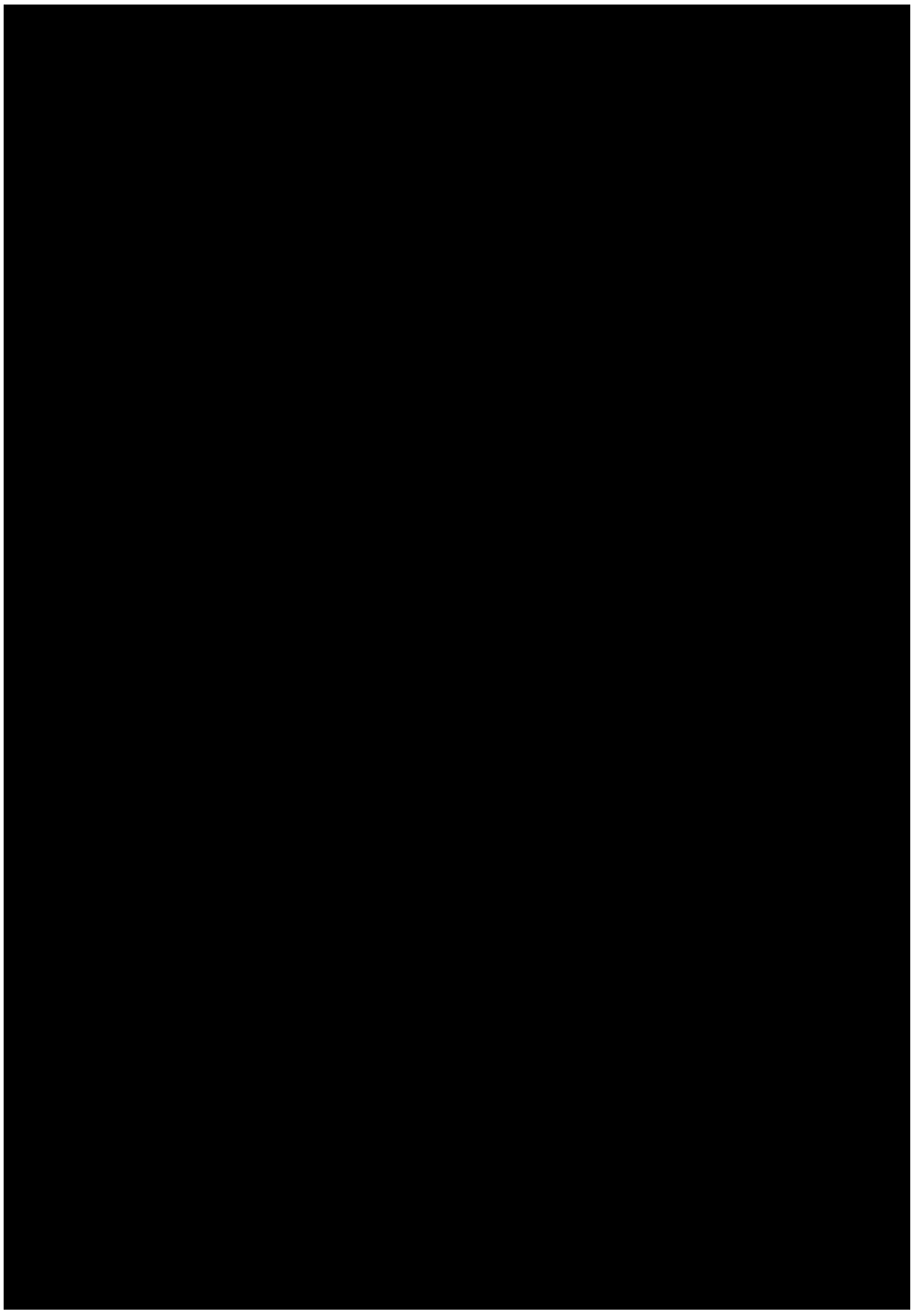
If the medication end date is completely missing, do not impute a date but consider it as concomitant.

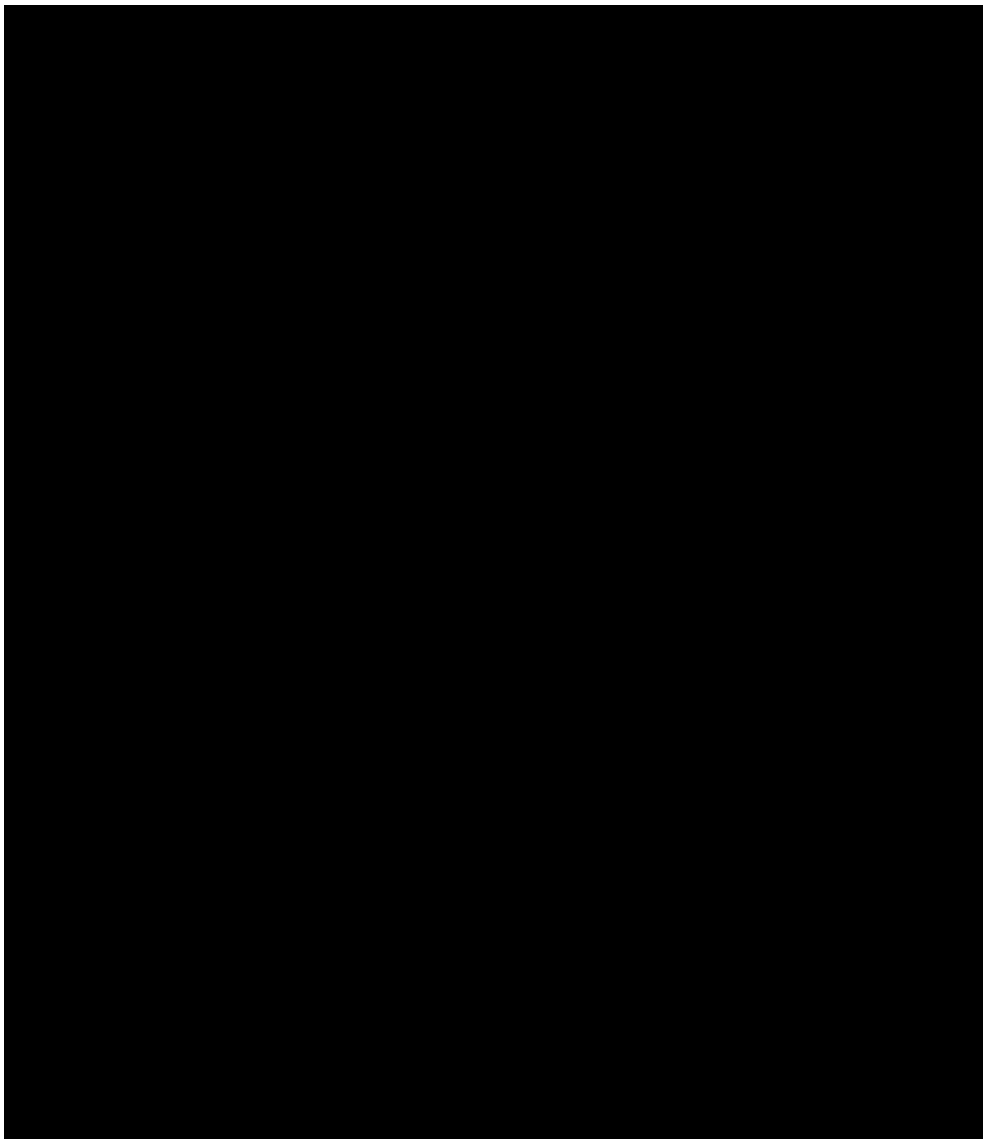
For the partial end date of medication:

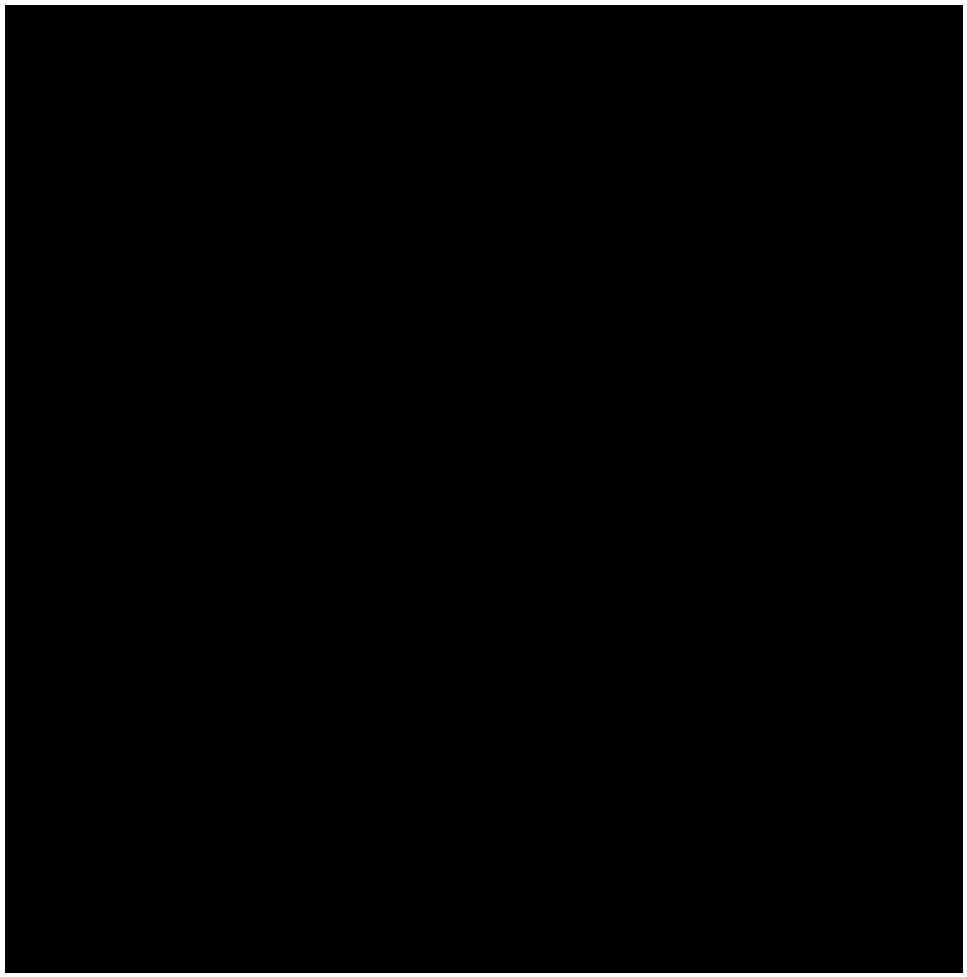
- If the year is present and the month and day are missing, then the month and day /will be set to December 31.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month.
- If the year and day are present and the month is missing, then treat it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

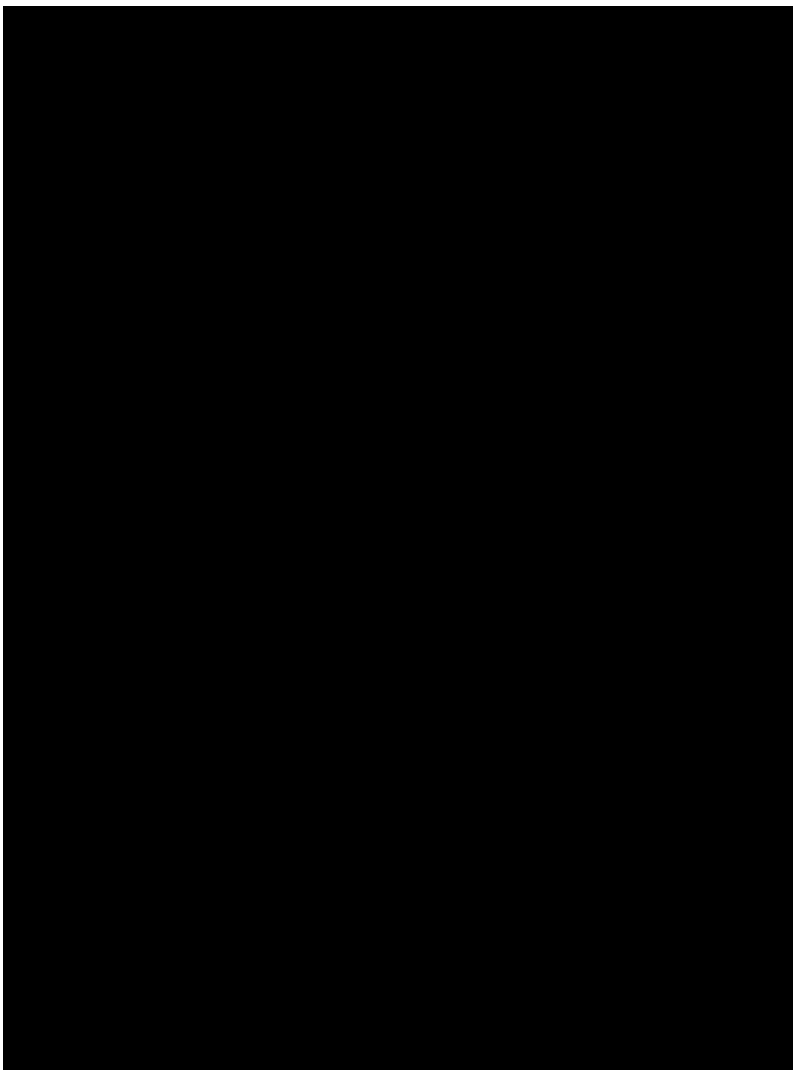


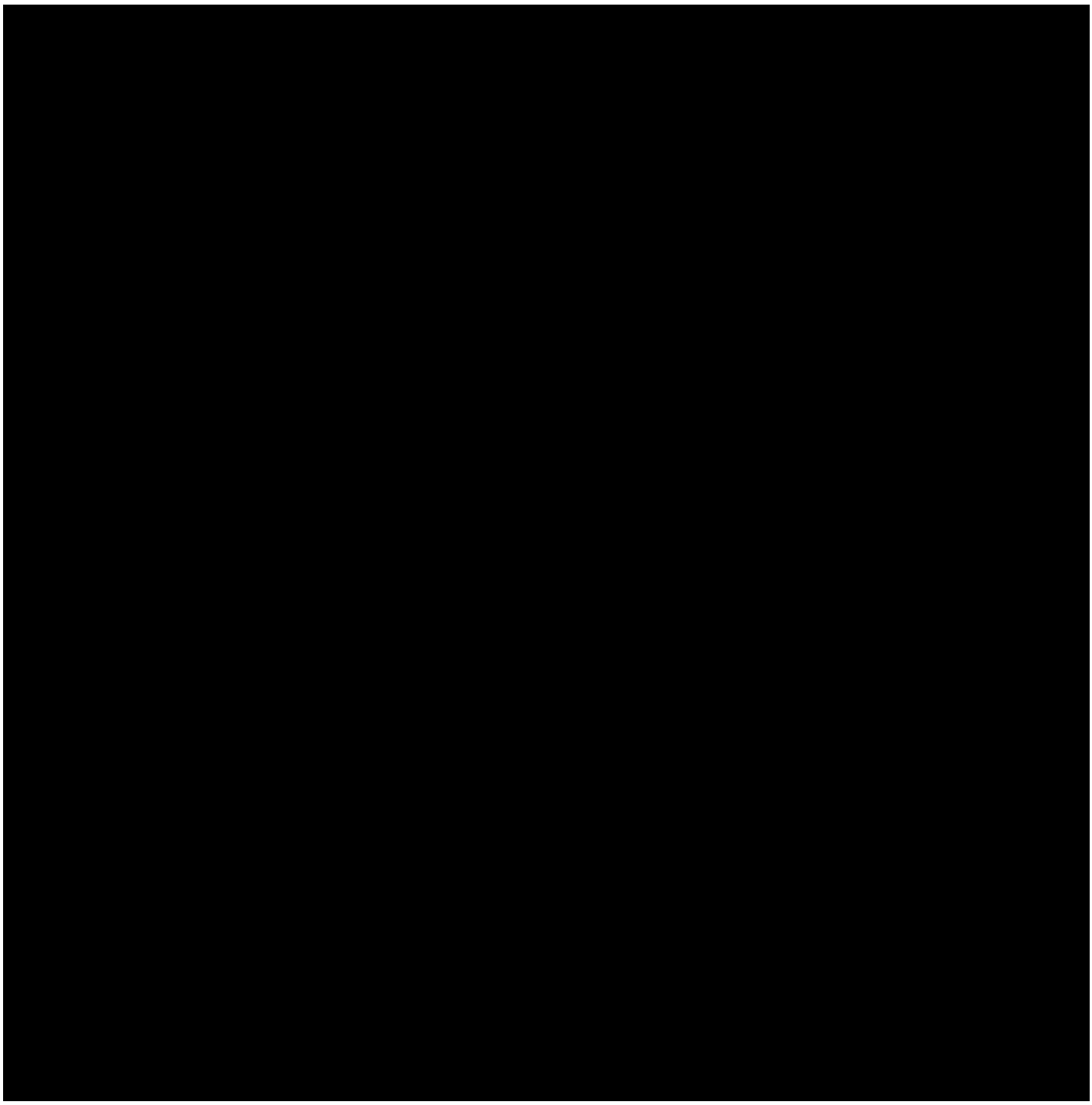












APPENDIX F. ANTIDOPAMINERGIC MEDICATIONS

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

Neuroleptics:

Aripiprazole

Quetiapine

Olanzapine

Risperidone

Clozapine

Ziprasidone Hydrochloride

Anti-Chorea Meds:

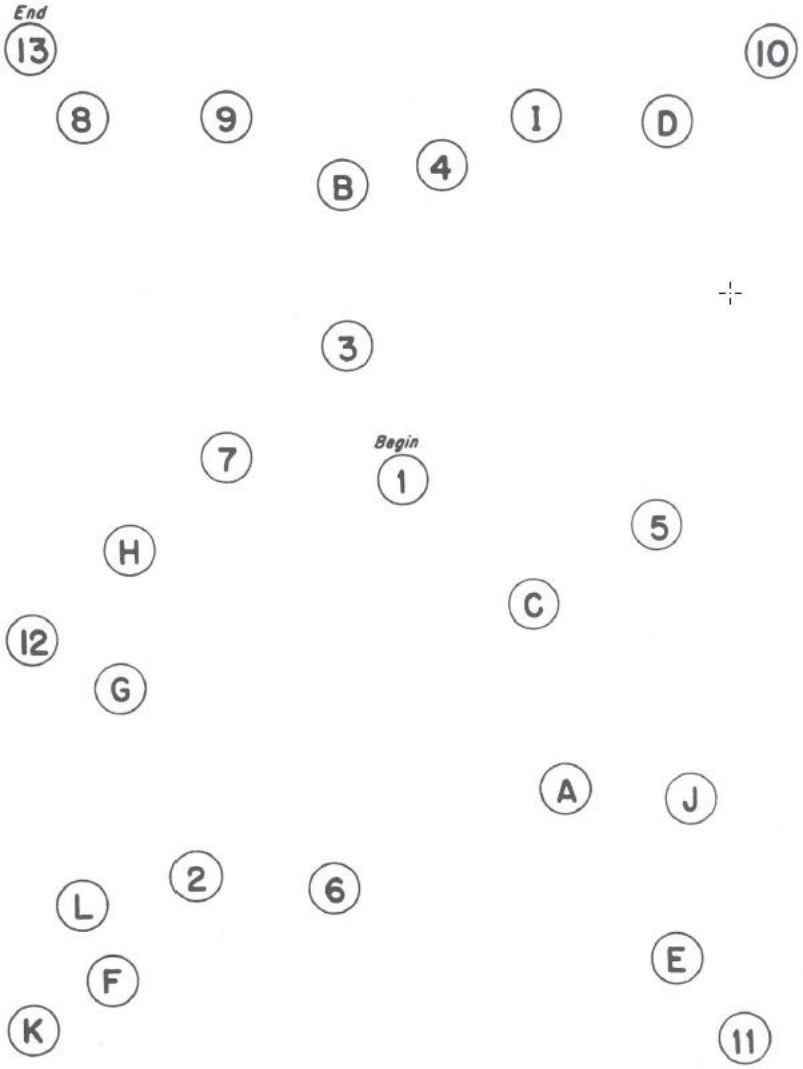
Valbenazine

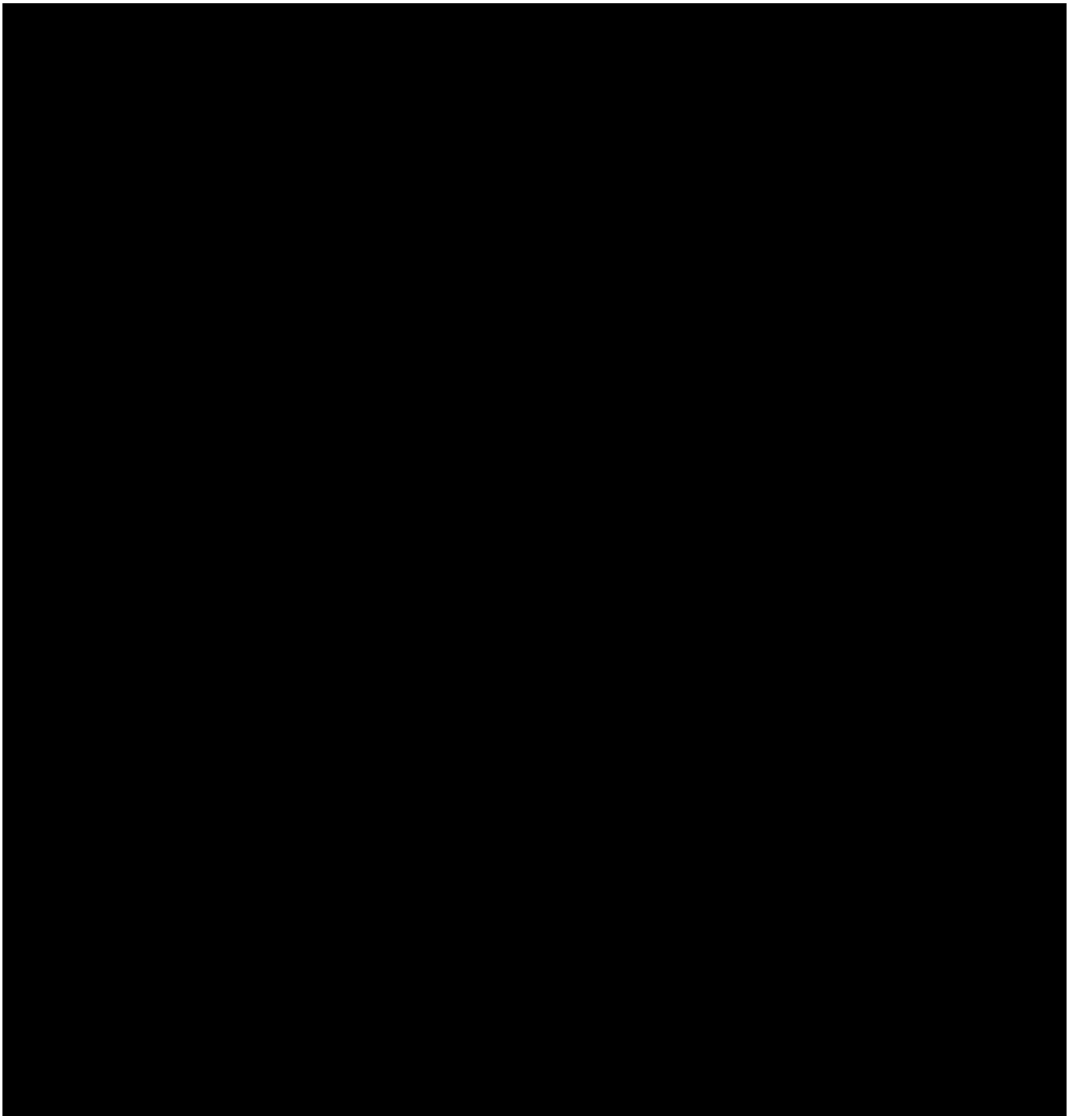
Tetrabenazine

Deutetrabenazine

APPENDIX G. TRAIL MAKING TEST: TRIAL B

An example of the Trail Making Test: Trial B (TMT B) is presented below. The number in the path can be ordered as 1 is 1st, A is 2nd, 2 is 3rd, B is 4 th, …, 13 is 25th. As you can see, the test has 25 symbols and their numbers of order will be used in the calculations of TMT B outcomes as defined in Section 8.3.1.1.





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