Official Title:	**An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease**
NCT Number:	NCT04602624
Document Date:	SAP Version 1.0: 01 November 2021

9. STATISTICAL METHODS ANALYSIS PLAN

Statistical Analysis Plan (SAP) v1.0, 01 Nov 2021

[redacted]

Statistical Analysis Plan (SAP)

Protocol Title:	An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive Impairment or Mild Dementia Due to Alzheimer's Disease
Protocol Version No./Date:	2.0/23-Sep-2020
CRF Version No./Date:	1.0/07-Apr-2021
SAP Version No./Date:	1.0/01-Nov-2021

1.0 Approvals

Sponsor	
Sponsor Name:	Sage Therapeutics, Inc.
Representative/ Title:	[redacted] DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 01-Nov-2021 | 11:34 EDT [redacted]
Signature /Date:	
Representative/ Title:	[redacted] DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 01-Nov-2021 | 11:49 EDT [redacted]
Signature /Date:	
PRA	
[redacted] **/ Title:**	[redacted]
Signature /Date:	[redacted] Signed by: [redacted] Reason: I am approving this document Date & Time: 01 Nov 2021 08:44 AM -06:00 DocuSign
Biostatistician (Owner) / Title:	[redacted], Principal Biostatistician
Signature /Date:	[redacted] Signed by: [redacted] Principal Biostatistician Reason: I am approving this document. Date & Time: 01 Nov 2021 10:24 AM -04:00 DocuSign

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
0.1 / 28-Oct-2020	Created as a new, Stable version
1.0 / 01-Nov-2021	Final Signed version

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Sage Therapeutics Protocol 718-CNA-201: An Open-Label Evaluation of the Safety and Tolerability of SAGE-718 in Participants with Mild Cognitive or Mild Dementia due to Alzheimer's Disease (AD).

5.0 Scope

This SAP describes the statistical methods to be used during the reporting and analyses of data collected from Sage Therapeutics Protocol 718-CNA-201, titled "An Open-Label Evaluation of the Safety and Tolerability of Sage-718-201 in Participants with Mild Cognitive or Mild Dementia due to AD

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Endpoints
- The Analysis sets
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This is an open-label study evaluating the safety and tolerability of SAGE-718 [redacted] s in participants with MCI or mild dementia due to AD. Eligible participants with a confirmed diagnosis of MCI or Mild dementia due to AD, according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines, which will be confirmed via the CDR® Dementia Staging Instrument at screening will receive a 3.0 mg dose of SAGE-718 daily for 14 days.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol Version 2, dated 23 September 2020 and CRF dated 07-Apr-2021.

Changes to the protocol will require an SAP amendment ONLY if the changes are to a principal feature of the protocol.

Final approval of the SAP by the Sponsor and PRA will occur prior to database lock. Any changes made to the SAP after the clinical database lock, along with the justification for the changes, will be described in the CSR.

6.1 Changes from the Protocol

- Protocol section 13.6.6 mentions the prior and concomitant medications will only be listed. Along with the listing a summary table will also be provided.
- Protocol section 13.4 mentions that Medical history will be only listed. Besides listing medical history will also be summarized.

- Alzheimer's disease history will be summarized and listed as per the data collected on the CRF page.

[redacted]

7.0 Protocol Modifications

7.1 Modifications to the Approved Clinical Study Protocol

Protocol version 2.0 is amended to revise the scheduled procedures and eligibility criteria to include more prospective participants.

7.2 Modifications to the Approved Statistical Analysis Plan

This is the first version of SAP

7.3 Modifications to the Approved DMC Charter

Not applicable

8.0 Study Objectives

8.1 Primary Objective

- Evaluate the safety and tolerability of orally administered SAGE-718 in participants with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD).

[redacted]

9.0 Study Endpoints

9.1 Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs)

9.2 Secondary Endpoints

- Change from baseline in vital signs, clinical laboratory analytes, and electrocardiograms (ECGs).
- Change from baseline for responses on the Columbia–Suicide Severity Rating Scale (C-SSRS).

[redacted]

[redacted]

10.0 Study Design

10.1 Overall Design

This study will enroll up to 22 participants that complete 14 days of dosing in this study. Additional participants may be dosed if the early discontinuation rate is >10%. Participants will be enrolled from approximately 5 sites in the US.

This is an open-label study evaluating the safety and tolerability of SAGE-718 [redacted] in participants with MCI or mild dementia due to AD. Eligible participants with a confirmed diagnosis of MCI or mild dementia due to AD, according to the National Institute on Aging-Alzheimer's Association 2011 diagnostic guidelines, which will be confirmed via the CDR® Dementia Staging Instrument will receive a 3.0 mg dose of SAGE-718 daily for 14 days within 1 hour of 30g fat meal.

The study consists of a Screening Period, a Baseline Period, a Treatment Period, and a Follow-Up Period. The Screening Period begins with the informed consent process for prospective participants, including caregivers. Subsequent screening assessments will be performed between Day -21 and Day -8 to determine eligibility, including assessments of [redacted] vital signs, clinical laboratory tests, electrocardiogram (ECG), magnetic resonance imaging (MRI) of the brain, and C-SSRS. An electroencephalogram (EEG) will also be performed preferably not in a fasting state.

The Baseline Period will occur from Day -7 through Day -1. During this period, each participant will receive dietary counseling to aid in choosing a morning meal containing approximately 30 g fat for dosing. On Day -7 (±1 day), participants will visit the clinic for confirmation of continued eligibility

and collection of baseline [redacted] safety data.

The Treatment Period will begin on Day 1 and continue through Day 14. During this time, participants will self-administer 3.0 mg SAGE-718 (as six 0.5-mg oral tablets), once per day in the morning within 1 hour after initiating a meal containing approximately 30 g of fat. Participants will continue [redacted] in the clinic at scheduled visits and will track IP dosing and predose food intake in a participant diary. Participants will complete daily remote assessments [redacted]. Treatment Period clinic visits will occur on Day 1, Day 7 (±1 day), and Day 14. Following pre-dose procedures, participants will eat a morning meal and take the IP under staff supervision within 1 hour after initiating the meal. At scheduled clinic visits during the Treatment Period, safety, [redacted] will be performed, and study staff will dispense a sufficient amount of SAGE-718 for daily administration until the next scheduled study visit. In addition to weekly clinic visits, study staff will contact participants by telephone on Day 4 to document any TEAEs and/or changes in concomitant medications

The Follow-Up Period, study staff will contact participants by telephone on Day 21 to document any TEAEs and/or changes in concomitant medications. Participants will then return to the clinic on Day 28 (±2 days) for a follow-up visit.

No formal interim analysis or DSMB review are planned for this study.

10.2 Sample Size Considerations

No formal sample size calculation was made for this study. Twenty participants completing 14 days of dosing are considered sufficient to assess preliminary safety and tolerability and for preliminary signal-finding [redacted] after 14 days of repeated dosing with of SAGE-718. Assuming a 10% dropout rate, approximately 22 total participants will be required to obtain 20 completers. Additional participants may be dosed if the early discontinuation rate is >10%.

10.3 Randomization

This study does not involve any randomization of participants.

11.0 Analysis Sets

11.1 Safety Set

The Safety Set will include all participants who were administered at least one dose of investigational product (IP). Safety set will be used to describe the safety data.

[redacted]

12.0 Interim Analyses

There are no planned interim analyses for this study.

13.0 Statistical Methods

13.1 General Statistical Methodology

All analyses will use SAS version 9.4 or higher.

Unless otherwise noted, continuous variables will be summarized using the number of observations (n), mean, standard deviation (std), median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. The minimum and maximum values will be displayed to the same level of precision as the raw data; the mean, median, Q1, and Q3 values to one additional decimal place and the standard deviation to two additional decimal places.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places, and percentages will not be displayed for zero counts.

All participants will be used in the analyses as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data.

For the purpose of all safety, [redacted] analyses, where applicable, baseline is defined as the last assessment prior to the first dose of study IP.

[redacted]

Prior and concomitant medication start/stop date imputation and adverse event start/stop date imputation are described in Appendix-B and Appendix-C, respectively.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. All TEAEs are defined as an AE with onset after the first dose of IP.

13.2 Participant Analysis Sets

The number and percentage of participants in the FAS, Safety, [redacted] sets will be provided.

13.3 Participant Disposition

The number and percentage of participants screened, screen failed, enrolled in the study will be presented, together with the number and percentage of participants who discontinued from the study prematurely and a breakdown of the corresponding reasons for discontinuation as well as the number and percentage of participants who discontinued early from treatment and corresponding reasons.

Participant disposition will be summarized overall for the Safety analysis set, including the following:

- Number and percent of participants who completed the study
- Number and percent of participants who did not complete the study and reasons for early discontinuation of study

A by-participant disposition listing will be provided. In addition, a separate listing of screening failures with the primary reason for screen failures will be provided.

13.4 Eligibility Criteria Violations and Protocol Deviations

Protocol deviations identified during the study will be captured and categorized by the study team review as major and minor deviations on an ongoing basis. 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, investigational product administration, and others will be documented and analyzed as appropriate.

[redacted]

A by-participant listing of all protocol deviations will be provided with columns identifying the following: date of the deviation, type of deviation (Major/Minor), deviation category, and verbatim description.

13.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics, such as sex, race, age, height (cm), baseline weight (kg) body mass index (BMI) (kg/m^2), and Clinical Dementia Rating (CDR) will be summarized using the Safety analysis set. Data will be summarized using descriptive statistics including sample size (n), mean, std, median, Q1, Q3, minimum, and maximum for continuous variables and numbers and percentages of participants for categorical variables.

Alzheimer's disease history will be summarized and listed by participants.

The baseline for weight, height and BMI is defined as the last non-missing value prior to the first dose of investigational product.

13.6 Medical and Surgical History

Medical/surgical history collected at screening will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1. Medical/surgical history data will be summarized by system organ class (SOC) and preferred term (PT). A summary of medical/surgical history that is ongoing at the time of screening will be provided separately. Medical/surgical history will also be listed.

MRI results and amyloid-PET results will be listed by participants.

13.7 Physical/Neurological Examinations

A physical examination will be conducted at Screening (Day -21 to Day -8) and baseline (Day -7 and Day -1), as well as Days 14 and ET.

A full physical examination will occur at Screening and will include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as neurological examination. Thereafter abbreviated physical examinations will include assessment of general appearance, cardiovascular, respiratory, gastrointestinal, and neurological systems, followed by a targeted physical examination as needed.

Clinically significant abnormalities found during Screening or during clinic visits will be reported on the medical history CRF; record clinically significant abnormalities or worsening conditions will be reported on the adverse event CRF, hence will be captured in AE displays. Therefore, no summaries will be provided for physical/neurological examinations.

13.8 Prior and Concomitant Medications

The following analyses will use the Safety Set

All medications taken and procedures undergone during the study will be recorded.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken prior to the initiation of the start of the investigational product, and that ended prior to the IP. Concomitant medications are defined as those with a start date on or after the first dose of investigational product or those with a start date before the first dose of investigational product that is ongoing or with a stop date on or after the first dose of investigational product.

13.9 Treatments

13.9.1 Extent of Investigational Product Exposure and Treatment Adherence

The following analyses will use the Safety Set.

Total drug exposure (in mg) is defined as the total investigational product in mg for SAGE-718 that was taken during the study.

Total exposure duration to investigational product (in days) is defined as Date of last dose – date of first dose + 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. For participants who complete the treatment period, planned exposure is 14 days of treatment planned times 3 mg. For participants who discontinued the treatment early, the planned exposure is the number of days (last date – first dose date + 1), times 3 mg.

Investigational product adherence (%) is defined as the number of tablets taken, divided by the number of tablets planned to be taken, times 100. The schedule of investigational product is six tablets per day. The number of tablets planned to be taken is defined as follows:

If the participant discontinues treatment within Day 2 and Day 14 (both inclusive), the number of tablets planned to be taken is the last dose day of investigational product × 6.

If the participant does not discontinue treatment, the number of tablets planned to be taken is 84 (6x14).

Investigational product exposure and adherence will be summarized descriptively and listed. The number and percentage of participants with investigational product adherence in categories(<80%, 80-100%, >100%) will be provided. Investigational product accountability will be listed.

All investigational product exposure data will be in by-participant listings, as well as a summary of treatment adherence.

13.10 Visit Windows

The scheduled visits will not be windowed and will be used at a nominal visit value for analysis purposes. The unscheduled and early termination (ET) visit will be mapped to a scheduled visit for analysis. In order to accommodate as much data as possible into analysis, the windows in the table below have been widened compared to protocol-specified operational window, to have no gap between them; these windows are used for analysis purposes only. Once analysis visit windows are assigned, all visits, including scheduled visits, unscheduled visits, and ET visits will be eligible for being flagged as the "analyzed record" within the analysis window; a participant's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in

case of a tie, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If the data from the scheduled visit is available, then the scheduled visit data will be used.
- If there is no data from the scheduled visit is available, the data closest to the scheduled study day for that window will be used.
- If there is a tie between the data in the number of days before and after the scheduled day, the later data will be used.

Table 1: Visit Windows for [redacted] Analysis

Scheduled Visit (+/1 window days) in protocol	Target Study Day	Study Day Window for Visit in Analysis
Day 1	Day 1 (predose)	Day 1 (predose) or last non-missing assessment before pre-dose regardless of scheduled or unscheduled visits
Day 7 (±1 day)	Day 7	Day 2 - Day 10
Day 14 (+1 day)	Day 14	Day 11 - Day 17
Day 28 / last dose + 14 days (±2 day)	Day 28 (last dose date + 14 days)	>= Day 26 (last dose date +12 days)

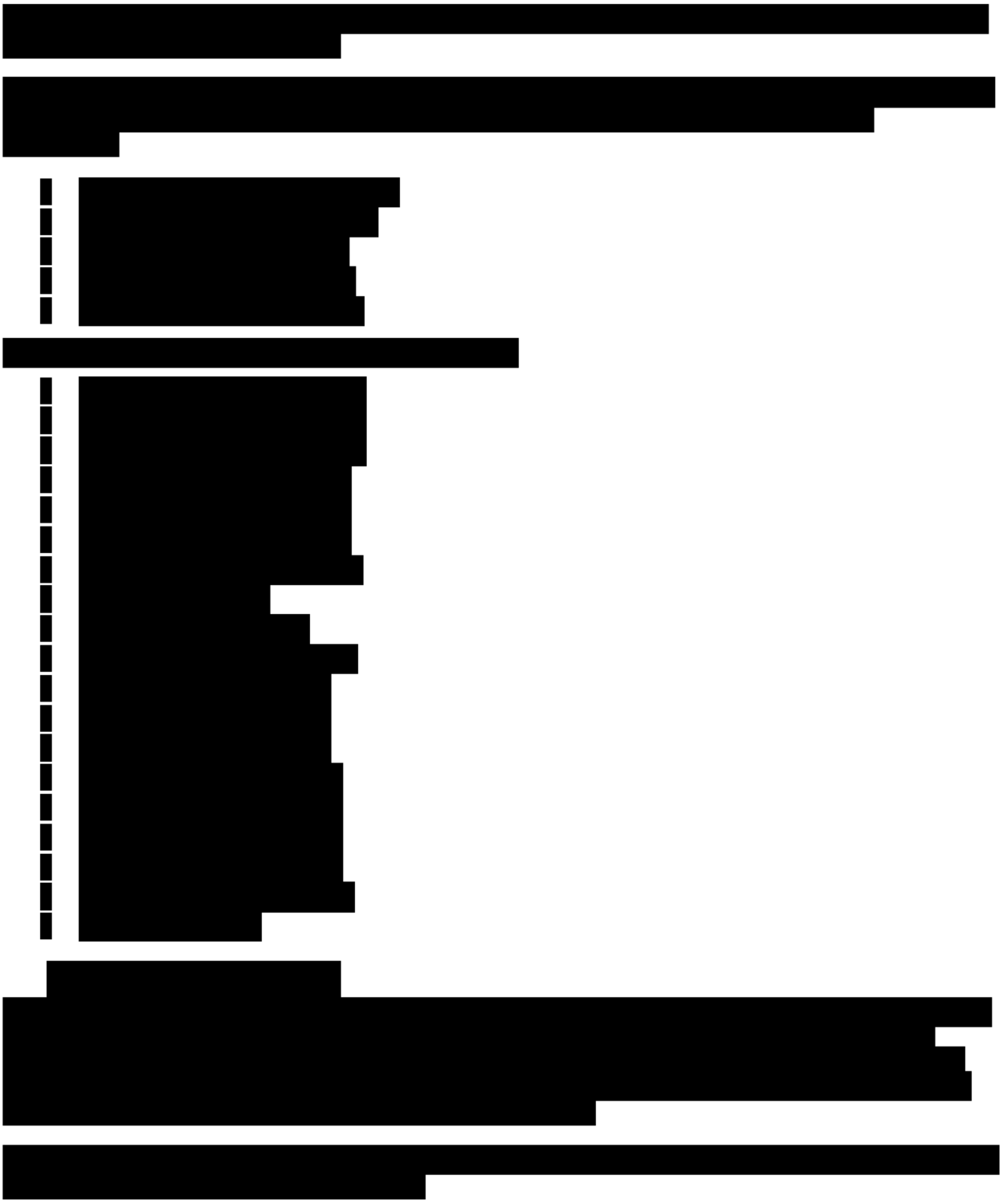
Note: Parenthesized study day and study day window are for unscheduled visits, EOT and ET for participants who have discontinued treatment prematurely and such visit date is ≥4 days from the last dose of investigational product intake (ie, visit date – last dose date + 1 > 4).

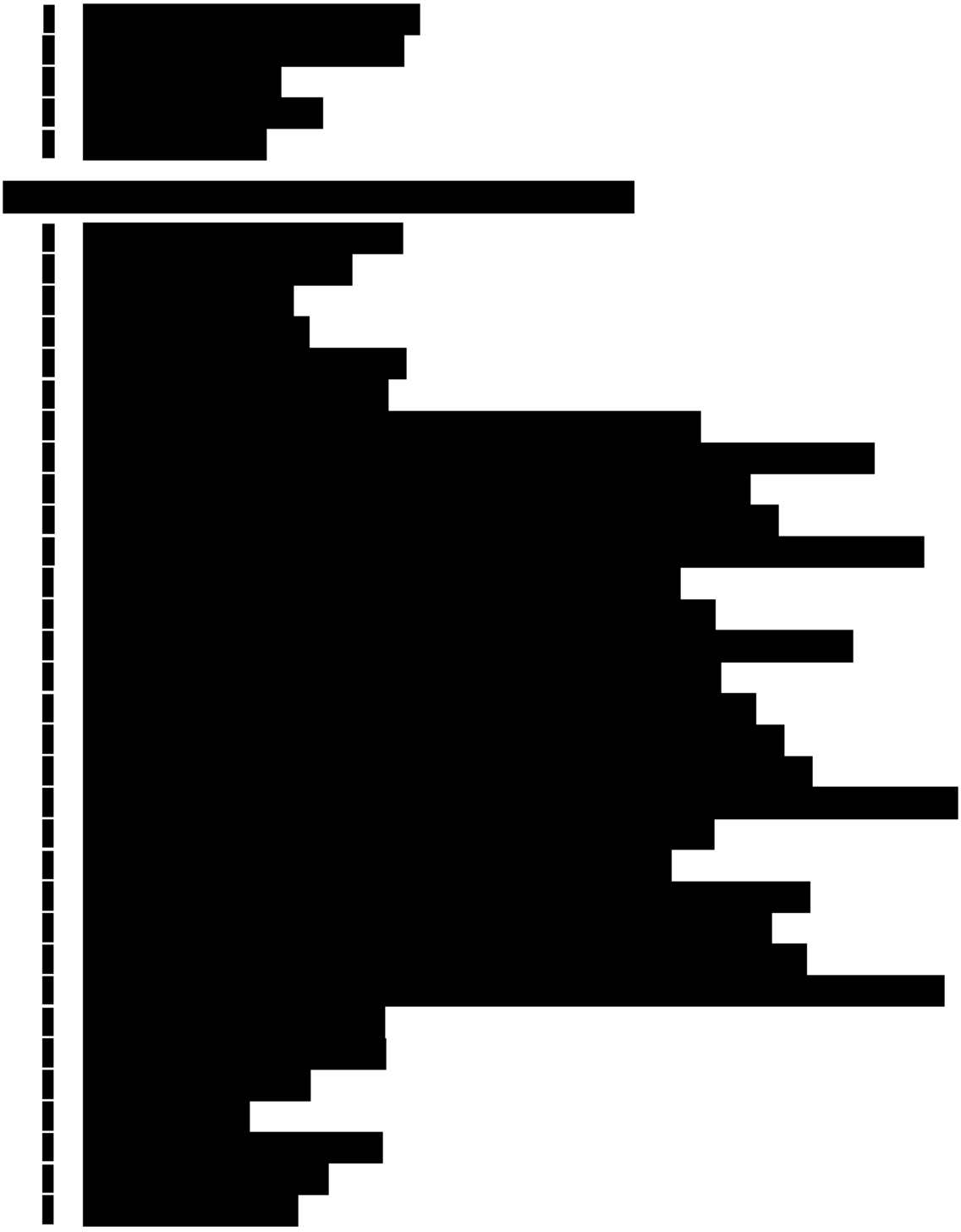
The summary by visit will use the "analyzed records" only – at most one per participant. The data not flagged as the "analyzed record" will be included in listings. An unscheduled visit that does not fall under any analysis window will remain in the database and will be included in the listings.

[redacted]

[redacted]

[redacted]





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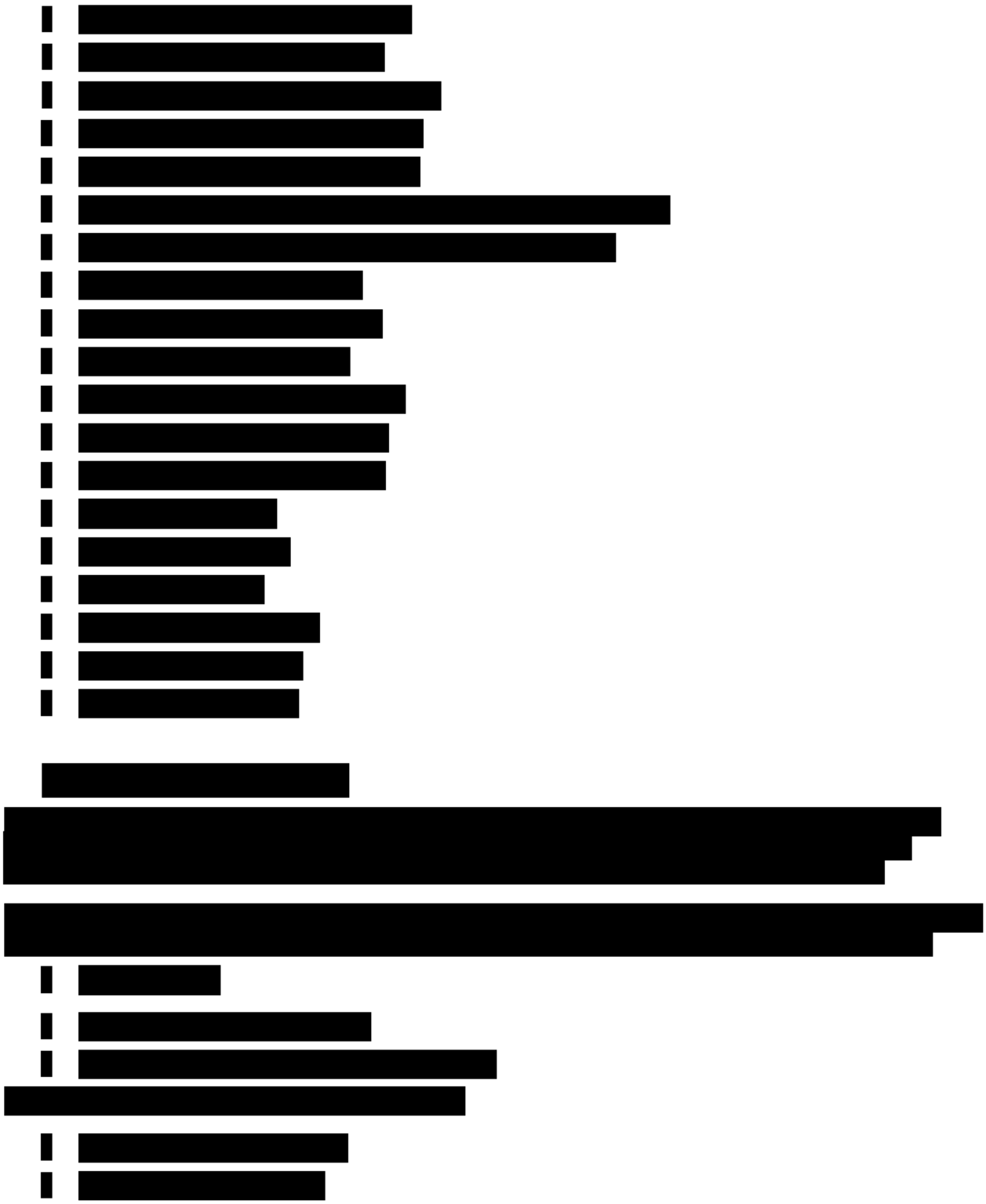

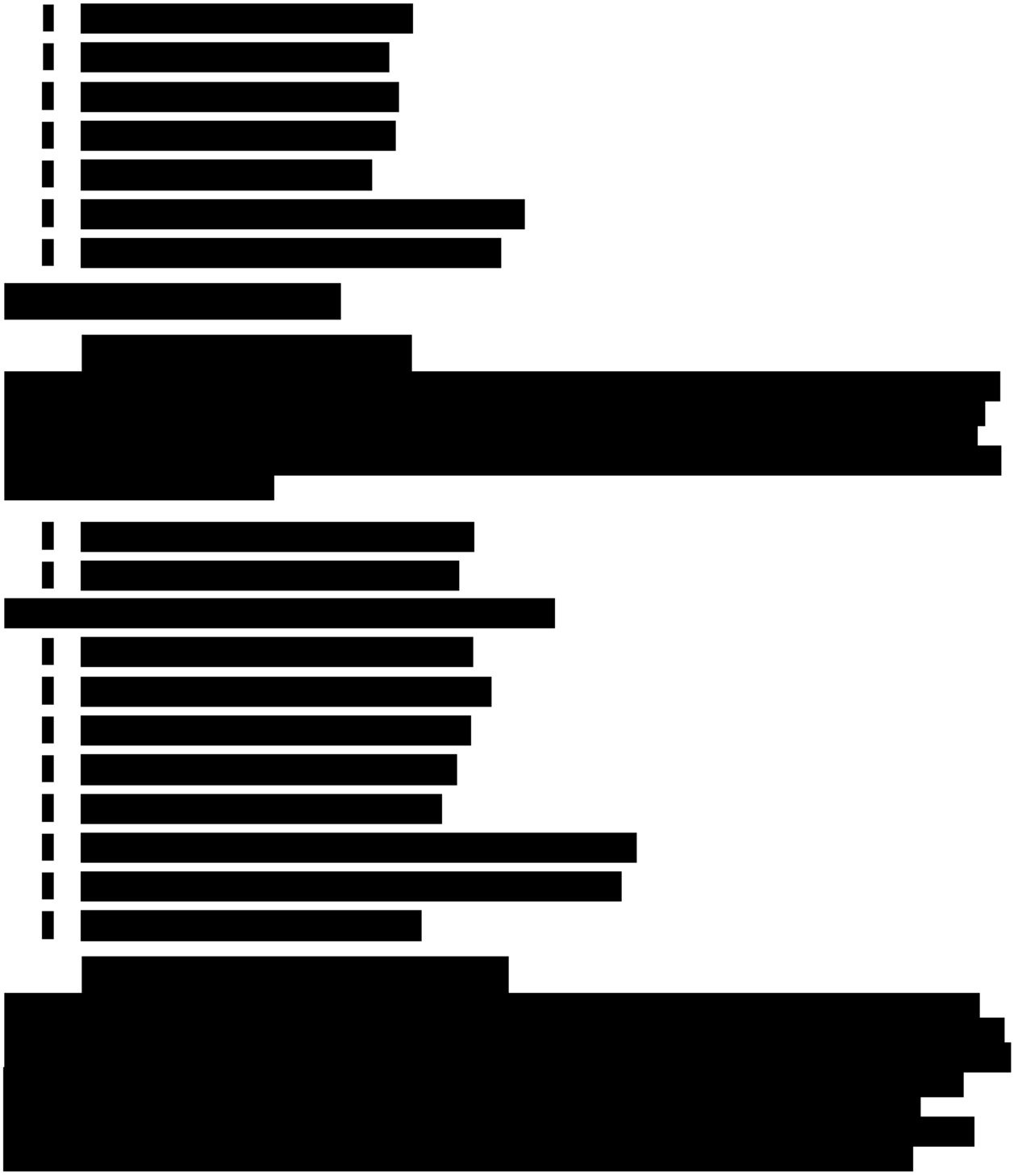

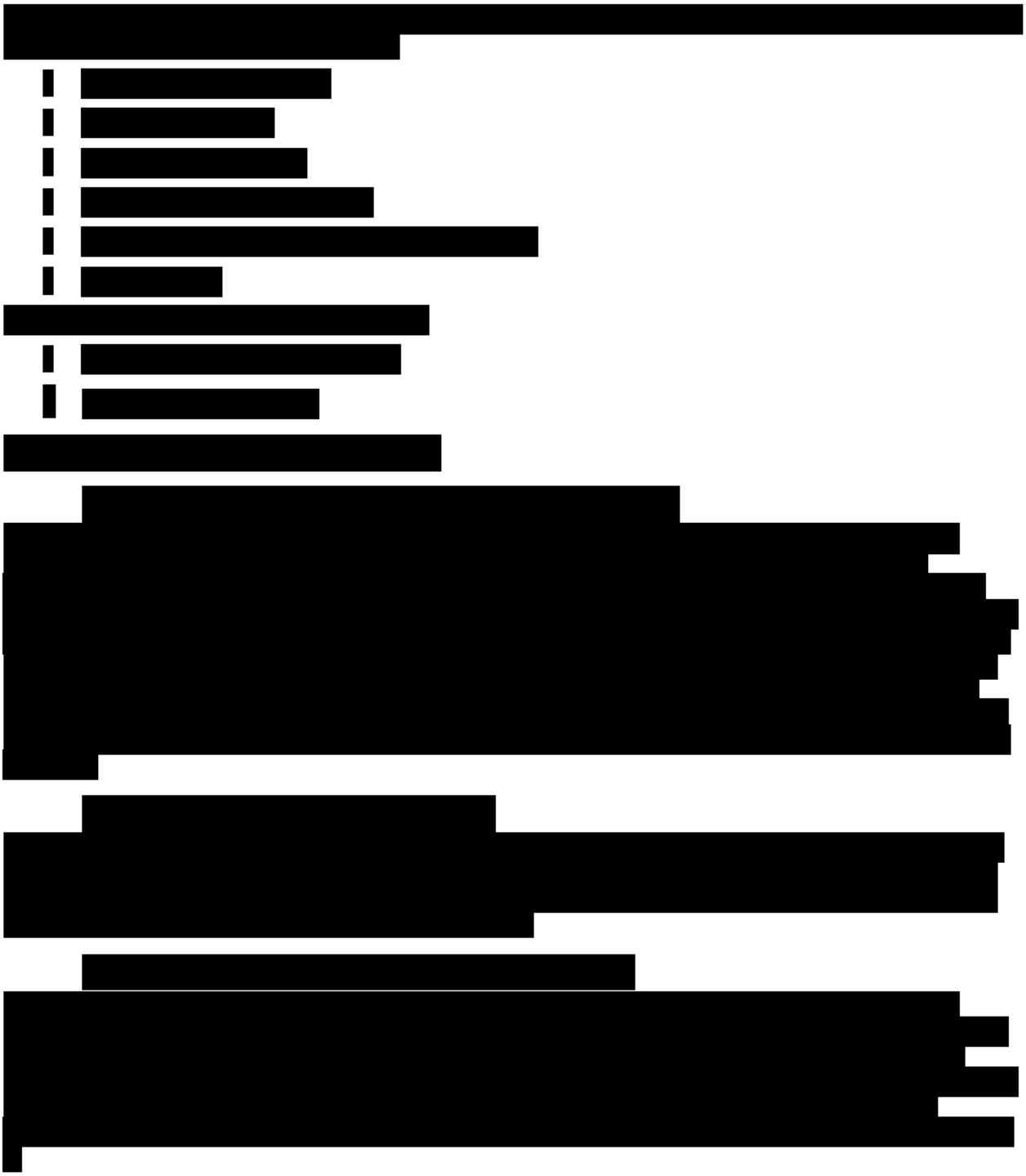

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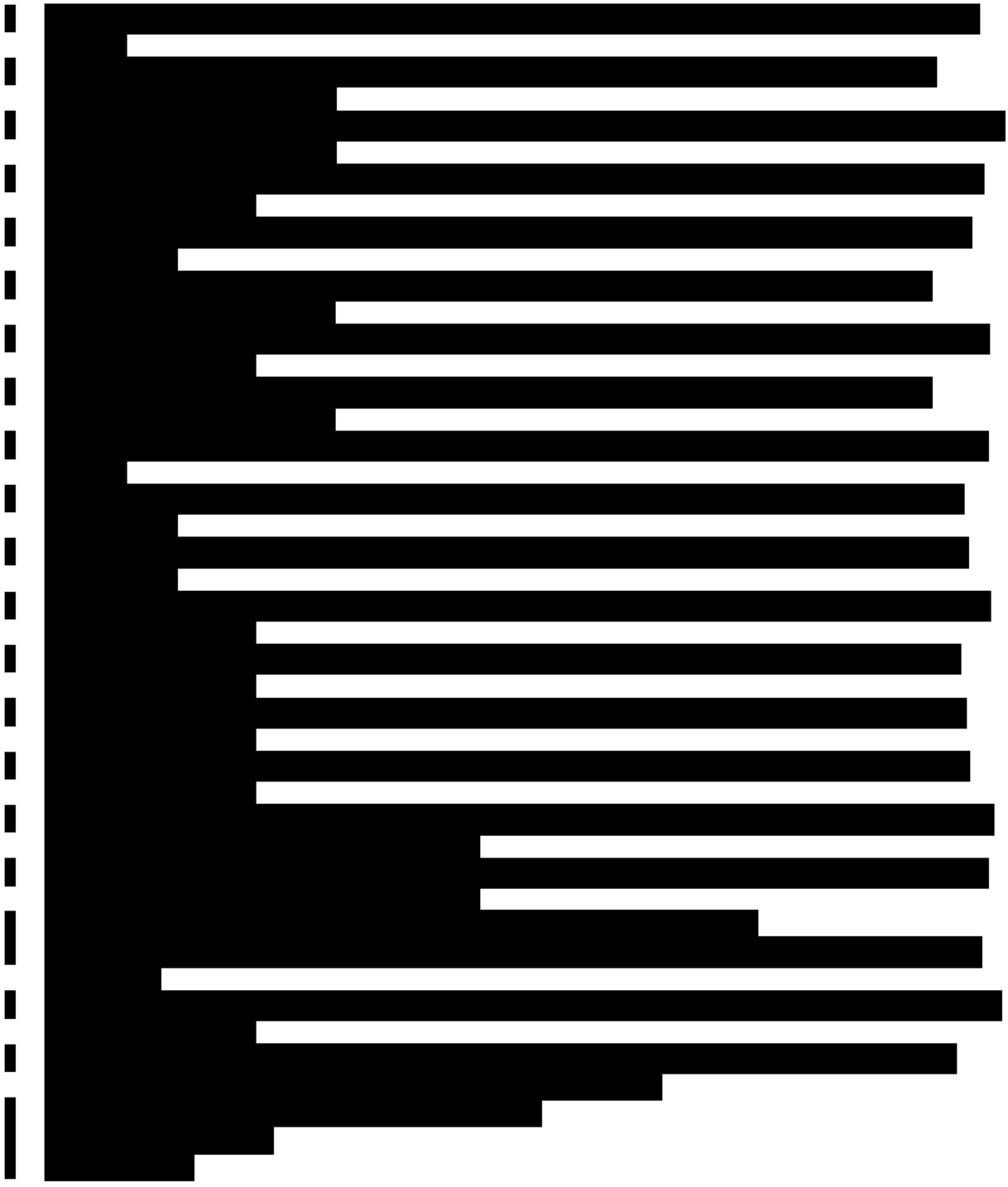

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16.0 Safety and Tolerability Analyses

All safety analyses will be performed using the safety analysis set. Baseline for safety data is defined as the last non-missing value prior to the first dose of the investigational product.

Safety and tolerability of SAGE-718 will be evaluated by treatment-emergent adverse events (TEAEs) and change from baseline vital signs, clinical laboratory analytes, electrocardiograms (ECGs), safety electroencephalogram (EEG), and responses on the Columbia–Suicide Severity Rating Scale (C-SSRS). Safety data will be listed by the participant and summarized using descriptive statistics (mean, median, range, percentages).

16.1 Adverse Events

TEAEs are defined as any AEs with an onset date on or after the date of the first dose of IP or any worsening of a preexisting medical condition/AE with onset after the start of IP and throughout the study. An AE leading to treatment discontinuation is defined as an AE with action taken of the investigational product as Drug Withdrawn. AEs will be coded using the Medical Dictionary for Regulatory Activities MedDRA version 23.1.

An overall summary of TEAEs, including the number of events, reported, the number and percentage of participants reporting at least one TEAE, the number and percentage of participants reporting at least one related TEAE, Number and percentage of participants by maximum severity, the number and percentage of participants discontinuing due to an adverse event, the number and percentage of participants with at least one serious adverse event, and the number and percentage of deaths will be presented.

A breakdown of the number and percentage of participants reporting each TEAEs, categorized by System Organ Class (SOC) and preferred term (PT), will be presented. Note that counting will be by a participant, not event, and participants are only counted once within each SOC and PT.

A further tabulation of these data, categorized by relationship (to SAGE-718), will be presented. Participants with multiple events within a particular body system or preferred term will be counted under the category of their drug-related event (related and not related) within SOC and PT. Relationship to SAGE-718 is categorized as related or not related.

A summary of events reported, categorized by severity, will also be provided. Participants with multiple events within a particular SOC and PT will be counted under the category of their most severe event in the following order: severe> moderate> mild within that SOC and PT.

A summary of adverse events leading to discontinuation of SAGE-718 will be provided, grouped by body system and preferred term.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

Handling of missing AE start dates is defined in Appendix-C. Missing data for severity or relatedness to treatment will not be imputed.

16.1.1 Deaths and Serious Adverse Events (SAEs)

All deaths and SAEs will be provided in by-participant listings.

16.2 Clinical Laboratory Evaluations

Laboratory assessments for biochemistry, coagulation, hematology, urinalysis, and serology, will be collected at screening, Day -1, Day 7, Day 14, and Day 28. The clinical laboratory tests to be performed for monitoring safety are listed in **Table 4.** Laboratory assessments will be summarized (n, mean, std,

median, Q1, Q3, minimum, and maximum) along with the change from baseline by each scheduled post-baseline visit. The International System of Unit (SI) will be used.

For the laboratory results that is "< 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. 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.

Summary tables on lab parameters will include descriptive statistics for the observed values and changes from baseline by scheduled assessment timepoint in hematology, serum chemistry, coagulation, and quantitative urinalysis test results.

Table 4 Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Coagulation
Red blood cell count Hemoglobin Hematocrit White blood cell count with differential Platelet count Red Blood Cell Indices (MCV, MCH, MCHC) Reflex to Red blood cell morphology if indices are abnormal	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin Indirect bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase Gamma-glutamyl transferase Potassium Sodium Lactate dehydrogenase Glucose Chloride Bicarbonate Calcium Phosphate Triglycerides Thyroid stimulating hormone (TSH)	pH Protein Glucose Red blood cell Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen	Activated partial Thromboplastin time Prothrombin time International normalized ratio

If a normal range is provided for the parameter, out-of-range values will be flagged as low or high, where applicable, in the participant data listings

The number and percentage of participants with potentially clinically significant (PCS) values will be provided in separate displays in hematology, serum chemistry, and liver function tests provided for such occurrence by time point.

PCS values will be identified for specific laboratory parameters as outlined in Table 5.

Liver function tests will be monitored closely for PCS values, and will be summarized for occurrence any time post-baseline for the following parameters for these PCS thresholds (for conditions 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)
Total Bilirubin >2xULN **AND** Alkaline Phosphatase >2xULN **AND** (Alanine Aminotransferase or Aspartate Aminotransferase >3xULN)

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

Pregnancy test results will be listed but not summarized.

Table 5 Potentially Clinically Significant Values for Specific Laboratory Parameters

Laboratory Parameter	Gender	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

Laboratory Parameter	Gender	Units	Criteria for PCS Values (Observed values)	
			High	**Low**
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
		mmol/L	>120	<90
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

16.3 Physical/Neurological Examinations

The occurrence of a physical examination, Neurological examination (yes/no), and the date performed will be listed by the participant.

16.4 Vital Signs

Vitals for the following parameters - respiratory rate (breaths/minute), oral temperature (degrees C), supine heart rate (beats/minute), supine systolic blood pressure (mmHg), supine diastolic blood pressure (mmHg), standing heart rate (beats/minute), standing systolic blood pressure (mmHg), standing diastolic blood pressure (mmHg), – are collected at Screening and on Days -7, -1, 1, 7, 14, and 28. Descriptive summaries of observed values and changes from baseline will be provided for vital sign parameters - by scheduled assessment time point. Additionally, the number and percentage of participants with PCS and potentially clinically significant change (PCSC) values will be summarized for such occurrence any time post-baseline. Potentially clinically significant values will be identified for vital sign parameters as outlined in Table 6.

Table 6 Potentially Clinically Significant Values and Change for Vital Sign Parameters

Vital Sign	**Units**	**Criteria for PCS Values (Observed values)**		**Criteria for PCSC values (Change from Baseline values)**	
		High	Low	Increase	Decrease
Heart rate (supine and standing)	Beats/min	>120	<40	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			
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			

The orthostatic vital sign - the change from supine to standing (Supine – Standing) in heart rate, systolic and diastolic blood pressure – will be summarized by scheduled assessment timepoint, at 1 and 3 minutes.

Any vital signs result considered clinically significant by the investigator will be captured as adverse events, hence will show up in AE displays. All vital sign assessments along with PCS will be listed in the listing.

16.5 12-Lead Electrocardiogram

Supine 12-lead ECGs will be performed in triplicate, and are collected on screening, days -1, 1, 7, 14, and 28. The following ECG parameters will be listed for each participant: heart rate (beats per minute), PR (msec), QRS (msec), QT (msec), and QTcF (msec).

The average of the triplicate values will be used in the summary, including baseline ECG values. The observed value at each time point and change from baseline at each post-baseline scheduled time point will be summarized. Each ECG is evaluated as 'normal', 'abnormal, not clinically significant' and 'abnormal, clinically significant'; the number and percentage of participants with at least one of the triplicate values in the categories of 'abnormal, clinically significant' and 'abnormal, not clinically significant' will be provided at baseline and each post-baseline scheduled assessment time point.

The number and percentage of participants with PCS and PCSC values will be summarized for such occurrence any time post-baseline. Potentially clinically significant values will be identified for ECG parameters as outlined in Table 7. A listing of ECG and QTcF PCS values will be provided.

Table 7 Potentially Clinically Significant Values and Change for ECG Parameters

ECG	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline)	
		High	Low	Increase	Decrease
QTcF Interval	msec	>450 but <=480 >480 but <=500 >500	NA	>=30 to 60 >60	NA

16.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality will be monitored during the study using the C-SSRS. The C-SSRS is a questionnaire used to measure the presence and intensity of suicidal ideation and behavior. The C-SSRS will be completed at Screening, Days -7, -1, 1, 7, 14, and 28. The "Baseline/Screening" C-SSRS form will be completed at screening (lifetime history and past 24 months). The "Since Last Visit" C-SSRS form will be completed at subsequent time points.

Suicidal behavior and suicidal ideation will be summarized by visit for the Safety analysis set. The proportion of participants who meet the criterion for each of these categories at any post-baseline visit will be summarized as described in Table 8.

Table 8 C-SSRS Categories for Analysis

Category	C-SSRS Item response is "YES"
Suicidal ideation	• Wish to be dead • Non-specific active suicidal thoughts • Active Suicidal Ideation with Any Methods • Active Suicidal Ideation with Some Intent • Active Suicidal Ideation with Specific Plan
Suicidal behavior	• Preparatory Acts or Behaviour • Aborted Attempt • Interrupted Attempt • Actual Attempt(non-fatal) • Completed suicide [1]
Suicidal Ideation or Behavior	• Participant Engaged in Non-Suicidal Self-Injurious Behavior

[1] Completed suicide is not collected at the screening visit.

17.0 References

1. ICH Harmonized Tripartite Guideline. Statistical Principles for Clinical Trials E9. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. 05 February 1998. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
2. ICH Harmonized Tripartite Guideline. Structure and Content of Clinical Study Reports E3. International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. 30 November 1995. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline_.pdf
3. SAS/STAT 14.2 User's Guide, The Mixed Procedure. SAS Institute, Cary NC, 2016, pp. 6138-6275.
4. SAS Programming to Calculate AUC in Pharmacokinetic Studies – Comparison of Four Methods in Concentration Data. J. He. 2008. https://www.lexjansen.com/pharmasug/2008/sp/SP06.pdf

18.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AD	Alzheimer's Disease
AE	Adverse event
ATC	Anatomic Therapeutic Chemical
AUC_{0-t}	Area under the plasma concentration-time curve, from time 0 to time t
AUC_{0-last}	Area under the curve from the time of dosing to the time of the last measurable (positive) concentration
BLQ	Below the Limit of Quantification
CI	Confidence Interval
CV	Coefficient of Variation
C_{max}	Maximum observed concentration.
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
[redacted]	[redacted]
IP	Investigational Product
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially Clinically Significant
[redacted]	[redacted]
PT	MedDRA Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAP	Statistical Analysis Plan
SAE	Serious Treatment-emergent Adverse Event
SI	International System of Units
SOC	MedDRA System Organ Class
Std	Standard Deviation
TEAE	Treatment Emergent Adverse Event
WHO	World health Organization
[redacted]	[redacted]

19.0 Appendix

19.1 Appendix-A Schedule of Study Assessment

Study Period	Screening	Baseline		Treatment				Follow Up	
Study Day	D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 [a]	D 7 (±1 d)	D 14 or ET	D 21 [a] (±1 d)	D 28 (±2 d)
Informed consent [b]	X								
Inclusion/exclusion criteria	X	X	X						
Medical history and demographics [c]	X								
Body weight	X			X		X	X		X
Body height	X								
CDR	X								
[redacted]									
Test of Premorbid Functioning	X								
Vital signs [d]	X	X	X	X		X	X		X
Physical examination [e]	X	X	X				X		
EEG [f]	X								
12-lead ECG [g]	X		X	X		X	X		X
C-SSRS [h]	X	X	X	X		X	X		X
Clinical laboratory tests [i]	X		X			X	X		X
Alcohol test [j]	X	X							
Urine drug test	X	X	X	X		X	X		
FSH test [k]	X								
Pregnancy test [l]	X		X				X		X
Serology test [m]	X								
MRI [n]	X								
[redacted]									
Study Period	Screening	Baseline		Treatment				Follow Up	

Study Day	D -21 to D -8	D -7 (±1 d)	D -1	D 1	D 4 [a]	D 7 (±1 d)	D 14 or ET	D 21 [a] (±1 d)	D 28 (±2 d)
[redacted]									
Participant training [p, q]		X	X						
[redacted]									
Remote assessments [v]		X							
IP self-administration [w]				X (once daily)					
IP dispensation [x]				X		X			
IP accountability [y]				X					
Safety telephone call					X			X	
TEAEs/SAEs	X								
Concomitant medications [z]	X								

Abbreviations: CDR = Clinical Dementia Rating Dementia Staging Instrument®; C-SSRS = Columbia–Suicide Severity Rating Scale; d = days; ECG = electrocardiogram; EEG = electroencephalogram; ET = early termination; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; IP = investigational product; MRI = magnetic resonance imaging; PET = positron emission tomography; [redacted] SAE = serious adverse event; TEAE = treatment-emergent adverse event

Notes: In the event of ET, efforts should be made to collect the Day 14 visit assessments.

When scheduled for the same time point, procedures should be performed in the following order: vital signs, ECG, blood draws, morning meal, IP dosing, then any scheduled postdose [redacted] assessments.

In the setting of public health advisories due to COVID-19, assessments scheduled to be conducted at the study site may be performed via telephone/video if feasible. For assessments that cannot be conducted by phone or video, an in-home visit may be conducted. Information about COVID-19 diagnosis, treatment, and quarantine status will be collected with the medical history, AEs, and prior and concomitant medications.

a Day 4 and Day 21 visits will occur via scheduled telephone calls.

b Both study partners and participants are to be consented during the Screening Period.

c In addition to full medical history, all nonpharmacological methods (eg, [redacted] used to treat or prevent [redacted] of AD are to be recorded.

d Vital signs to 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. When scheduled for the same visit, vital signs are to be assessed prior to ECG and blood collection.

e Full physical examination to be conducted at Screening, abbreviated examinations thereafter. Unscheduled, symptom-directed physical examinations may also be conducted at the investigator's discretion.

f EEG to be performed for all participants during Screening. If clinical events suspicious for seizure occur, an unscheduled 1-hour EEG will be performed (with a second follow-up 1-hour EEG at the discretion of the investigator).

g ECG will be measured after the participant has been in the supine position for at least 5 minutes.

h "Baseline/Screening" C-SSRS form at Screening and "Since Last Visit" C-SSRS form thereafter.

i Samples for clinical laboratory assessments for hematology, biochemistry, coagulation, urinalysis, and serology to be collected ≤2 hours prior to dosing during the Treatment Period, and any time of day at other time points. Participants are to be in a fasted state for screening assessments only.

j Alcohol testing will be performed in the clinic, either by urine dipstick or breathalyzer.

k To confirm self-reported postmenopausal status in women only.

l Serum pregnancy tests for all female participants at Screening; urine pregnancy tests will be conducted for all female participants who are not postmenopausal or surgically sterile at other scheduled time points.

m To include testing for hepatitis B and C, HIV-1, and HIV-2

n Only in participants without an MRI report obtained within the 2 years preceding the Baseline Period

[redacted]

p Where participant informed consent is given, samples for exploratory biochemical research and genetic testing will be collected after the collection of [redacted] samples, according to the schedule in Table 3.

q Participants and study partners will be trained to use all study-related software and devices. Additional guidance will be provided on choosing a meal with approximately 30 g of fat.

[redacted]

v Daily reminders will be sent to participants to complete assessments of [redacted] or in the clinic during the Treatment Period (with observation by study staff during scheduled clinic visits).

w On visit days during the Treatment Period, participants will self-administer IP in the clinic under the supervision of study staff after the predose assessments and consumption of a morning meal.

x Study staff will dispense sufficient IP for daily dosing at home until the next scheduled visit. On Days 7 and 14, participants will return used IP packaging and any unused IP for site staff to document.

y On Days 7 and 14, participants will return used IP packaging and any unused IP for site staff to document.

z At Screening, include all psychotropic medications used within 12 weeks of informed consent, any other medications and supplements taken within 60 days of informed consent, and all medication used to treat AD, regardless of timing. After Screening, all changes to any medication or supplements should be captured.

19.2 Appendix-B Prior and Concomitant Medication Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y same as M and Y of investigational product administration	Date of investigational product administration
		M and/or Y not same as date investigational product administration	First day of month
	M and D	Y same as Y of investigational product administration	Date of investigational product administration
		Y not same as Y of investigational product administration	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date investigational product administration
Stop date for con meds	D only	M and Y same as M and Y of investigational product administration	Date of investigational product administration
		M and/or Y not same as date of investigational product administration	Last day of month
	M and D	Y same as Y of investigational product administration	Date of investigational product administration
		Y not same as Y of investigational product administration	Use Dec 31
	M, D, and Y	None - date completely missing and NOT ongoing	Date of investigational product administration

19.3 Appendix-C Adverse Event Start/Stop Date Imputation

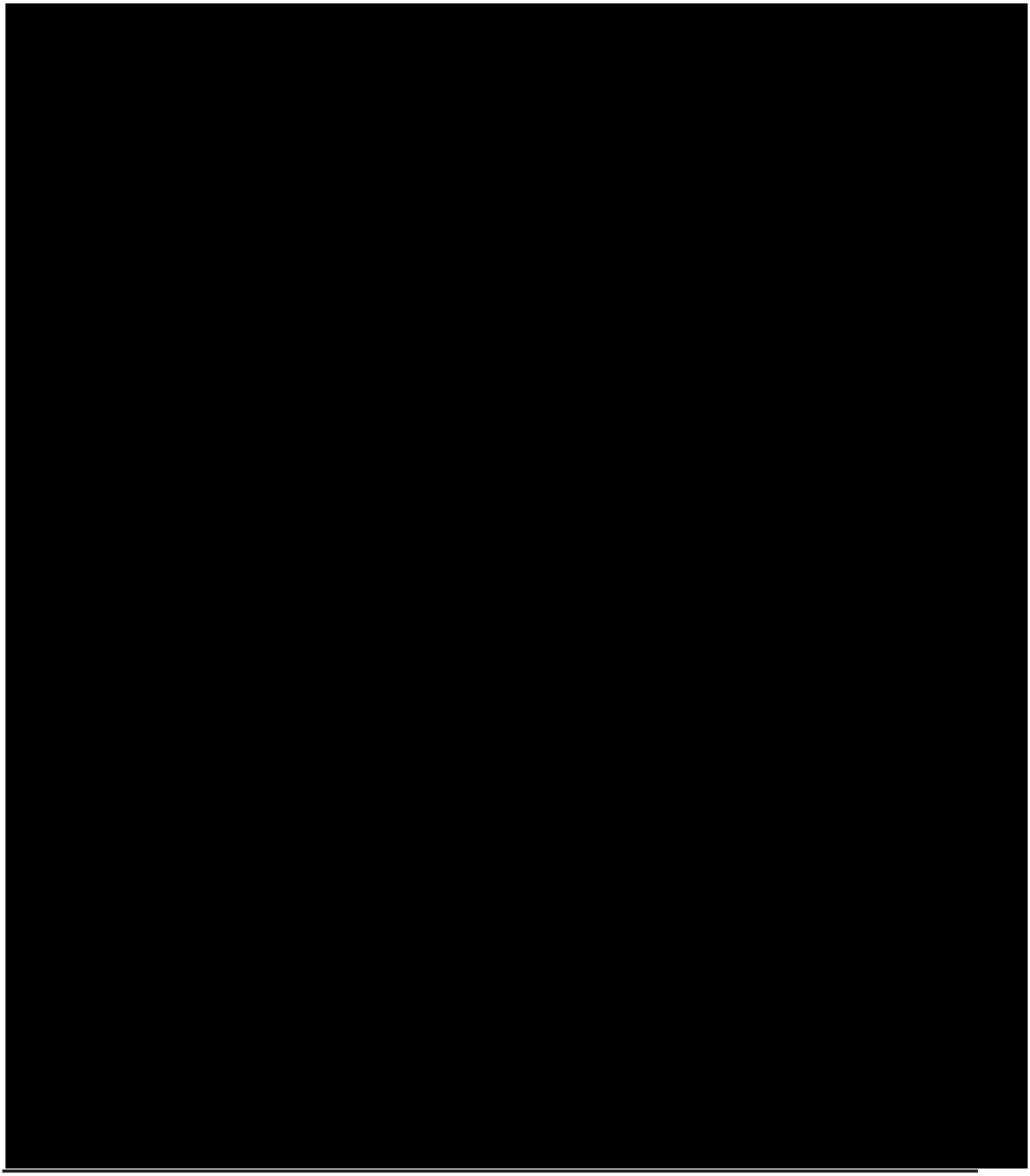
Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of investigational product administration	Date of investigational product administration
		M and/or Y not same as date investigational product administration	First day of month
	D and M	Y same as Y of investigational product administration	Date of investigational product administration
		Y prior to Y of investigational product administration but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of investigational product
Stop date for AEs	D	M and Y same as M and Y of investigational product administration	Date of investigational product administration
		M and/or Y not same as date of investigational product administration	Use last day of month
	D and M	Y same as Y of investigational product administration	Date of investigational product
		Y not same as Y of investigational product administration	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

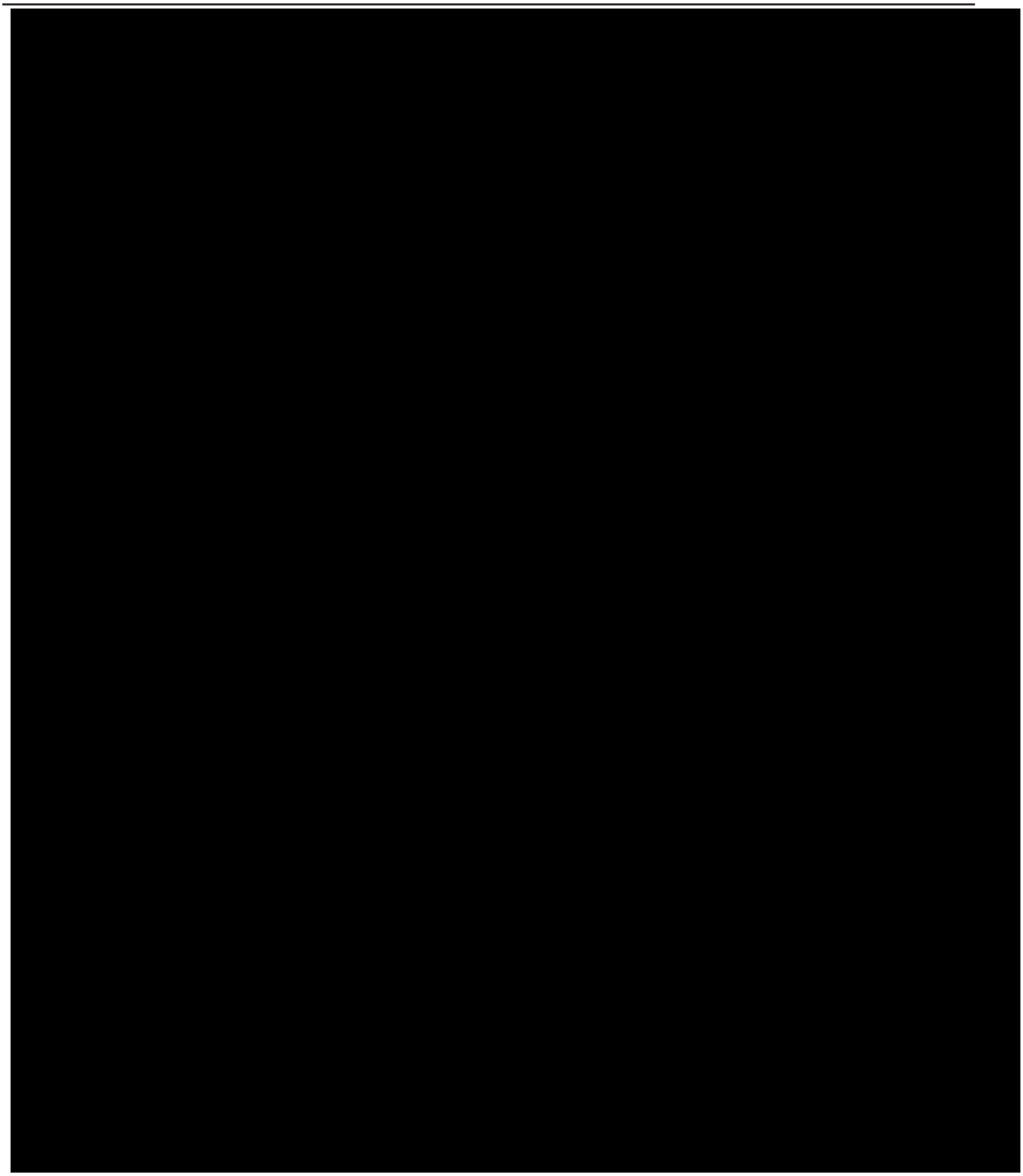
19.4 Appendix-D Calculation of years since diagnosis of Alzheimer Disease

Observed	Missing	Formula to Calculate Duration
D,M,Y		(Date of Enrollment – Date of Diagnosis + 1)/365.25
M and Y	D	[Year (Date of Enrollment) – Year (Date of Diagnosis)] + [Month (Date of Enrollment) – Month (Date of Diagnosis)]/12
Y	D and M	[Year (Date of Enrollment) – Year (Date of Diagnosis)]

Note : The number of years from the date of diagnosis to the date of enrollment, which will be derived based on the table above. No imputation will be done for missing diagnosis date (Year, Month, Day).



[redacted]



[redacted]

19.6 Appendix-F Tables, Figures, and Listings

Table Number	Title	Population
Table 14.1.1.1	Subject Analysis Sets	All Screened Subjects
Table 14.1.1.2	Subject Disposition	Safety Analysis Set
Table 14.1.1.3	Major Protocol Deviations	Full Analysis Set
Table 14.1.2.1	Demographic Characteristics	Safety Analysis Set
Table 14.1.3	Prior Medications by ATC Classification and WHO Drug Dictionary Preferred Term	Safety Analysis Set
Table 14.1.4	Concomitant Medications by ATC Classification and WHO Drug Dictionary Preferred Term	Safety Analysis Set
Table 14.1.5	Medical and Procedures by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.1.6	Medical and Surgical History that are Ongoing at the time of Screening by WHO Drug Dictionary Preferred Term	Safety Analysis Set
Table 14.1.7	Alzheimer Disease History	Safety Analysis Set
Table 14.1.8	Summary of Exposure and Adherence	Safety Analysis Set
[redacted]		

[redacted]

[redacted]

Table 14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Analysis Set
Table 14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.3	Treatment-Emergent Adverse Events Leading to Discontinuation of the Study by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.4	Treatment-Emergent Adverse Events Leading to Interruption of Study treatment	Safety Analysis Set
Table 14.3.1.5	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.6	Treatment-Emergent Adverse Events with Outcome of Death by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.7	Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term	Safety Analysis Set
Table 14.3.1.8	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to IP	Safety Analysis Set
Table 14.3.1.9	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Analysis Set

Table 14.3.3.1.1	Hematology and Coagulation Results by Time Point	Safety Analysis Set
Table 14.3.3.1.2	Potentially Clinically Important Postbaseline Hematology Results by Time Point	Safety Analysis Set
Table 14.3.3.2.1	Biochemistry Results by Time Point	Safety Analysis Set
Table 14.3.3.2.2	Potentially Clinically Important Postbaseline Biochemistry Results	Safety Analysis Set
Table 14.3.3.3.1	Urinalysis Results by Time Point Part 1 Continuous Variables	Safety Analysis Set
Table 14.3.3.3.2	Urinalysis Results by Time Point Part 2 Categorical Variables	Safety Analysis Set
Table 14.3.4.1	Vital Sign Results by Time Point	Safety Analysis Set
Table 14.3.4.2	Potentially Clinically Important Vital Sign Results	Safety Analysis Set
Table 14.3.5.1	Electrocardiogram Results	Safety Analysis Set
Table 14.3.5.2	Electrocardiogram Interpretations by Time Point	Safety Analysis Set
Table 14.3.5.3	Potentially Clinically Important Electrocardiogram Results	Safety Analysis Set
Table 14.3.6	Summary of Columbia–Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior	Safety Analysis Set
[redacted]		

[redacted]

Listing 16.1.7	Subject Enrollment	All Screened Subjects
Listing 16.2.1.1	Discontinued Subjects from Study	Safety Analysis Set
Listing 16.2.1.2	Completion / Discontinuation of Investigational Product (IP)	Safety Analysis Set
Listing 16.2.2	Protocol Deviations	Safety Analysis Set
Listing 16.2.3.1	Subject Analysis Sets	All Enrolled Subjects
Listing 16.2.4.1	Demographic and Baseline Data	Safety Analysis Set

Listing 16.2.4.2	General Medical History	Safety Analysis Set
Listing 16.2.4.3	Prior and Concomitant Medications	Safety Analysis Set
Listing 16.2.4.4	Prior and Concomitant Procedures	Safety Analysis Set
Listing 16.2.5.1	Administration of Investigational Product (Oral)	Safety Analysis Set
Listing 16.2.5.2	Drug Accountability	Safety Analysis Set
Listing 16.2.5.3	Treatment Adherence	Safety Analysis Set
[redacted]		
Listing 16.2.7.1	Adverse Events	Safety Analysis Set
Listing 16.2.7.2	Subjects with Adverse Events with Outcome of Death	Safety Analysis Set
Listing 16.2.8.1	Hematology and Coagulation Results and Change from Baseline	Safety Analysis Set

Listing 16.2.8.2	Biochemistry Results and Change from Baseline	Safety Analysis Set
Listing 16.2.8.3	Urinalysis Results and Change from Baseline	Safety Analysis Set
Listing 16.2.8.4	Pregnancy Test Results (Females of Childbearing Potential only)	Safety Analysis Set
Listing 16.8.5	Urine Drug Screen	Safety Analysis Set
Listing 16.2.9	Vital Signs	Safety Analysis Set
Listing 16.2.10.1	Electrocardiogram Results Part 1	Safety Analysis Set
Listing 16.2.10.2	Electrocardiogram Results Part 2	Safety Analysis Set
Listing 16.2.11.1	Physical Examinations	Safety Analysis Set
Listings 16.2.11.2	Neurological Examination	Safety Analysis Set
Listing 16.2.12	Columbia–Suicide Severity Rating Scale (C-SSRS)	Safety Analysis Set
Listing 16.2.13	Electroencephalogram (EEG) Monitoring Test	Safety Analysis Set
Listing 16.2.14	Magnetic Resonance Imaging (MRI) Test	Safety Analysis Set
Listing 16.2.15	Positron Emission Tomography (PET) Test	Safety Analysis Set
Listing 16.2.16	Alzheimer Disease History	Safety Analysis Set