VIGIL NEUROSCIENCE, INC.

Statistical Analysis Plan

Protocol Title: A Natural History Study of Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)

Short Title: Illuminate

Study Number: VGL101-01.002

Compound: Not Applicable (Non-interventional study)

Study Phase: Observational

Regulatory Agency Identifier Number(s):

IND: 156071
NCT: 05020743
EU Trial Number: N/A
IRAS ID: 303729

Sponsor: Vigil Neuroscience, Inc.
[redacted]

Authorization Signature Page

Author:

[redacted]

[redacted]

Date

Approved by:

[redacted]

[redacted]

Date

[redacted]

[redacted]

Date

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Version History

This Statistical Analysis Plan (SAP) is based on protocol version 5, dated 02 October 2024

SAP Version	Date	Change(s)	Rationale
Final V1.0	19Oct2023	Not Applicable	Original Version
Final V2.0	19Feb2025	1. Added required info to title page 2. Updated description to accommodate newly planned interim analysis and timing 3. Added the following sections that were not present in V1.0: - Sample size calculation - Handling of outliers - p-value reporting and critical threshold - Protocol deviations 4. Reduced number of correlations 5. Added details about derived variable calculations 6. Removed section on MRI Data Exclusion 7. Changed Bone Marrow Transplant (BMT) to Hematopoietic stem cell transplant (HSCT). BMT and HSCT are interchangeable terms for the purposes of this study and in comparison to the protocol and SAP V1.0 8. Updated the Analysis section to clarify differences from Protocol V5.0 9. Minor edits to clarify language and terminology throughout 10. Brief Assessment of Cognition (BAC) test has been removed from the SAP 11. Removed sensor-based gait and balance assessment	Updated to incorporate FDA feedback, ICH E9 SAP guidelines, and newly planned use of Natural History Study (NHS) data in integrated analysis with a separate Phase 2 study (VGL101-01.201). Note that NHS Study Objective 3 is to use NHS as external control; the analysis planned here are consistent with that aim. The BAC was removed because vendor was unable to provide traceability of the derived variable calculation. The sensor-based gait and balance assessment was removed due to collection discontinuation (see study protocol).

Note: Author of Final V1.0 was Jim MacDougall. Edits incorporated for v2.0 were done via collaboration of Vigil and Parexel study statisticians.

List of Abbreviations and Definition of Terms

Abbreviation	Term
2MWT	2-Minute Walk Test
ADRG	Analysis Data Reviewer Guide
AE	Adverse Event
ALSP	Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia
ATC	Anatomical Therapeutic Chemical
BAC	Brief Assessment of Cognition
BMI	Body Mass Index
CBFS	Cortical Basal Ganglia Functional Scale
CBFS-M	CBFS – Motor
CBFS-NM	CBFS – Non-motor
CDISC	Clinical Data Interchange Standards Consortium
CDR®+NACC-FTLD	Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center - Frontotemporal Lobar Degeneration
CDR®+NACC FTLD-SB	CDR®+NACC FTLD - Sum of Boxes
CGI-C	Clinical Global Impression - Change
CGI-S	Clinical Global Impression – Severity of Illness
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CSF1R	Colony-stimulating Factor 1 Receptor
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
CVA	Cerebrovascular Accident
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDL	Experiences in Daily Living
ET	Early Termination
FAQ	Functional Activities Questionnaire
GCP	Good Clinical Practice
GFAP	Glial Fibrillary Acidic Protein

Abbreviation	Term
HLT	High Level Term
HSCT	Hematopoietic Stem Cell Transplant
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Council for Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effects Model for Repeated Measures
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NfL	Neurofilament Light Chain
NHS	Natural History Study
NPI-12	Neuropsychiatric Inventory – 12 Item Version
PGI-C	Patient Global Impression - Change
PGI-S	Patient Global Impression – Severity of Illness
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
sTREM2	Soluble Triggering Receptor Expressed on Myeloid Cells 2
TUG	Timed Up and Go
WHO	World Health Organization
WOCBP	Women of Child-bearing Potential
ZBI	Zarit Burden Interview

1 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be included in the Clinical Study Report (CSR) for the Protocol, "A Natural History Study of Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)" (VGL101-01.002), known as the Illuminate study.

Background information is provided for the overall study design and objectives. Details regarding study conduct and data collection procedures are provided in the study protocol and corresponding case report forms (CRFs), which include comprehensive descriptions of the study design, methodologies, and data collection processes. This SAP references the latest version of the study protocol (Version 5.0). The SAP may contain modifications to the analysis plans as outlined in the protocol. In such cases, the SAP serves as the governing document for all analyses to be performed. Protocol revision history is summarized below.

Table 1. Protocol Revision Chronology

Version 1.0	14 May 2021	Original
Version 2.0	29 Jul 2021	Amendment 1
Version 3.0	01 Mar 2022	Amendment 2
Version 4.0	03 Oct 2023	Amendment 3
Version 5.0	02 Oct 2024	Amendment 4

An important consideration in this analysis is that some study subjects may early terminated to enroll in the clinical study, "A Phase 2 Safety, Tolerability, and Proof-of-Concept Study of VGL101 in Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids Pigmented Glia (ALSP)" (VGL101-01.201), also known as the Ignite study.

2 Study Overview

The Illuminate study is a non-interventional, prospective, multicenter, observational, natural history study (NHS) of patients with ALSP and asymptomatic carriers of colony-stimulating factor 1 receptor (CSF1R) gene mutations, the causative mutation for ALSP. Potential study patients will be screened for study eligibility. Individuals who satisfy the study inclusion and exclusion criteria and who provide written informed consent will be enrolled in the study and followed for up to 36 months. Approximately 60 subjects are planned for enrollment. Inclusion and exclusion criteria are detailed in the study protocol.

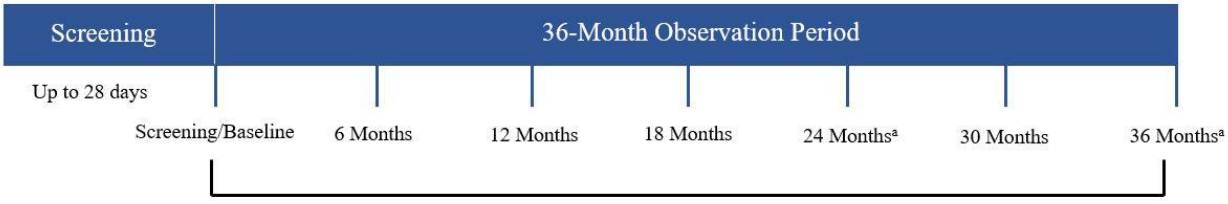
Clinic visits to assess disease status will be conducted at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36. Each clinic visit will include clinical assessments (cognitive, motor, functional, psychiatric, severity of illness, and caregiver burden assessments) and imaging studies. Blood for biomarker analysis will be collected at Screening/Baseline and at Months 6, 12 18, 24, 30, and 36. Adverse events (AEs) and concomitant medications and procedures will be recorded throughout the 36-month study.

An optional sub-study to evaluate levels of biomarkers in cerebrospinal fluid (CSF) is also included in this study and will be conducted at select study sites. A CSF sample will be obtained at Screening/Baseline and at Months 6 (Brazil only), 12, 24, 36, and early termination (ET) visits for from subjects who provide informed consent to participate in the optional CSF Biomarker Sub-study. ET visit is mapped in the Electronic Data Capture (EDC) system as the nearest relevant visit in based on days from screening, typically the next subsequent visit.

Subjects who, in the discretion of the investigator, may be eligible for an iluzanebart (VGL101) clinical study may be discontinued from this study at any time. For subjects who discontinue from this study to enroll in an iluzanebart (VGL101) clinical study, all procedures, except the Magnetic Resonance Imaging (MRI), blood biomarker sampling, and CSF collection (for subjects in the CSF Biomarker sub-study), which will be collected once for the ET Visit of this study and for the Screening or Baseline Visit of the iluzanebart (VGL101) clinical study and will be analyzed as part of both studies. If CSF biomarker collection is not included at the Screening or Baseline Visit of the iluzanebart (VGL101) clinical study, CSF biomarker collection will be performed at the ET Visit of this study.

The study schema is presented below, and the Schedule of Assessments is provided in the Appendix (Section 6.1).

Figure 1. Schema for the Illuminate Natural History Study



a. Attempts will be made to determine the survival status (alive or deceased) of any subject who fails to return for a final visit or who discontinues from the study before completing the 24-month (for subjects who withdraw from the study before implementation of Amendment 3 or 36-month (for subjects who withdraw from the study after implementation of Amendment 3) observation period. Study staff will contact the subject or the subject's caregiver by telephone to determine survival status 24 or 36 months, respectively, after the date of the subject's Screening Visit or at the end of the study, whichever occurs sooner.

3 Objectives and Endpoints

3.1 Study Objectives

The Illuminate NHS objectives are as follows:

- To understand the phenotypic heterogeneity and phenotype/genotype correlation and natural history of ALSP.

- To develop and evaluate biomarkers for assessing disease progression in patients with ALSP.
- To create the foundation for a future external control arm and provide run-in data for patients who qualify for interventional studies.

3.2 Study Endpoints

Study endpoints and respective analysis methods are described in Section 4.3.

3.3 Analysis Populations and Subgroups

Analysis populations and subgroups are defined in the following sections.

Hematopoietic Stem Cell Transplant (HSCT) at baseline is used for select analysis population and subgroup criteria. A subject is programmatically determined to have HSCT if there exists any occurrence of "Blood and blood product treatment" or "Haematological therapeutic procedures NEC" in the subject's Medical History High Level Term (HLT) data.

3.3.1 Analysis Populations

The populations used for this analysis will include a Screened Population, Study Population, Study Population (Non-HSCT), CSF Population, Ambulatory Population, and the Caregiver Population. These populations are defined below.

3.3.1.1 Screened Population

The Screened Population consists of all subjects who sign informed consent (i.e., consented to participate in this clinical study).

3.3.1.2 Study Population

The Study Population consists of all subjects who met the inclusion/exclusion criteria for the study (i.e., as defined in Section 5 of the study protocol) and who signed informed consent (i.e., consented to participate in this clinical study).

3.3.1.3 Study Population (Non-HSCT)

The Study Population (Non-HSCT) consists of all subjects in the Study Population who have not had HSCT procedure. This population includes Prodromal and Symptomatic ALSP subjects.

3.3.1.4 CSF Population

The CSF Population consists of all subjects from the Study Population who consented to participate in the optional CSF Biomarker sub-study and have an evaluable baseline CSF biomarker measurement.

3.3.1.5 Ambulatory Population

The Ambulatory Population consists of all subjects in the Study Population who have the ability to ambulate with or without assistance, as collected in the CRF.

3.3.1.6 Caregiver Population

The Caregiver Population consists of all subjects in the Study Population who have a caregiver that has consented to the study.

3.3.2 Subgroups

Analyses will be performed on the following set of subgroups, as defined at baseline:

- **Prodromal**: ALSP subjects with CSF1R mutation, radiographic evidence of ALSP and who do not meet clinical criteria for Symptomatic ALSP.

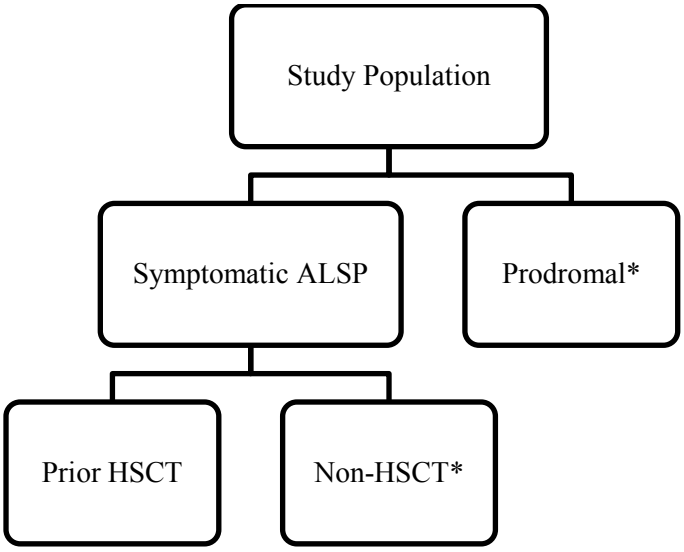
  Note: The criteria for Symptomatic ALSP is an answer of "*Yes*" to the questions Symptomatic ALSP on the demographics electronic Case Report Form (eCRF) page.

- **Symptomatic ALSP**: ALSP subjects with CSF1R mutation, radiographic evidence of ALSP and meeting clinical criteria.

- **Symptomatic ALSP (Non-HSCT)**: Symptomatic ALSP subjects who have not had HSCT procedure.

- **Symptomatic ALSP (Prior HSCT)**: Symptomatic ALSP subjects who have had HSCT procedure.

Figure 2. Subgroup Allocation



Note: Groups denoted with an asterisk (*) are included in the Study Population (Non-HSCT).

4 Statistical Methods

4.1 General Considerations

4.1.1 Timing of Analyses

The data from this NHS will be reviewed on an ongoing basis. Interim summaries of the data may be performed to support ALSP clinical development. The purpose of an interim analysis (IA) is to provide an initial check of modeling and analysis assumptions and characterization of disease progression. An IA of data from 42 subjects in this study was conducted using a data cutoff of 22 September 2023, SAP dated 19 October 2023, and an interim database freeze date of 01 November 2023.

This SAP covers a second IA, with the database freeze date timed to coincide with the Phase 2 Study database freeze, helping to facilitate an integrated analysis of the two studies. The Phase 2 study protocol is titled, "A Phase 2 Safety, Tolerability, and Proof-of-Concept Study of VGL101 in Patients with Adult-Onset Leukoencephalopathy With Axonal Spheroids and Pigmented Glia (ALSP)" (VGL101-01.201), also known as the Ignite study, with its protocol V9.0 and corresponding SAP V2.0.

4.1.2 Interim Analysis

An IA of the integrated Illuminate Study was conducted in September 2023 with NHS data occurring on or before 22 September 2023. A second IA of the study will be conducted with NHS database freeze occurring on or around 11 April 2025.

4.1.3 Software and Verification

The statistical analyses will be conducted with the SAS® System software version 9.4 or higher with specific version details to be described in the Analysis Data Reviewer Guide (ADRG). Analysis datasets will be created following Clinical Data Interchange Standards Consortium (CDISC) standards. All analyses will undergo formal verification procedures to ensure accuracy and consistency. Specifically, results will be independently verified through separate programming prior to the release of draft statistical reports. Additionally, all documentation and reports will be reviewed by the lead statistician to confirm the accuracy and alignment of the analyses with the study objectives and planned methodologies.

4.1.4 Sample Size and Power

The sample size of approximately 60 subjects was determined without a formal power calculation and is expected to provide sufficient information to address the study objectives in this rare disease.

4.1.5 Level of Significance

Unless otherwise noted, all statistical tests will be two-sided with a significance level of 0.05.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001"; p-values greater than 0.999 will be

presented as ">0.999". Confidence intervals will be presented to one more decimal place than the point estimate.

4.1.6 Multiplicity Control

Given the exploratory nature of this study, there are no planned adjustments to individual p-value or intervals for multiple comparisons or multiplicity.

4.1.7 Descriptive Statistics

Descriptive statistics will be used to summarize data from this study.

In general, continuous data will be summarized with number of subjects (N), number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. For fluid biomarker variables, percent coefficient of variation (%CV), geometric mean, and percent geometric coefficient of variation (%gCV) will also be presented.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile 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.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n) and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n (the number of observations with non-missing values) 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 were no missing values for that variable.

4.1.8 Definition of Baseline

Unless otherwise specified, for all endpoints, baseline visit is defined as Study Day 1. If the Baseline visit is performed over more than 1 day, then the last day of the baseline assessments will be designated as Study Day 1.

4.1.9 Definition of Study Day

Study day is defined as:

- Pre-Baseline study day = Date of Assessment – Date of Baseline
- Post-Baseline study day = Date of Assessment – Date of Baseline +1

As per these algorithms, there is no Study Day 0.

4.1.10 Study Visit

Scheduled subject visits (i.e., Screening/Baseline, Month 6, Month 12, Month 18, Month 24, Month 30, Month 36) will be determined by the visit as specified in the eCRF. That is, scheduled visits will not be windowed and the nominal visit value will be used for analysis.

To utilize as much data as possible for analysis, unscheduled and ET visits will be mapped to a scheduled visit for analysis using windows as defined below, which are to be used for analysis purposes only. Once analysis visit windows are assigned, all visits, including unscheduled and ET visits, are eligible to be flagged as the "analyzed record" within the analysis window. As such, a subject may have more than one record for each analysis visit window. The following rule for determining which record is flagged as the "analyzed record" is as follows:

- When available, data from the scheduled visit is always used.
- If data from the scheduled visit is not available, then data from the unscheduled or ET visit closest to the scheduled visit study day for that analysis window will be used, if available.

Table 2. Study Visit Windows

Analysis visit	Nominal visit	Analysis visit window (days)		
		Start	End	Target
Baseline	Baseline	-28	1	1
Month 6	Month 6	93	273	183
Month 12	Month 12	275	455	365
Month 18	Month 18	458	638	548
Month 24	Month 24	640	820	730
Month 30	Month 30	823	1003	913
Month 36	Month 36	1006	1186	1096

Unless unscheduled or early termination visits are assigned to a visit window and flagged for analysis, they will be excluded from the summary tables by visit but will be included in the listings.

4.1.11 Handling of Missing data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects. In situations where it is not possible to obtain all data, imputations of missing data may be necessary. Common situations are described below, and details for how missing data will be handled for specific clinical scales is detailed in the Appendix.

4.1.11.1 Missing Severity or Relationship for Adverse Events

AEs with missing severity will have the severity imputed as 'Severe'. AEs with missing relationship to study drug will have the relationship imputed as 'Related'. Actual values will be presented in the data listing.

4.1.11.2 Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. However, a complete date is often necessary to determine if the event should be included in the analysis or to establish the duration of an event. In such cases, incomplete dates will be imputed.

Incomplete or missing start and end dates will be imputed for the following:

- Adverse events
- Medications to determine when the medication was taken (i.e., prior to Baseline or concomitant).
- Procedures to determine when the procedure occurred (i.e., prior to Baseline or concomitant).
- Date of birth will be imputed to determine age at Baseline and age at time of ALSP diagnosis. (Note: if "Birth Date" is incomplete/missing but "Age at Diagnosis of ALSP" is not missing, then the imputed birth date will not be used for the calculation of "Age at Diagnosis of ALSP" and the value recorded in the EDC will be used).
- ALSP diagnosis date will be imputed to determine duration from time of ALSP diagnosis to Baseline.

For the purposes of handling partially reported start and end dates for AEs, medications, procedures, and therapies, the following algorithm will be applied:

Start Date Imputation Rules

- **Missing start day, but month and year present:**
    - If the event occurs in the same month and year as Baseline, then the start day of the event will be assigned to the day Baseline (i.e., Day 1).
    - Otherwise, the start day will be set to the first day of the month.
- **Missing start day and month, but year present:**
    - If event occurs the same year as Baseline, then the start date of the event will be assigned to Day 1.
    - Otherwise, the start day and month will be set to 01 January.

- **In the unlikely event of a completely missing start date, the start date will be imputed as Day 1.**

- **If the year and day are present, but month is missing, apply imputation rules as though the day is also missing, and only year is present.**

- **If the imputed start date is after the non-imputed end date, then the start date will be set to the end date.**

End Date Imputation Rules

- **Missing end day, but month and year present:**

    - The day will be set to the last day of the month.

- **Missing end day and month, but year present:**

    - The end day and month will be set to the date of study completion.

    - However, if study completion year is greater than the year of the event, then the day and month will be set to 31 December.

- **Missing all components of an end date and the event is not marked as ongoing:**

    - The event will be considered as 'ongoing' and will be considered study-emergent for AEs and concomitant for medications if the start date is on or after Day 1.

- **If the year and day are present, but month is missing, apply imputation rules as though the day is also missing, and only year is present.**

- **If the imputed end date is before the start date, then the start date will be set as the end date.**

- **If the imputed date is later than the date of study withdrawal, then the date of study withdrawal will be imputed for the date.**

In subject data listings, start and end date of events will be displayed as reported on the CRF (i.e., imputed values will not be listed).

4.1.11.3 Imputation for Alphanumeric Data

Should there be instances where a clinical laboratory parameter is reported with imbedded non-numeric characters, as for example, "<0.1" or ">10", the data will be imputed for quantitative summaries. The actual values as reported in the database will be presented in data listings.

For incorporation in quantitative summaries, the following imputation rules will be employed:

- The lower limit of quantification will be replaced with ½ the value of the lower limit. For example, < 0.1 will be replaced with 0.05.

- The upper limit of quantitation will be increased by one level of precision that precedes the value. For example, ">0.1" will be imputed to "0.11", and ">10" will be imputed to "10.1".

4.1.12 Handling of outliers

Outliers will be identified to ensure the validity and robustness of the statistical analyses. The following methods may be used to detect outliers in the dataset:

- **Data visualization:** Boxplots, scatterplots and histograms may be used to visually identify points that appear to deviate from the overall distribution.

- **Statistical criteria:** For select continuous variables, values falling more than +/- 3 standard deviations above or below the mean will be flagged as potential outliers. For select categorical variables, frequencies containing <3% of the overall data will be reviewed to identify any unusual, improbable, or implausible categories.

- **Clinical context:** Outlying data points will also be assessed in the context of clinical plausibility and data collection procedures to determine whether outliers are likely data errors or true anomalies. For example, 2-Minute Walk Test (2MWT) distances exceeding 300 meters will be excluded from analyses as these values are implausible for this study patient population (Bohannon, 2017).

Once identified, outliers may be handled by any or a combination of the following procedures:

- **Verification:** Data flagged as outliers may be cross-checked against EDC, eCRF and source records to rule out data entry errors and confirm true anomalies.

- **Documentation:** Outliers will be documented as likely data entry errors, likely valid but extreme observations, or data with an unknown cause.

For outliers that are deemed to be valid but extreme observations:

- Sensitivity analysis may be conducted with and without outliers to assess their impact on results
- Outliers will be included in the primary analysis but may be interpreted jointly with sensitivity analysis if their influence impacts the resulting conclusions and yields findings that are not robust

All decision regarding handling outliers, including their identification and inclusion/exclusion from analyses, will be documented in detail in a Statistical Report and in the CSR.

4.1.13 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Protocol deviations will be recorded on the source documents and with an explanation for the deviation. All protocol deviations will also be recorded as specified in the monitoring plan. Protocol deviations will be identified by site staff, through medical reviews, and by clinical research associates during site monitoring.

Deviations will be classified as minor or major prior to the database lock. Major protocol deviations are defined as those that result in harm to the study subjects or significantly affect the scientific value of the reported results of the study. Other deviations will be considered minor.

All protocol deviations will be summarized in a table and well as presented in a listing, including their assigned severity (major/minor). Major protocol deviations will be analyzed separately, and sensitivity analysis may be conducted to assess whether conclusions change when excluding subjects with major deviations. Subgroup analysis may be conducted to evaluate whether protocol deviations disproportionately affect specific subject groups.

Note that visits that occurred outside of visit windows may be identified as a protocol deviation, and these are expected to be relatively common in this study. Some out of window visits may have already been mapped to the appropriate closest visit in the data collection and therefore will not be excluded from the population analysis sets. Protocol deviations due to out of window visits are classified as ‘minor’ unless they occur 90 or more days out of window, in which case they are classified as ‘major.’

4.2 Background Characteristics

The following sections describe outputs to be generated for subject background characteristics. In addition to the tables specified in this section, supportive listings will be produced.

4.2.1 Subject Disposition and Accountability

The number of subjects who were enrolled, completed the study, and discontinued from the study, along with the reason for discontinuation, will be summarized.

4.2.2 Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized for the following Populations and Subgroups:

- Study Population
    - Prodromal
    - Symptomatic ALSP (Non-HSCT + Prior HSCT)
        - Symptomatic ALSP (Non-HSCT)
        - Symptomatic ALSP (Prior HSCT)

- Study Population (Non-HSCT)
    - Prodromal
    - Symptomatic ALSP (Non-HSCT)

The following Demographics and Baseline Characteristics will be summarized:

- Age at baseline (continuous variable), calculated as [(Date of Baseline – Date of Birth) / 365.25] and rounded down to the nearest integer
- Age at diagnosis (continuous variable)
- Duration since diagnosis in years, calculated as [(Date of Baseline - ALSP Diagnosis Date)/365.25] and rounded to 1 decimal place.
- If subject had prior HSCT, time in months from HSCT procedure to Baseline visit, rounded to 1 decimal place
- Sex (categorical variable)
- If Female, woman of child-bearing potential (WOCBP) (categorical variable)
- Height (continuous variable)
- Weight (continuous variable)
- Body Mass Index (BMI), calculated as weight/height^2, i.e., kg/m^2
- Country of origin (categorical variable)
- Ethnicity (categorical variable)
- Race (categorical variable; note more than race may be selected)
- Location where the subject was initially consulted (categorical variable)
- Genetically confirmed CSF1R mutation (categorical variable)
    - If genetically confirmed:
        - Exon Number frequency between 18-21 (i.e., inside the tyrosine kinase domain) versus exons 2, 4, 8, 11, 12, 13, 14, 15, 16, 17 (i.e., outside the tyrosine kinase domain)
        - Amino Acid sequence (categorical variable)
        - Nucleic Acid sequence (categorical variable)
- Cognitive Assessments
    - MoCA
    - CDR®+NACC-FTLD Global Score
    - CDR®+NACC-FTLD Sum-of-Boxes
    - CBFS Total Score
- Motor Assessments (Ambulatory Population)
    - 2MWT
    - TUG
- Severity of Illness Scales
    - CGI-S
    - PGI-S
- Other Functional and Psychiatric Assessments (Caregiver Population)
    - FAQ
    - NPI-12
    - ZBI

- Biomarkers
  - Neurofilament light chain (NfL) (Serum)
  - Glial fibrillary acidic protein (GFAP) (Serum)
  - GFAP (CSF)
  - NfL (CSF)
  - sCSF1R (CSF)
  - Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) (CSF)
- MRI
  - Ventricle Volume
  - Adjusted total gray matter volume
  - Corpus callosum thickness
  - Corpus callosum volume
  - Whole brain volume
  - White matter lesion volume
  - Brain volume composite
  - ALSP MRI Severity score

4.2.3 Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher and summarized for the Study Population. Medical History will be summarized by System Organ Class (SOC) and Preferred Term (PT).

4.2.4 Family History

The following Family History variables will be summarized for the Study Population by Subgroup:

- Have any family members been diagnosed with ALSP, have ALSP symptoms, and or have genetic confirmation of CSF1R mutation? (categorical "Yes/No" variable)
  - If Yes:
    - Relationship with the Subject (categorical variable)
    - Family member diagnosed with ALSP? (categorical variable)
    - Age at Diagnosis (continuous variable)
    - Does the family member have a documented CSF1R mutation? (categorical variable)
      - If Yes:
        - Exon Number frequency between 18-21 (i.e., inside the tyrosine kinase domain) versus exons 2, 4, 8, 11, 12 13, 14, 15, 16, 17 (i.e., outside the tyrosine kinase domain).
        - Amino Acid sequence (categorical variable)
        - Nucleic Acid sequence (categorical variable)
        - Mutation Type (categorical variable)
    - Symptoms observed in family member:
      - Cognitive Impairment / Dementia (categorical variable)

- Psychiatric Symptoms (categorical variable)
- Motor Impairment (categorical variable)
- Gait Disorder (categorical variable)
- Seizures (categorical variable)
- Oromotor and Speech Disturbance (categorical variable)
- Sensory and Visual Disturbance (categorical variable)
- Autonomic Symptoms (categorical variable)
- Other Findings (categorical variable)

4.2.5 Prior and Concomitant Medications

All prescription and over-the-counter medications that have been taken during the 30 days before Screening/Baseline through the last study visit will be documented. A complete history of medications taken for the treatment of ALSP will be collected.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary March 2021, or later, and summarized for the Study Population. Prior and concomitant medications will be summarized separately by Anatomical Therapeutic Chemical (ATC) classification and WHO Drug generic term.

4.2.6 Prior and Concomitant Procedures

Procedures will be documented and coded using MedDRA version 24.0 or higher. Prior and concomitant procedures will be described in a listing.

4.3 Study Endpoints and Analysis Methods

The following sections outline the set of proposed endpoints and corresponding analyses. In addition to the tables specified in this section, supportive listings will be produced.

4.3.1 Pharmacodynamic (Biomarker) Endpoints

The following endpoints will be analyzed to determine change over time within the Study Population and if changes from baseline differ across the subgroups. CSF biomarkers are collected in only a subset of subjects from the optional CSF Biomarker sub-study. In addition to descriptive statistics, the geometric mean and geometric CV% will also be included and will be presented by Population and Subgroup for observed value, change from baseline, and percentage change from baseline, where appropriate.

4.3.1.1 Fluid Biomarker Endpoints

Fluid Biomarker endpoints include:

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in NfL and other exploratory marker(s) (e.g., GFAP) in blood

- Change from Baseline to Months 12, 24, and 36 in sTREM2, sCSF1R, NfL and other exploratory marker(s) (e.g., GFAP, Osteopontin) for the CSF Population

4.3.1.2 MRI Endpoints

MRI parameters will all be listed, and parameters will be summarized by Visit, Subject and Subgroup. Listings will include Visit, observed values, change from baseline value and percent change from baseline values. Descriptive statistics (number, arithmetic mean, SD, minimum, median, and maximum) will be presented by Population and Subgroup.

Data from the retrospective pre-screening MRIs are not included with the MRI analysis.

MRI endpoints include:

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in regional brain volume measures (ventricle volume, total gray matter volume, whole brain volume, corpus callosum thickness, corpus callosum volume, white matter lesions and brain volume composite)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in ALSP MRI Severity Score

4.3.2 Clinical Outcome Endpoints

The following endpoints will be analyzed to determine change over time within the Study Population and if changes from baseline differ across the Subgroups.

Descriptive statistics (as described in Section 4.1.7) will be presented by Subgroup for observed, change from baseline, and percentage change from baseline, where appropriate.

4.3.2.1 Cognitive Assessments

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the MoCA
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the CDR®+NACC-FTLD Global Score and Sum of Boxes Score
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the CBFS Motor, Non-motor, and Total Score

4.3.2.2 Motor Assessments (Ambulatory Subjects)

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the 2MWT
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the TUG test

4.3.2.3 Severity of Illness Assessments

- CGI-C at Months 6, 12, 18, 24, 30, and 36
- PGI-C at Months 6, 12, 18, 24, 30, and 36
- Shift tables for CGI-S at Baseline to CGI-C at Months 6, 12, 18, 24, 30, and 36
- Shift tables for PGI-S at Baseline to PGI-C at Months 6, 12, 18, 24, 30, and 36

4.3.2.4 Other Functional and Psychiatric Assessments (Caregiver Population)

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the FAQ Score
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the NPI-12 Total Score
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the CBFS Motor, Non-motor, and Total Score
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Total ZBI Score

4.3.3 Exploratory Endpoints

Exploratory endpoints were added to this SAP, but not to the main study protocol, to help facilitate an integrated analysis of this NHS as a control group compared to a Phase 2 study with a treated population. The outcomes below are not included in study protocol v5.0. The third study objective in the protocol is to create the foundation for a future synthetic control arm, and the exploratory endpoints are consistent with meeting that aim.

4.3.4 Repeated Measures Analysis

Mean changes from baseline in Ventricle Volume, MoCA, and CBFS will be analyzed using restricted maximum likelihood-based mixed effects models for repeated measures (MMRM). Separate models will be generated that consider study visit as a categorical variable, and study day as a continuous variable.

In addition the analyses described below, exploratory analyses may be conducted in which additional covariates are added to the previously described MMRM analyses to understand the influence of these covariates and how imbalance in them across may have influenced results. Additionally, if meaningful outliers are identified by the descriptive analyses, the corresponding MMRM analyses may be replicated as a sensitivity analyses in which the outlier observation(s) is omitted.

MMRM analyses may also be performed with percent change from baseline as the dependent variable for the MRI and biomarker endpoints.

Specifically, the following MMRM models will be explored as the primary models of interest:

- Mean change from baseline to last follow-up in Ventricle volume
- Mean changes from baseline to last follow-up in MoCA
- Mean changes from baseline to last follow-up in CBFS

4.3.4.1 MMRM with Visit as a Categorical Variable

The MMRM model will assess changes from baseline as the dependent variable and include the following parameters:

- ***Subgroup (categorical variable):*** Prodromal, Symptomatic ALSP subjects (Non-HSCT), Symptomatic ALSP (Prior HSCT).

- ***Visit (categorical variable):*** Corresponding to the set of post-baseline scheduled visits for the endpoint as defined in the schedule of assessments.

- ***Baseline score (continuous variable):*** The corresponding baseline value for the dependent variable.

- ***Subgroup × Visit Interaction Effect***

- ***Baseline score × Visit Interaction Effect***

The within-subject covariance will be modeled using a compound symmetric with heterogeneous variance structure (TYPE = CSH). If this analysis fails to converge a simpler compound symmetric structure will be used (TYPE = CS). If this analysis fails to converge the baseline score by visit interaction will be deleted from the model. Denominator degrees of freedom will be determined using the Kenward-Roger approximation.

For each of the 3 subgroups defined above for the categorial Subgroup variable, least squares mean with corresponding SEs, lower and upper bounds of the 95% confidence interval, and p-values will be reported for the within group changes from baseline. The least squares mean difference from the Prodromal subgroup will be similarly presented. Additionally, least squares means and least squares mean difference (versus Prodromal) statistics for the Symptomatic ALSP subgroup (i.e., estimated using a weighted average of the Symptomatic ALSP (Non-HSCT) and Symptomatic ALSP (Prior HSCT) subgroups) may also be estimated.

For each MMRM analysis, a figure will be produced which depicts the least squares mean changes from baseline along with the SE for each of the 3 subgroups by visit.

Sample SAS® code for an MMRM model with study visit as a categorical variable is as follows:

```
PROC MIXED DATA = ADEFF;
     CLASS SUBGR1(REF='PRODROMAL') AVISIT(REF='BASELINE');
     MODEL CHG = SUBGR1 AVISIT BASE SUBGR1*AVISIT BASE*AVISIT /
DDFM=KR;
```

```
      REPEATED AVISIT / SUBJECT=USUBJID TYPE=CSH;
      LSMEANS SUBGR1*AVISIT / DIFF=ALL CL ALPHA=0.05;
RUN;
```

4.3.4.2 MMRM with Study Day as a Continuous Variable

The MMRM model will assess changes from baseline as the dependent variable and include the following parameters:

- **Subgroup** (categorical variable): Prodromal, Symptomatic ALSP subjects (Non-HSCT), Symptomatic ALSP subjects (Prior HSCT)
- **Study Day** (continuous variable)
- **Subgroup × Study Day** (interaction)

Within subject errors will be modeled using an unstructured covariance matrix. Denominator degrees of freedom will be determined using the Kenward-Roger approximation. If this analysis fails to converge, Heterogeneous Toeplitz, Heterogeneous Auto-regressive, and Heterogeneous Compound Symmetric structures will be tested. The first structure to yield convergence will be considered the primary analysis for each respective dependent variable.

For each of the 3 subgroups (i.e., as defined above for the categorial Subgroup variable), estimated change from baseline values at Months 6, 12, 18, 24, 30, and 36 will be presented with corresponding SEs, lower and upper bounds of the 95% confidence interval, and p-values will be reported for the within group changes from baseline. The difference from the Prodromal subgroup will be similarly presented for the Months 6, 12, 18, 24, 30, and 36 estimates. Additionally, values at Months 6, 12, 18, 24, 30, and 36 for the Symptomatic ALSP subgroup (i.e., estimated using a weighted average of the Symptomatic ALSP (Non-HSCT) and Symptomatic ALSP (Prior HSCT) subgroups) and corresponding difference from the Prodromal subgroup may also be estimated.

For each MMRM analysis, a figure will be produced which depicts the regression lines for each of the subgroups with the SE of the estimate being presented at Months 6, 12, 18, 24, 30, and 36.

Sample SAS® code for an MMRM model with study day as a continuous variable is as follows:

```
PROC MIXED DATA = ADEFF;
     CLASS USUBJID SUBGR1(REF='PRODROMAL');
     MODEL CHG = SUBGR1 ADY SUBGR1*ADY / DDFM = KR;
     REPEATED / SUBJECT = USUBJID TYPE = UN;
RUN;
```

4.4 Clinical Biomarker Correlations

Correlations will be performed using both Pearson and non-parametric Spearman correlations. The correlations and corresponding p-value will be presented. The correlations of primary

interest are change from baseline in ventricle volume to month 12 with change from baseline to month 12 in MoCA (and CBFS) for the Study Population.

There are three types of correlations:

- ***Correlations of change:*** Correlations between change from baseline in MRI and biomarker endpoints and change from baseline in clinical endpoints
- ***Prognostic correlations:*** Correlations between baseline values in MRI and biomarker endpoints and change from baseline in clinical endpoints
- ***Cross-sectional correlations:*** Correlations between values at each timepoint.

Endpoints include the following:

- ***MRI endpoints:*** Ventricle volume, adjusted total gray matter volume, corpus callosum thickness, corpus callosum volume, whole brain volume, white matter lesion volume, brain volume composite, and ALSP MRI Severity score
- **F*luid biomarker endpoints:*** NfL (Serum), GFAP (Serum), GFAP (CSF), NfL (CSF), sCSF1R (CSF), sTREM2 (CSF)
- **Clinical endpoints*:*** MoCA, CBFS Total Score, CGI-S/C, CDR®+NACC-FTLD Sum-of-Boxes

Tables in the Appendix (Section 6.3) provide the set of correlations to be calculated for the key clinical, fluid biomarker and MRI endpoints provided above for two populations.

4.5 Safety Endpoints

Safety summaries will be performed for the Study Population and the following subgroups:

- Prodromal
- Symptomatic ALSP subjects
  - Symptomatic ALSP subjects (Prior HSCT)
  - Symptomatic ALSP subjects (Non-HSCT)

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

The C-SSRS “Baseline/Screening” and “Since Last Visit” versions will be summarized with frequency counts (i.e., as a categorical variable) at each scheduled assessment visit, for baseline and post-baseline visits, respectively.

4.5.2 Concomitant Therapies

Concomitant therapies will be recorded and will be presented in listings. Supportive summary tables may be produced.

4.5.3 Adverse Events

AEs will be mapped to a MedDRA version 24.0 or higher. Severity will be assessed by the investigator.

The following AE summaries will be performed:

- AEs summarized by PT and SOC
- AEs summarized by PT and SOC by severity
- AEs related to study procedures summarized by PT and SOC.
- Serious AEs (SAEs) summarized by PT and SOC

4.5.4 Survival

The number and percentage of subjects who have died will be summarized.

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6 Appendices

6.1 Schedule of Assessments

Table 3. Schedule of Assessments

	Assessment[a]	Visit						
		Screening/ Baseline[b]	Month 6 (±14 d)	Month 12 (±14 d)	Month 18 (±14 d)	Month 24 (±14 d)	Month 30 (±14 d)	Month 36/ET[c] (±14 d)
Study Entrance & Disease History	Informed consent[d]	X						
	Eligibility	X						
	Documentation of *CSF1R* gene mutation	X						
	Medical/family history and demographics	X						
	Prior/concomitant medications/procedures[e]	X	X	X	X	X	X	X
	Urine drug screen	X						
	Urine pregnancy test (WOCBP)	X	X	X	X	X	X	X
	COVID-19 assessment[f]	Per SOC	Per SOC	Per SOC	Per SOC	Per SOC	Per SOC	Per SOC
Safety Assessments	C-SSRS[g]	X	X	X	X	X	X	X
	Physical and neurological examinations	X	X	X	X	X	X	X
	Height and weight	X						
	Adverse events[h]	X	X	X	X	X	X	X
	Survival assessment[i]					X		X
	Coagulation for *Optional* CSF Biomarker Sub-study[j]	X		X		X		X[o]
Biomarkers	Blood sampling (for biomarker analysis)	X	X	X	X	X	X	X[p]
	Optional CSF Biomarker Sub-study[k]	X		X		X		X[o]
	Magnetic Resonance Imaging (MRI)[l]	X	X	X	X	X	X	X[q]
Cognitive Assessments	MoCA	X	X	X	X	X	X	X
	CDR®+NACC-FTLD[m]	X	X	X	X	X	X	X
	BAC	X	X	X	X	X	X	X
	CBFS	X	X	X	X	X	X	X
Motor Assessments	2MWT	X	X	X	X	X	X	X
	TUG	X	X	X	X	X	X	X
Severity of Illness Scales	CGI-S	X						
	CGI-C		X	X	X	X	X	X
	PGI-S	X						
	PGI-C		X	X	X	X	X	X
Functional, Psychiatric & Other Assessments	FAQ[n]	X	X	X	X	X	X	X
	NPI-12[n]	X	X	X	X	X	X	X
	Zarit Burden Interview[n]	X	X	X	X	X	X	X

Abbreviations: 2MWT = 2-Minute Walk Test, ALSP = adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, BAC = Brief Assessment of Cognition, CBFS = Cortical Basal ganglia Functional Scale, CDR®+NACC-FTLD = Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center-Frontotemporal Lobar Degeneration, CGI-C = Clinical Global Impression - Change, CGI-S = Clinical Global Impression – Severity of Illness, CSF = cerebral spinal fluid, CSF1R = colony-stimulating factor 1 receptor, C-SSRS = Columbia-Suicide Severity Rating Scale, ET = early termination, FAQ = Functional Activities Questionnaire, LP = lumbar puncture, MoCA = Montreal Cognitive Assessment, NPI-12 = Neuropsychiatric Inventory – 12-Item Version, PGI-C = Patient Global Impression - Change, PGI-S = Patient Global Impression - Severity of Illness, SOC = standard of care, TUG = Timed Up and Go, WOCBP = women of childbearing potential.

a. At each clinic visit, whenever feasible, the cognitive and motor assessments should be prioritized. Study visits should be scheduled at approximately the same time each day to ensure that scales are completed at consistent times during the study.
b. Screening/Baseline assessments may be completed at more than 1 study visit; all assessments must be completed within 28 days.
c. Subjects who permanently discontinue from the study before completing the Month 36 Visit will be required to return for an Early Termination (ET) Visit.
d. Written informed consent must be obtained before any study related procedures are conducted.
e. All prescription and over-the-counter medications that have been taken during the 30 days before Screening/Baseline (i.e., Day 1) through the last study visit will be documented. A complete history of medications taken for the treatment of ALSP will be collected. Prior medical procedures will also be recorded.
f. COVID-19 assessments will be performed per local guidelines and standard of care at the site.
g. The "Baseline Screening" (lifetime and last 6 months) C-SSRS form will be completed at Screening to determine eligibility. The "Since Last Visit" C-SSRS form will be completed at Months 6, 12, 18, 24, 30, and 36.
h. All adverse events/serious adverse events will be monitored until resolution or stabilization.
i. Attempts will be made to determine the survival status (alive or deceased) of any subject who fails to return for the final visit or who discontinues from the study before completing the 24-month (subjects who withdraw from the study before implementation of Amendment 3) to 36-month (subjects who withdraw from the study after implementation of Amendment 3) observation period. Study staff will contact the subject or the subject's caregiver by telephone to determine survival status 24 or 36 months, respectively, after the date of the subject's Screening Visit or at the end of the study, whichever occurs sooner.
j. Local blood coagulation panel will need to be completed prior to lumbar puncture (LP) for subjects that volunteer to participate in the optional CSF sample collection.
k. Biomarkers in CSF will be determined in subjects who provide informed consent to participate in an optional CSF Biomarker Sub-study.
l. The MRI scans may be obtained ±2 days before the scheduled visit.
m. At the investigator's discretion, the CDR®+NACC-FTLD may not need to be administered if there are no signs or symptoms of cognitive impairment (i.e., normal score on the MoCA) or if the subject does not have a caregiver who has provided informed consent for the study.
n. The FAQ, NPI-12, and Zarit Burden Interview will not be completed if the subject does not have a caregiver who has provided informed consent for the study.
o. For subjects who participate in the CSF sub-study and who discontinue from this study to enroll in a VGL101 clinical study, CSF biomarker collection will be performed at the Screening or Baseline Visit of the VGL101 clinical study and will be analyzed as part of both studies. If CSF collection is not included at the Screening or Baseline Visit of the VGL101 clinical study, CSF biomarker collection will be done at the ET Visit of this study.
p. For subjects who discontinue from this study to enroll in a VGL101 clinical study, blood biomarker collection will be performed once for both the ET Visit of this study and the Screening/Baseline Visit of the VGL101 study and will be analyzed as part of both studies.
q. For subjects who discontinue from this study to enroll in a VGL101 clinical study, an MRI will be collected once for both the ET Visit of this study and the Screening/Baseline Visit of the VGL101 clinical study and will be analyzed as part of both studies.

6.2 Study Assessments

The following are the set of study variables to be collected, following the Schedule of Assessments.

6.2.1 Study Entrance and Disease History

- Documentation of CSF1R gene mutation
- Medical/family history and demographics
- Prior/concomitant medications/procedures
- Urine drug screen
- Urine pregnancy test for WOCBP
- COVID-19 assessment

6.2.2 Safety Assessments

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

The C-SSRS is a semi-structured tool used to assess suicidal ideation and behavior (Posner et al, 2011). It does not use a simple numerical sum, but rather classifies individuals into different risk categories based on their highest level of ideation and presence of suicidal behavior.

At study baseline, the C-SSRS "Baseline/Screening" version is administered to assess suicidal ideation over two distinct timeframes:

- ***Lifetime Assessment:*** Subjects are asked about the presence and intensity of suicidal ideation at any point in their entire lifetime.

- ***Past 6 months:*** Subjects are also asked about the presence and intensity of suicidal ideation occurring within the past 6 months to capture more recent risk.

For subsequent study visits, the "Since Last Visit" version of the C-SSRS will be used to evaluate any new or ongoing suicidal ideation and behavior that occurred since the subject's prior visit.

- ***Since Last Visit:*** Subjects are asked about the presence and intensity of suicidal ideation since their last study visit.

The study protocol contains additional detail about using the C-SSRS to determine subject eligibility and continuation in the study, and care for the subject.

6.2.2.2 Physical and Neurological Examinations

A complete physical examination will include measurement of height and weight (Screening/Baseline only) and examination of general appearance and the skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities. Genital, rectal, and breast examination may be excluded if not clinically indicated.

The neurological examination will include assessment of mental status (level of consciousness, orientation, speech, memory, etc.), examination of cranial nerves II-XII, motor examination (muscle appearance, tone, strength, and reflexes), sensory examination, reflexes, coordination, stance, gait, and balance.

Physical and neurological examinations will be conducted at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET.

6.2.2.3 Adverse Events

An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to a study procedure.

All AEs and SAEs that are reported by the subject (or, when appropriate, by a caregiver, surrogate, or legally authorized representative) or observed by the investigators from the time the Informed Consent Form (ICF) is signed through the Month 24 Visit (subjects who complete the study before implementation of Amendment 3), the Month 36 Visit (subjects who complete the study after implementation of Amendment 3), or ET Visit will be recorded. All AEs/SAEs will be monitored until resolution or stabilization.

6.2.2.4 Survival Assessment

Attempts will be made to determine the survival status (alive or deceased) of any subject who is lost to follow-up or who discontinues from the study before completing the 24-month (subjects who withdraw from the study before implementation of Amendment 3) or 36-month (subjects who withdraw from the study after implementation of Amendment 3) observation period. Study staff will contact the subject or the subject's caregiver by telephone to determine survival status 36 months after the date of the subject's Screening Visit or at the end of the study, whichever occurs sooner.

6.2.3 Biomarkers

Concentration data for pharmacodynamic blood and CSF biomarker variables will be obtained from central testing laboratory.

If more than one concentration is reported for an analyte for a given subject(s) and timepoint(s) (e.g., duplicate analysis inadvertent or otherwise), then the value reported from the batch that included all longitudinal time points for that given analyte and subject will be included in the analysis. Note that this will be identified by the "Assay/Run-ID" that is provided with each batch.

6.2.3.1 Blood Sampling (for Biomarker Analysis)

Blood samples for NfL will be obtained at Screening/ Baseline and at Months 6, 12, 18 24, 30, and 36/ET. Other exploratory biomarkers (e.g., GFAP) will also be obtained.

6.2.3.2 Cerebrospinal Fluid (CSF) Biomarker: Optional Sub-study

Cerebrospinal fluid samples for NfL, sTREM2, and soluble CSF1R will be obtained at Screening/Baseline and at Months 12, 24, and 36/ET from subjects who provide informed consent to participate in the optional CSF Biomarker Sub-study to provide further insight into the onset and progression of ALSP. Other exploratory biomarkers (e.g., Osteopontin, GFAP) will also be obtained. The completion of these investigations will be based on the results of this or other exploratory work.

6.2.3.3 Magnetic Resonance Imaging (MRI)

Regional brain volume measures and ALSP MRI Severity Scores will be obtained at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET. Regional brain volume key measures include ventricle volume, total gray matter volume, whole brain volume, corpus callosum thickness, corpus callosum volume, and white matter lesion volume.

The gray matter region will be adjusted (Total Gray Matter Adjusted) to account for tissue identified as gray matter within in the white matter lesion. This will be done using the following equation:

$$Adjusted\ Total\ Gray\ Matter = Gray\ Matter - Gray\ Matter\ in\ White\ Matter\ Lesions$$

6.2.4 Cognitive Assessments

6.2.4.1 Montreal Cognitive Assessment (MoCA)

The MoCA is a screening tool that is used to evaluate cognitive abilities and dementia (Nasreddine et al., 2005). The MoCA evaluates different types of cognitive domains, including orientation, short-term memory, delayed recall, abstraction, visuospatial, and executive functioning; language; and attention. Scores range from 0 to 30.

MoCA Tasks and Points:

- Visuospatial/executive score = 5 points
- Naming score = 3 points
- Attention: Digits forward and backward score = 2 points
- Attention: Letter tapping score = 1 point
- Attention: Serial 7 subtraction score = 3 points
- Language: Repeat score = 2 points
- Language: Fluency score = 1 point
- Abstraction score = 2 points
- Delayed recall only score = 5 points
- Orientation score: 6 items (date, month, year, day, place, city) = 6 points

Additionally, the MoCA can be adjusted for education to help account for differences in cognitive abilities due to education.

- Less than or Equal to 12 years of education (1 points if 'yes', 0 point if 'no')

When all items are complete, the education-adjusted MoCA is a sum of 11 items:

$$MoCA_{Total} = \sum_{i=1}^{11} Tasks_i + Education$$

Where:

- $Tasks_i$ = cognitive domain tasks (point totals from each of *i* tasks)
- *Education* is a dichotomous variable coded as:
  - 1 indicates less than or equal to 12 years of education
  - 0 indicates > 12 years of education
- Education is collected at each study visit, and the education component from each visit will be used (i.e., the baseline education value will not be carried forward to all subsequent visits)
- The maximum possible score is 30, therefore, if a subject scores 30/30, a point is not added if the subject has 12 years of education or less.

If data are missing from one of the tasks, or if education is missing, $MoCA_{Total}$ will be missing. Because the individual item tasks in the MoCA are not collected in the electronic data, and only the point totals are recorded, available item averaging is not an applicable option. If missing data are >20%, a weighted task averaging will be explored in sensitivity analysis.

The MoCA will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET.

6.2.4.2 Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center-Frontotemporal Dementia (CDR®+NACC-FTLD)

The CDR®+NACC-FTLD is a semi-structured global assessment measure that was developed to measure the severity of dementia symptoms in Alzheimer's disease and related dementias (Miyagawa et al. 2020).

The 8 domains of the CDR®+NACC-FTLD-SB are:

- Memory (5-point scale ranging from 0-3)
- Orientation (5-point scale ranging from 0-3)
- Judgement and Problem Solving (5-point scale ranging from 0-3)
- Community Affairs (5-point scale ranging from 0-3)
- Home and Hobbies (5-point scale ranging from 0-3)
- Behavior/Comportment/Personality (5-point scale ranging from 0-3)
- Language (5-point scale ranging from 0-3)
- Personal Care (4-point scale ranging from 0-3)

The first 7 domains are rated on a 5-point scale (0 = normal, 0.5 = questionably or minimally impaired, 1 = mildly but definitely impaired, 2 = moderately impaired, and 3 = most severely impaired). The eighth domain, Personal Care, does not have a rating of 0.5 and, therefore, is rated on a 4-point scale.

The total score of CDR®+NACC-FTLD-SB (sum of boxes) is defined as the sum of all 8 domain ratings.

$$\text{CDR®. NACC. FTLD. SB}_{Total} = \sum_{i=1}^{8} DomainRating_i$$

If one or more domains are missing for the sum of boxes calculation, a proportional adjustment will be made, scaling the sum of the observed scores to an equivalent full-score range:

$$\text{CDR®. NACC. FTLD. SB}_{Total\_adj} = \frac{\sum X_i}{N_{Answered}} \times 8$$

Where:

- X_i = 8 domains with item scores ranging from 0-3
- $N_{Answered}$ = number of domain items with a valid response
- 8 = total number of domains in the full CDR®+NACC-FTLD
- Range of the score is 0-24

The Global CDR®+NACC-FTLD uses the same 8 items as the SB (sum of boxes) version. The Global score ranges from 0 to 3 (the lower the better) and is determined using specific scoring rules:

1. If all domains are 0, then the global CDR®+NACC-FTLD score is 0.
2. If the maximum domain score is 0.5, the global CDR®+NACC-FTLD score is 0.5.
3. If the maximum domain score is above 0.5 in any domain, the following applies:
   a. If the maximum domain score is 1 and all other domains are 0, the global CDR®+NACC-FTLD score is 0.5.
   b. If the maximum domain score is 2 or 3, and all other domains are 0, the global CDR®+NACC-FTLD score is 1.
   c. If the maximum score occurs only once, and there is another rating besides 0, the global CDR®+NACC-FTLD score is one level lower than the level corresponding to maximum impairment.
4. If the maximum domain score occurs more than once, then the global CDR®+NACC-FTLD score is the maximum domain score.

The CDR®+NACC-FTLD will be administered by trained site personnel at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET. At the investigator's discretion, the CDR®+NACC-FTLD may not need to be administered if there are no signs or symptoms of cognitive impairment (i.e., normal score on the MoCA) or if the subject does not have a caregiver who has provided informed consent for this study.

6.2.4.3 Cortical Basal Ganglia Functional Scale (CBFS)

The CBFS is a novel rating scale that evaluates experiences in daily living (EDL) and behavioral, language, and cognitive impairments in subjects with 4 repeat tauopathies (Lang et. al., 2020). The CBFS consists of 14 questions on motor EDLs and 17 questions on non-motor EDLs, each of which is rated on a Likert 5-point scale that rates function from 0 to 4, where 0 = normal or no problems and 4 = severe problems. The questions are for the subject but should be answered by the subject and caregiver working together. Responses are to be based on the usual or average function over the past 2 weeks.

The Total scores for the Motor Experiences, Non-Motor Experiences, and Overall will be summarized.

6.2.4.3.1 CBFS Motor Experiences of Daily Living (CBFS-M)

The CBFS-M Assesses how motor symptoms impact daily activities. The CBFS-M is calculated by summing (adding) the scores from 14 items.

If all 14 items are answered, the formula for the CBFS-M is a simple sum:

$$CBFSm_{Total} = \sum_{i=1}^{14} X_i$$

If only one (<10% of data) of 14 motor EDLs is missing, the available item mean multiplied by 14 will be used.

$$CBFSm_{Total\_Adj} = \left(\frac{\sum X_i}{N_{Answered}}\right) \times 14$$

Where:

- X_i = individual motor-related item scores (from 0 to 4)
- $N_{Answered}$ = number of motor-related items with a valid response
- 14 = total number of items in the full CBFS-M score
- Range of the score is 0 to 56

If 2 or more of the 14 items are missing, the total CBFS-M score will be set to missing.

6.2.4.3.2 CBFS Non-Motor Experiences of Daily Living (CBFS-NM)

The CBFS-NM evaluates cognitive, emotional, and autonomic dysfunction. The CBFS-NM is calculated by summing (adding) the scores from 17 items.

If all 17 items are answered, the formula for the CBFS-NM is a simple sum:

$$CBFSnm_{Total} = \sum_{j=1}^{17} X_j$$

If only one (<10% of data) of 17 non-motor EDLs is missing, the available item mean multiplied by 17 will be used.

$$CBFSnm_{Total\_Adj} = \left(\frac{\sum X_j}{N_{Answered}}\right) \times 17$$

Where:

- X_j = individual non-motor related item scores (from 0 to 4)
- $N_{Answered}$ = number of non-motor-related items with a valid response
- 17 = total number of items in the full CBFS-NM score
- Range of the score is 0 to 68

If 2 or more of the 17 items are missing, the total CBFS-NM score will be set to missing.

6.2.4.3.3 CBFS Total Score (Overall Functional Impact)

The CBFS Total Score (overall functional impact) is the sum of the motor and non-motor components.

$$CBFS_{Total} = \sum_{i=1}^{14} X_i + \sum_{j=1}^{17} X_j$$

To ensure that the total CBFS is a sum of the CBFS-M and CBFS-NM, the available item mean is used separately by the number of items missed in each component.

$$CBFS_{Total\_Adj} = \left[\left(\frac{\sum X_i}{N_{Answered}}\right) \times 14\right] + \left[\left(\frac{\sum X_j}{N_{Answered}}\right) \times 17\right]$$

- X_i = individual motor-related item scores (from 0 to 4)
- X_j = individual non-motor related item scores (from 0 to 4)
- $N_{Answered}$ = number of items with a valid response

- 14 = total number of items in the full CBFS-M score
- 17 = total number of items in the full CBFS-NM score
- Range of score is 0 to 124

The CBFS will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30 and 36/ET.

6.2.5 Motor Assessments

Motor assessments will be shown for the Ambulatory Population.

6.2.5.1 2-Minute Walk Test (2MWT)

The 2MWT is a measure of self-paced walking ability and functional capacity, particularly for individuals who cannot manage longer periods of walking. The 2MWT has been used as an outcome measure in a variety of health conditions, including neuromuscular diseases in the adult and pediatric populations. The test measures the distance a person can walk in 2 minutes. Individuals are encouraged to walk as fast as they can, safely, for 2 minutes, and to cover as much ground as possible without running. Rest breaks are allowed, if needed, but the timer is not stopped. Walking aids can be used, if needed, but should be kept consistent from test to test. Rest breaks and use of aids should be recorded. As normal subjects aged <59 years can walk up to 200 meters in 2 minutes, a testing area that allows a minimum number of turns should be available.

The 2MWT will be done at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET.

2MWT distances exceeding 300 meters will be excluded from analyses as these values are implausible for this study population (Bohannon, 2017).

6.2.5.2 Timed Up and Go (TUG)

The TUG is used to determine the time (in seconds) needed to progress from sitting to standing and walking. In addition, the test helps to evaluate the probability for falls. The TUG, which was initially designed for elderly persons, is also used in populations with conditions that can affect ambulation and balance. This tool is validated for populations with Parkinson's disease, multiple sclerosis, hip fracture, Alzheimer's disease, cerebrovascular accident (CVA), Huntington's disease, and post-CVA. The individual starts in a seated position in a chair with armrests and, upon command, stands up, walks 3 meters, turns around, walks back to the chair, and sits down. The time stops when the subject is seated. The use of walking aids should be recorded and kept consistent between tests.

The TUG will be done at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET.

6.2.6 Severity of Illness Scales

6.2.6.1 Clinical Global Impression – Severity of Illness (CGI-S)

The CGI-S scale is a 1-item 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of the assessment relative to the clinician's past experience with patients who have the same diagnosis. Raters select one response based on the following question: "Considering your total clinical experience with this particular population, how ill is the patient at this time?" Scores are as follows: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

The CGI-S will be completed at Screening/Baseline.

6.2.6.2 Clinical Global Impression - Change (CGI-C)

The CGI-C is a 1-item 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to the baseline state at the beginning of the intervention. Raters select one response based on the following question, "Compared to your patient's condition at the beginning of study, how much has your patient changed?" Scores are as follows: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; and 7 = very much worse.

The CGI-C will be completed at Months 6, 12, 18, 24, 30, and 36/ET.

6.2.6.3 Patient Global Impression – Severity of Illness (PGI-S)

The PGI-S is a 1-item questionnaire that is designed to assess a patient's impression of disease severity (Guy, 1976). It may be interpreted as the patient-reported outcome counterpoint to the CGI-S, which is assessed by a clinician. The PGI-S item asks subjects to describe their current symptoms on the following 4-point scale: 1 = normal, 2 = mild, 3 = moderate, or 4 = severe.

The PGI-S will be completed at Screening/Baseline.

6.2.6.4 Patient Global Impression - Change (PGI-C)

The PGI-C is a 1-item measure used to assess a patient's perception of overall improvement or worsening in response to treatment. It may be interpreted as the patient-reported outcome counterpoint to the CGI-C. The qualitative assessment of meaningful change is determined by the patient in response to the question, "Compared to your condition at the beginning of study, how much has your condition changed?" Scores are as follows: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; and 7 = very much worse.

The PGI-C will be completed at Months 6, 12, 18, 24, 30, and 36/ET.

6.2.7 Functional, Psychiatric and Other Assessments

The assessments described in this section are only completed if the subject has a study partner who has provided informed consent for the study. Results will be shown for the Caregiver Population.

6.2.7.1 Functional Activities Questionnaire (FAQ)

The FAQ is a 10-item questionnaire that measures instrumental activities of daily living, such as preparing balanced meals and managing personal finances. Functional changes in instrumental activities of daily living that require a higher cognitive ability are noted earlier in the dementia process than changes in basic activities of daily living. Therefore, the FAQ is useful to monitor these functional changes over time in subjects with mild dementia and has been used in clinical trials of subjects with mild cognitive impairment and in subjects with mild to moderate and severe dementias.

The FAQ assesses 10 functions related to personal finances, shopping, playing games, meal preparation, watching television, following the news, taking medications, and traveling. Each function is rated from 0 to 3 (0 = normal, 1 = has difficulty but can do alone, 2 = requires assistant, and 3 = totally dependent on others to do). The FAQ demonstrates high correlation with cognitive measures and is sensitive to change over time.

A total FAQ score is calculated by summing (adding) the scores of 10 items together.

If all 10 items are answered, the formula for the FAQ is a simple sum:

$$FAQ_{Total} = \sum_{i=1}^{10} X_i$$

If only one (10% of the data) FAQ item is missing, the available item mean multiplied by 10 will be used.

$$FAQ_{Total\_Adj} = \left(\frac{\sum X_i}{N_{Answered}}\right) \times 10$$

Where:

- X_i = individual item scores (from 0 to 3)
- $N_{answered}$ = number of items with a valid response
- 10 = total number of FAQ items
- Range of the score is 0 to 30

If 2 or more of the 10 items are missing, the total FAQ (FAQ_{Total} and FAQ_{Total_Adj}) will be set to missing. To reduce bias due to missing data, FAQ_{Total_Adj} will serve as the primary variable for reporting on the FAQ, and FAQ_{Total} will be included in the ADaM datasets for future sensitivity analyses beyond the scope of this SAP.

The FAQ will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30 and 36/ET.

6.2.7.2 Neuropsychiatric Inventory – 12 Item Version (NPI-12)

The NPI-12 is a 12-item inventory that provides a brief assessment of neuropsychiatric symptomatology in clinical practice settings and in clinical trials. The NPI-12 assesses the following 12 behavioral domains that are common in dementia: hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and nighttime behavior change, and appetite and eating change.

The NPI-12 is administered by the clinician to the caregiver. The caregiver is usually a family member who is involved in the daily care of the subjects but can be administered to a professional caregiver or other involved person as long as the person has detailed knowledge of the patient's behavior. The clinician reads each question to the caregiver as it is written. After reading the screening question, the caregiver is asked if the behavior that was described is present, if the answer is "no" then the clinician proceeds to the next section and reads the next screening question. If the answer is "yes" to the screening question, the rater then rates the frequency (rarely, sometimes, often, very often), severity of the symptoms that have been present within the last month (mild, moderate, or severe), and the associated impact of the symptom manifestations on them (i.e., caregiver distress; not at all, minimally, mildly, moderately, severely, or very severely or extremely). The total scores can be used for monitoring the worsening of or improvement in neuropsychiatric symptoms.

Each of the 12 NPI domain items are rated on:

- Frequency (*F*): 1 (Rarely) to 4 (Very Often)
- Severity (*S*): 1 (Mild) to 3 (Severe)
- Caregiver distress rating (D): 0 (Not at all) to 5 (Very Severely or Extremely)

The NPI-12 will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET.

6.2.7.2.1 NPI Total

The NPI-12 Total score quantifies the severity and frequency of neuropsychiatric symptoms across 12 domains.

If all 12 frequency and severity items are answered, the NPI-12 Total is calculated by summing the severity x frequency scores for each of the 12 domains:

$$NPI12_{Total} = \sum_{i=1}^{12} (F_i \times S_i)$$

If one frequency item and/or one severity item are missing, the available item mean multiplied by 12 will be used:

$$NPI12_{Total\_Adj} = \left(\frac{\sum F_i \times S_i}{N_{Answered}} \right) \times 12$$

Where:

- F_i = Frequency of symptom for domain *i* (scored 1-4)
- *Si* = Severity of symptom for domain *i* (scored 1-3)
- *i* = Each of the 12 NPI domains
- $N_{Answered}$ = Number of non-missing domains
- 12 = total number of domains
- Range of the score is 0 to 144

If 2 or more of the any frequency or severity items are missing, the NPI Total scores ($NPI12_{Total}$ and $NPI12_{Total\_Adj}$) will be set to missing. To reduce bias due to missing data, $NPI12_{Total\_Adj}$ will serve as the primary variable for reporting on the NPI12 Total, and $NPI12_{Total}$ will be included in the ADaM datasets for future sensitivity analyses beyond the scope of this SAP.

6.2.7.2.2 NPI-12 Distress Total

The NPI-12 Distress Total score measures how distressing each symptom is to the caregiver, rated from 0 to 5 for each domain.

If all 12 distress items are answered, the NPI-12 Distress Total is calculated by summing the caregiver distress ratings:

$$NPI12_{Distress} = \sum_{i=1}^{12}(D_i)$$

If distress item is missing, the available item mean multiplied by 12 will be used:

$$NPI12_{Distress\_Adj} = \left(\frac{\sum D_i}{N_{Answered}}\right) \times 12$$

Where:

- D_i = Caregiver distress score for domain *i* (scored 0-5)
- *i* = Each of the 12 NPI domains
- $N_{Answered}$ = Number of non-missing domains
- 12 = total number of domains
- Range of the score is 0 to 60

If more than 1 of the distress items are missing, the NPI Distress Total score ($NPI12_{Distress}$ and $NPI12_{Distress\_Adj}$) will be set to missing. To reduce bias due to missing data, $NPI12_{Distress\_Adj}$ will serve as the primary variable for reporting on the NPI12 Distress Total, and $NPI12_{Distress}$ will be included in the ADaM datasets for future sensitivity analyses beyond the scope of this SAP.

6.2.7.3 Zarit Burden Interview (ZBI)

The ZBI is a 22-item self-report questionnaire designed to evaluate the impact of caregiving on the primary caregiver (Zarit, Reever & Bach-Peterson, 1980). It assesses caregiver burden across 22 different domains, measuring physical, emotional, and social strain.

Each item on the interview is a statement that the caregiver is asked to rate using a 5-point scale that ranges from 0 ("never") to 4 ("nearly always"). The first 21 items are scored: 0-never, 1-rarely, 2-sometimes, 3-quite frequently, and 4-nearly always. The final item, "Overall, how burdened do you feel in caring for your relative?" is scored on a comparable 5-point scale: 0-not at all, 1- a little, 2-moderately, 3-quite a bit, and 4-extremely. A total score is computed by summing together the 22 items.

The ZBI will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30 and 36/ET.

A ZBI total score is calculated by summing (adding) the scores of the 22 item scores together.

If all 22 items are answered, the formula for the ZBI total is a simple sum:

$$ZBI_{Total} = \sum_{i=1}^{22} X_i$$

If only one or two (<10%) ZBI questionnaire items are missing, the available item mean multiplied by 22 will be used:

$$ZBI_{Total\_Adj} = \left(\frac{\sum X_i}{N_{Answered}}\right) \times 22$$

Where:

- X_i = individual item scores (from 0 to 4)
- $N_{Answered}$ = number of items with a valid response
- 22 = total number of items in the full ZBI scale
- Range of the score is 0 to 88

If 3 or more of the 22 items on the scale are missing, the total ZBI scores (ZBI_{Total} and ZBI_{Total_ADJ}) will be set to missing. To reduce bias due to missing data, ZBI_{Total_ADJ} will serve as the primary variable for reporting on the ZBI, and ZBI_{Total} will be included in the ADaM datasets for future sensitivity analyses beyond the scope of this SAP.

The foundational study introducing the ZBI (Zarit, Reever & Bach-Peterson, 1980) identified the basic scoring principles but did not explicitly detail handline missing items. Little & Rubin (2002) support the approach of using the mean of completed items in psychological scales when a small proportion of the times are missing.

6.3 Correlations

6.3.1 Correlations Endpoints and Visits for the Study Population

		MRI and Fluid Biomarker Endpoints														
		All[a]	Base[a]	M6[ab]	M12[a]	M18[ab]	M24[a]	M30[ab]	M36[a]	All CFB	M6 CFB[b]	M12 CFB	M18 CFB[b]	M24 CFB	M30 CFB[b]	M36 CFB
Clinical Endpoint	All	X														
	Base		X													
	M6			X												
	M12				X											
	M18					X										
	M24						X									
	M30							X								
	M36								X							
	All CFB									X						
	M6 CFB										X					
	M12 CFB										X	X				
	M18 CFB										X	X	X			
	M24 CFB										X	X	X	X		
	M30 CFB										X	X	X	X	X	
	M36 CFB										X	X	X	X	X	X

Abbreviations: Base= Baseline, M=Month, CFB=change from baseline.

a: All, Base, M6, M12, M18, M24, M30, M36 fluid biomarker endpoint correlations will not be generated

b: M6, M18, M30, M6 CFB, M18 CFB, and M30 CFB do not apply to CSF Fluid Biomarkers, which are not globally assessed at months 6, 18 or 30.

6.3.2 Correlations Endpoints and Visits for Prodromal + Symptomatic ALSP Subjects (Non-HSCT)

		MRI and Fluid Biomarker Endpoints														
		All	Base	M6 [a]	M12	M18 [a]	M24	M30 [a]	M36	All CFB	M6 CFB [a]	M12 CFB	M18 CFB [a]	M24 CFB	M30 CFB [a]	M36 CFB
Clinical Endpoint	All	X														
	Base		X													
	M6			X												
	M12				X											
	M18					X										
	M24						X									
	M30							X								
	M36								X							
	All CFB									X						
	M6 CFB		X								X					
	M12 CFB		X								X	X				
	M18 CFB		X								X	X	X			
	M24 CFB		X								X	X	X	X		
	M30 CFB		X								X	X	X	X	X	
	M36 CFB		X								X	X	X	X	X	X

Abbreviations: Base= Baseline, M=Month, CFB=change from baseline.

a: M6, M18, M30, M6 CFB, M18 CFB, and M30 CFB do not apply to CSF Fluid Biomarkers, which are not globally assessed at months 6, 18 or 30.