CLINICAL PROTOCOL

Protocol Title:	A Natural History Study of Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)
Short Title:	Illuminate
Protocol Number:	VGL101-01.002
Compound:	Not Applicable (Non-interventional Trial)
Study Phase:	Observational
Sponsor:	Vigil Neuroscience, Inc. [redacted]
Protocol Version:	5.0
Approval Date:	02 October 2024

Confidentiality Statement

SPONSOR SIGNATORIES

[redacted]

[redacted]

Date

PROTOCOL VERSION 5.0 SUMMARY OF CHANGES TABLE

Document History	
Document	**Date**
Version 5.0	02 Oct 2024
Version 4.0	03 Oct 2023
Version 3.0	01 Mar 2022
Version 2.0	29 Jul 2021
Original (Version 1.0)	14 May 2021

Amendment 4: Protocol Version 5.0 (02 Oct 2024)

Overall Rationale for Amendment

The overall rationale for this amendment is to allow for telephone visits, at the investigator's discretion, for study subjects who can no longer attend clinic visits due to their disease progression. This amendment also adds a provision to collect MRI data prior to each consenting subject's participation in the study.

Section No. and Title	**Description of Change**	**Brief Rationale**
Cover page	Updated Vigil Neuroscience, Inc. address.	Ensure correct address for Vigil Neuroscience is listed.
Sponsor Signatories	Updated Sponsor Signatory to Petra Kaufmann, MD	Change in Sponsor personnel
Throughout Protocol	Updated term "caregiver" to "study partner" where applicable.	Broaden term to clarify expected respondent for study assessments
1.3. Table 1, Schedule of Assessments 4.1. Overall Design	Addition of Telephone Visit for Month 18, Month 24, and Month 30 if subject's condition does not allow for in-clinic visit per Investigator discretion.	Allow for partial data collection in subjects that are not able to attend in-clinic visits
5.1. Inclusion Criteria, 10 and 13 8.1.1. Informed Consent 10.1.2. Informed Consent Process	Updated criteria to allow study participation for subjects who meet criteria for "Definitive ALSP" to enroll or continue in study without a study partner per Investigator discretion	Clarify study partner inclusion for subject's participation is per Investigator discretion
8.1.3., Retrospective Pre-screening MRI (Optional)	Added: "Retrospective pre-screening MRI scans obtained prior to participation in a Vigil-Sponsored study may be collected if available from the medical history of each consenting subject. This information will be used to explore the pre-study trajectory of MRI findings."	New section added to include the optional collection of retrospective pre-screening MRI data

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

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

Short Title

Illuminate

Study Rationale

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare, rapidly progressing, genetic, neurodegenerative disease for which no definitive treatment options and limited information on the natural history of the disease are available. The structural, genetic, and neuropathophysiological abnormalities of ALSP lead to the onset of neurologic symptoms, such as moderate to severe motor and neuropsychiatric impairments. Vigil Neuroscience is developing VGL101, a monoclonal antibody of triggering receptor on myeloid cells 2 (TREM2) agonist, for the treatment of ALSP. This natural history study will collect data to contribute to the development of future novel therapies, including VGL101, that focus on the neuropathophysiological features that underlie ALSP and that are essential to reverse, delay, or stop progression of this debilitating disorder.

Study Objectives

The objectives of the study are:

- 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 synthetic control arm and provide run-in data for patients who qualify for interventional studies.

Study Endpoints

<u>Pharmacodynamic (Biomarker) Endpoints</u>

- Change from Baseline to Months 6, 12, 24, and 36 in neurofilament light chain (NfL) in blood
- Change from Baseline to Months 12, 24, and 36 in NfL, cytokine(s), soluble TREM2, and soluble CSF1R in cerebral spinal fluid (CSF) in subjects who provide informed consent to participate in an optional CSF Biomarker Sub-study

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in structural and volumetric magnetic resonance imaging (MRI)

Clinical Outcome Endpoints

Cognitive Assessments

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Montreal Cognitive Assessment (MoCA)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center-Frontotemporal Lobar Degeneration (CDR®+NACC-FTLD)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Brief Assessment of Cognition (BAC) battery

Motor Assessments (Ambulatory Subjects)

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the 2-Minute Walk Test (2MWT)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Timed Up and Go (TUG) test

Severity of Illness Assessments

- Clinical Global Impression – Change (CGI-C) responses at Months 6, 12, 18, 24, 30, and 36
- Patient Global Impression - Change (PGI-C) responses at Months 6, 12, 18, 24, 30, and 36

Other Functional and Psychiatric Assessments

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Functional Activities Questionnaire (FAQ)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Neuropsychiatric Inventory – 12-Item Version (NPI-12)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Cortical Basal ganglia Functional Scale (CBFS)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Zarit Burden Interview

Safety Endpoints

- Adverse events (AEs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Brief Summary

This is a non-interventional, prospective, multicenter, observational, natural history study of patients with ALSP and asymptomatic carriers of *CSF1R* gene mutations, the causative mutation for ALSP. Potential study participants 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.

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 study partner 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 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 12, 24, and 36 from subjects who provide informed consent to participate in the optional CSF Biomarker Sub-study.

Subjects who, in the discretion of the investigator, may be eligible for a VGL101 clinical study may be discontinued from this study at any time. For subjects who discontinue from this study to enroll in a VGL101 clinical study, all procedures, except the MRI, blood biomarker sampling, and CSF collection (for subjects in the CSF Sub-study), will be collected once for the Early Termination (ET) Visit of this study and for the Screening or Baseline Visit of the 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 VGL101 clinical study, CSF biomarker collection will be performed at the ET Visit of this study.

Number of Subjects

Approximately 60 subjects are planned for enrollment.

The study will enroll subjects with prodromal or definitive ALSP. Prodromal ALSP is defined as ALSP that satisfies the radiologic, but not the full clinical, criteria (see Section 5.1, Inclusion Criteria). At sponsor discretion, enrollment of individuals with prodromal ALSP may be discontinued.

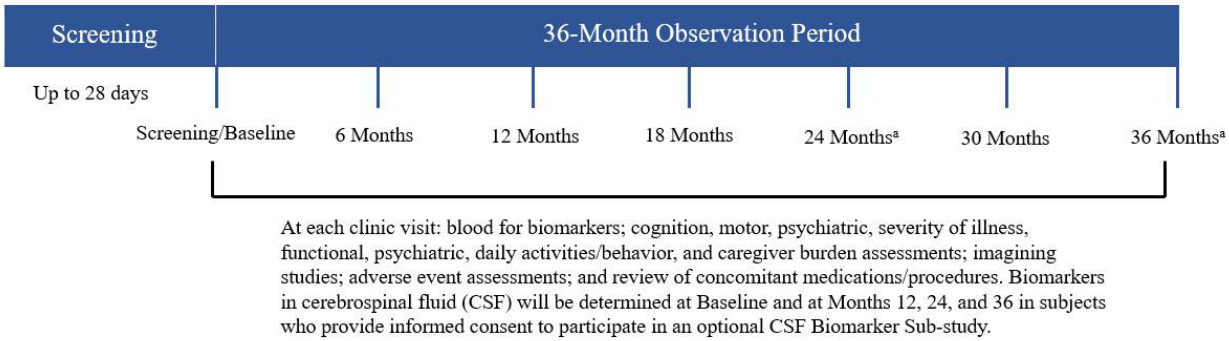
Treatment Groups and Duration

No study intervention will be administered. Subjects will be followed for up to 24 months (subjects who complete the study before implementation of Amendment 3) or 36 months (subjects who complete the study after implementation of Amendment 3).

1.2 Schema

An overview of the study design is presented in Figure 1.

Figure 1 Study Schema



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.

1.3 Schedule of Assessments

The schedule of assessments is shown in Table 1. 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.

Table 1 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)	Telephone Visit[r]
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	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	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	X
	Survival assessment[i]					X		X	X
	Coagulation for *Optional* CSF Biomarker Sub-study[j]	X		X		X		X	
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	X
	BAC	X	X	X	X	X	X	X	
	CBFS	X	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	X
	PGI-S	X							
	PGI-C		X	X	X	X	X	X	X
Functional, Psychiatric & Other Assessments	FAQ[n]	X	X	X	X	X	X	X	X
	NPI-12[n]	X	X	X	X	X	X	X	X
	Zarit Burden Interview[n]	X	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 study partner 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 patients 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 astudy partner 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 study partner 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.
r. If a subject is unable to attend on-site visits due to a decline in his/her condition and the subject is willing to remain in the study, telephone visits may be conducted at Month 18, Month 24, and Month 30 in lieu of clinic visits at the discretion of the Investigator. All other visits should occur in clinic. Telephone visits will also require participation of the study partner.

2 INTRODUCTION

2.1 Study Rationale

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare, rapidly progressing, genetic, neurodegenerative disease for which no definitive treatment options and limited information on the natural history of the disease are available. The structural, genetic, and neuropathophysiological abnormalities of ALSP lead to the onset of neurologic symptoms, such as moderate to severe motor and neuropsychiatric impairments. Vigil Neuroscience is developing VGL101, a monoclonal antibody of triggering receptor on myeloid cells 2 (TREM2) agonist, for the treatment of ALSP. This natural history study will collect data to contribute to the development of future novel therapies, including VGL101, that focus on the neuropathophysiological features that underlie ALSP and that are essential to reverse, delay, or stop progression of this debilitating disorder.

2.2 Background

2.2.1 Clinical Classification of ALSP

ALSP is a fatal, rare, inherited and rapidly progressing neurologic disorder with no definitive treatment options. ALSP is clinically delineated by 3 main groups of symptoms: impaired cognition, neuropsychiatric abnormalities, and motor dysfunction (Sundal & Wszolek, 2017; Konno et al, 2018; Oosterhoff et al, 2018; Tian et al, 2019; Kempthorne et al, 2020; Zhan et al, 2020; Zhou et al, 2020). The mean age for onset of symptoms is primarily in the 4th decade but can range from early adulthood to the 8th decade (Sundal & Wszolek, 2017). Symptoms tend to be present at an earlier age in women (40 years) than in men (47 years) (Konno et al, 2017b).

Signs and symptoms tend to be nonspecific in the early stages of ALSP and may be difficult to distinguish from other inherited autosomal neurological disorders. Early symptoms include cognitive impairment (59%); neuropsychiatric symptoms (44%), including anxiety, depression, apathy, indifference, abulia, irritability, disinhibition, and distraction; motor dysfunction (38%), including parkinsonian symptoms, gait disturbances, and spasticity; speech difficulty (19%); and other symptoms (8%), such as stroke-like episodes, sensory dysfunction, dizziness, fatigue, and epilepsy (Konno et al, 2017b).

Progression of the neuropsychiatric aspects and motor symptoms of ALSP can lead to further cognitive decline and loss of mobility. Additional progressive symptoms involve cortical disturbances (aphasia, agraphia, apraxia, etc.), pyramidal signs (hyperreflexia, spasticity, and Babinski signs), bulbar signs (dysarthria, dysphagia, and slurred speech), cerebellar abnormalities (ataxia, dysmetria, intention tremor, and gait disturbances), and seizures. In the final stages of the disorder, loss of speech and voluntary movements, confinement to bed, and a vegetative state are evident. Infections and pneumonia often result in death (Sundal & Wszolek, 2017).

Progression of the disorder from onset of symptoms to death varies from 2 to >30 years (mean, 6-8 years) (Sundal et al, 2012; Konno et al, 2017b). As there are no current regulatory-approved therapies that address the etiology and progression of ALSP, the prognosis is ominous, with a substantial burden of devastating symptoms that elicit deterioration of quality of life and a shortened life span.

2.2.2 Pathophysiology

ALSP is primarily inherited as an autosomal dominant disorder with colony-stimulating factor 1 receptor (*CSF1R*) gene mutations (Sundal & Wszolek, 2017; Du et al, 2019; Leng et al, 2019). At least 98 different *CSF1R* mutations have been identified in more than 200 cases worldwide. There is no obvious correlation of genotype and phenotype; family members with identical *CSF1R* gene mutations do not share the same clinical phenotype (Sundal & Wszolek, 2017; Konno et al, 2018). Although de novo mutations of *CSF1R* have been reported, they are less common (Rademakers et al, 2011). Penetrance of ALSP is high, but incomplete, due to de novo mutations and genetic mosaicism (Karle et al, 2013; Sundal et al, 2015; Konno et al, 2017b; Konno et al, 2018).

CSF1R gene mutations are specific diagnostic features of patients with ALSP. As phosphatase and kinase proteins associated with the *CSF1R* gene regulate functions of macrophages, microglia, and neuronal pathways, disturbances of these proteins due to gene mutation are implicated in the neuropathophysiology of ALSP (Rademakers et al, 2011; Lynch et al, 2016; Kraya et al, 2019). The strong link between *CSF1R* mutations and pathologic microglia has resulted in further classification of *CSF1R*-related leukoencephalopathy as a central nervous system (CNS) primary microgliopathy (Han et al, 2020).

Histopathologic evaluation (light and electron microscopy) of brain tissue from biopsies and autopsies and brain imaging of patients with ALSP display marked alterations. One of the principal neuropathologies consists of vacuolated and demyelinated white matter that is found primarily within the corpus callosum, pyramidal tracts, and periventricular region of the frontal and parietal lobes. White matter degeneration is often associated with deteriorating neurons and axons due to spheroids that are positive for neurofilaments, amyloid, and ubiquitin. The axonal pathology is accompanied by macrophages that are engorged with lipid and myelin. Other characteristic neuropathologies of ALSP are deformed astrocytes and pigmented (iron or lipofuscin) microglia cells that decrease in function and number with progression of the disorder (Sundal & Wszolek, 2017; Konno et al, 2018; Tian et al, 2019; Kempthorne et al, 2020; Zhan et al, 2020; Zhou et al, 2020).

Abnormal levels of cytoskeletal proteins, such as neurofilament light chain (NfL), tau, and glial fibrillary acid, were identified as potential biomarkers in cases of ALSP. A recent case control study demonstrated that NfL protein levels in serum and cerebrospinal fluid (CSF) were markedly higher in symptomatic and presymptomatic patients with ALSP and *CSF1R* mutations than in healthy control subjects or in patients with multiple sclerosis (Hayer et al, 2018). Elevated levels of NfL in blood and CSF are believed to be

indicative of neuron death and axonal deterioration in several neurodegenerative disorders.

2.2.3 Prevalence and Geographical Distribution

Mendelian adult-onset leukodystrophies are a spectrum of rare, chronic, complex, and progressive neurologic disorders. Worldwide incidence of these disorders has been reported to be 5 per 100,000 (Sassi et al, 2018), with a total prevalence of 300 cases per million (Ahmed et al, 2014). If 10% to 25% of these cases are patients with *CSF1R*-related ALSP (Sundal & Wszolek, 2017), the global prevalence of *CSF1R*-related ALSP is estimated to be in the range of 231,918 to 579,796. Although still rare, genetically diagnosed individuals with *CSF1R*-related ALSP have been increasingly recognized around the world (United States, Canada, United Kingdom, Germany, the Netherlands, Croatia, Italy, Greece, Norway, Sweden, Saudi Arabia, China, Taiwan, South Korea, and Japan) since 2012. It is apparent that this disease has global distribution and many patients may still be underdiagnosed (Konno et al, 2018).

2.2.4 Current Treatment of ALSP

Currently, there are no pharmacotherapies that can alter the course of ALSP. Patients are treated with a variety of medications to ameliorate clinical symptoms and improve quality of life. The medications include anti-Parkinson's disease drugs, cholinesterase inhibitors, antidepressants, antipsychotics, muscle relaxants, and antiepileptics.

Hematopoietic stem cell therapy (HSCT) has been used in small number of patients with variable results (Eichler et al, 2016; Mochel et al, 2019; Gelfand et al, 2020). Stabilization of cognition deficits and motor function, as well MRI lesions, have been reported up to 2 years after HSCT. Clinical trials in larger number of patients are currently ongoing to further explore the value of HSCT in the treatment of ALSP, especially in view of the significant risks associated with HSCT.

Physical therapy is recommended to positively impact motor dysfunction and to maintain some activities of daily living. Professional counseling is important to educate the patient and relatives on symptoms and progression of ALSP and to ensure a supportive family structure. Genetic counseling of patients and relatives is also necessary to address insecurity associated with inheritance of ALSP (Sundal & Wszolek, 2017; Konno et al, 2018; Zhan et al, 2020).

2.2.5 VGL101

ALSP is a rare, progressive, debilitating disorder that affects relatively young individuals and that causes a major impact on the life of patients and their families. Patients with ALSP lose employment, income, and require costly long-term care. Therefore, ALSP represents a major unmet medical need. Safe and effective novel therapies that address the etiology of ALSP and that can slow, halt, or even reverse the progression of this life-threatening disorder are urgently needed.

Vigil Neuroscience is developing VGL101, a monoclonal antibody TREM2 agonist, for the treatment of ALSP. The response of microglial cells to changes in the environment of the CNS is activated through TREM2 and its associated protein kinase complex, DAP12 (Konishi & Kiyama, 2018). The TREM2/DAP12 signal functions as the primary regulator that transforms microglia from a homeostatic to a neural disease-associated state and produces an anti-inflammatory response and neurotrophic factors to protect injured neurons and to enable nerve tissue regeneration. The activation of TREM2 by VGL101 is expected to slow disease progression and enhance the neural tissue repair mechanisms regulated by microglia.

This natural history study will provide information on the biomarkers and clinical outcome assessments that will allow for an assessment of therapeutic agents, such as VGL101, in therapeutic trials of ALSP.

2.3 Benefit/Risk Assessment

This natural history study may benefit patients with ALSP and carriers of the *CSF1R* mutation by facilitating the understanding and evaluation of the current standard-of-care practice and identifying ways to improve patient care. The subjects who participate in this study will receive no direct benefit other than thorough medical assessments, which will provide detailed information on their disease status. The risks of participation in the study are primarily those associated with collection of blood samples for biomarker analyses and lumbar puncture for subjects who participate in the optional CSF Biomarker Sub-study.

3 OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

The objectives of the study are:

- 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 synthetic control arm and provide run-in data for patients who qualify for interventional studies.

3.2 Study Endpoints

3.2.1 Pharmacodynamic (Biomarker) Endpoints

- Change from Baseline to Months 6, 12, 24, and 36 in NfL in blood
- Change from Baseline to Months 12, 24, and 36 in NfL, cytokine(s), soluble TREM2, and soluble CSF1R in CSF in subjects who provide informed consent to participate in an optional CSF Biomarker Sub-study
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in structural and volumetric magnetic resonance imaging (MRI)

3.2.2 Clinical Outcome Endpoints

3.2.2.1 Cognitive Assessments

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Montreal Cognitive Assessment (MoCA)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center-Frontotemporal Lobar Degeneration (CDR®+NACC-FTLD)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Brief Assessment of Cognition (BAC) battery

3.2.2.2 Motor Assessments (Ambulatory Subjects)

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the 2-Minute Walk Test (2MWT)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Timed Up and Go (TUG) test

3.2.2.3 Severity of Illness Assessments

- Clinical Global Impression – Change (CGI-C) responses at Months 6, 12, 18, 24, 30, and 36
- Patient Global Impression - Change (PGI-C) responses at Months 6, 12, 18, 24, 30, and 36

3.2.2.4 Other Functional and Psychiatric Assessments

- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Functional Activities Questionnaire (FAQ)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Neuropsychiatric Inventory – 12-Item Version (NPI-12)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Cortical Basal ganglia Functional Scale (CBFS)
- Change from Baseline to Months 6, 12, 18, 24, 30, and 36 in the Zarit Burden Interview

3.2.3 Safety Endpoints

- Adverse events (AEs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

4 STUDY DESIGN

4.1 Overall Design

This is a non-interventional, prospective, multicenter, observational, natural history study of patients with ALSP and asymptomatic carriers of *CSF1R* gene mutations, the causative mutation for ALSP. Potential study participants 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.

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 study partner 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 12, 24, and 36 from subjects who provide informed consent to participate in the optional CSF Biomarker Sub-study.

Given the nature of ALSP, subjects may progress while on study. If a subject is unable to attend on-site visits due to a decline in his/her condition and the subject is willing to remain in the study, telephone visits may be conducted at Month 18, Month 24, and Month 30 in lieu of clinic visits at the discretion of the Investigator (refer to schedule of assessments, Table 1) All other visits should occur in clinic. Telephone visits will also require participation of the study partner.

Subjects who, in the discretion of the investigator, may be eligible for a VGL101 clinical study may be discontinued from this study at any time. For subjects who discontinue from this study to enroll in a VGL101 clinical study, all procedures, except the MRI, blood biomarker sampling, and CSF collection (for subjects in the CSF Sub-study), will be collected once for the Early Termination (ET) Visit of this study and for the Screening or Baseline Visit of the 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 VGL101 clinical study, CSF biomarker collection will be performed at the ET Visit of this study.

4.2 Scientific Rationale for Study Design

4.2.1 Study Design

The open-label design is an appropriate design for a non-interventional study in which the natural course of the disease will be followed. The information that is collected in this study will be used to evaluate biomarkers for assessing disease progression in patients

with ALSP and, thereby, will contribute to the development of future novel therapies that focus on the neuropathophysiological features that underlie ALSP and that are essential to reverse, delay, or stop progression of this debilitating disorder.

4.2.2 Pharmacodynamic (Biomarker) Endpoints

Changes in NfL protein in blood (all subjects) and CSF (subjects who participate in the optional CSF Biomarker Sub-study) will be evaluated as potential neuropathophysiological biomarkers for ALSP. Studies have shown that NfL protein levels are markedly increased in the serum and CSF of patients with ALSP (Hayer et al, 2018), as well as in the blood and CSF of patients with other neurodegenerative diseases, including multiple sclerosis, amyotrophic lateral sclerosis (ALS), and frontal lobe dementia (Byrne et al, 2017; Niemelä et al, 2017; Merluzzi et al, 2019; Bäckström et al, 2020; Delaby et al, 2020). Thus, reduction in NfL levels may be predictive of clinical improvements and may serve as a surrogate endpoint in therapeutic studies of orphan neurodegenerative indications, including ALSP.

The response of microglial cells to changes in the environment of the central nervous system is activated through TREM2 and its associated protein kinase complex, DAP12 (Konishi & Kiyama, 2018). The TREM2/DAP12 signal functions as the primary regulator that transforms microglia from a homeostatic to a neural disease-associated state and produces an anti-inflammatory response and neurotrophic factors to protect injured neurons and enable nerve tissue regeneration. Animal and human genetic studies have demonstrated that microglia without TREM2 or with mutated TREM2 do not convert to an activated stage and, subsequently, lead to development and/or progression of neurologic disorders. Furthermore, animal models of Parkinson's disease, Alzheimer's disease, ALS, and demyelinating disease display dysregulation of TREM2/DAP12 signals that promotes pathogenesis of neurodegeneration (Konishi & Kiyama, 2018). TREM2 in CSF is a marker of CNS microglia activity. The utility of TREM2 as a target engagement biomarker warrants further evaluation; therefore, soluble TREM2 will be included as an exploratory biomarker in early clinical trials of VGL101.

CSF1R gene mutations are specific diagnostic features of patients with ALSP. As phosphatase and kinase proteins associated with the *CSF1R* gene regulate functions of macrophages, microglia, and neuronal pathways, disturbances of these proteins due to gene mutations, may also be implicated in the neuropathophysiology of ALSP (Rademakers et al, 2011; Lynch et al, 2016; Kraya et al, 2019). Additional research and case studies will likely confirm 1 or more of the above protein markers of neuronal, axonal, and glial cell damage and death as a meaningful surrogate endpoint for future novel therapies for ALSP. Thus, soluble CSF1R levels in CSF in an optional CSF Biomarker Sub-study. In addition to soluble CSF1R and soluble TREM2, measurement of cytokine levels will be included as an exploratory biomarker in CSF in an optional CSF Biomarker Sub-study. Cytokine assays may include, but are not limited to, the following: interferon gamma-inducible protein 10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1), which have been proposed to serve as additional markers of CNS immune dysregulation.

Magnetic resonance imaging of the brains of patients with ALSP reveals high signaling of white matter disfigurement with darkened fat (T2-weighted) and fluid-attenuated inversion recovery (FLAIR) (Van Gerpen et al, 2008; Sundal et al, 2012; Bender et al, 2014, Konno et al, 2014; Konno et al, 2017a; Konno et al, 2017b). The high signaling is generally confined to the bifrontal or bifrontal parietal regions of the brain in the deep, subcortical, and periventricular areas, as well as in the corpus callosum and corticospinal tracts. Early onset white matter lesions are scattered and localized but develop confluency with progression of the disorder. Images also confirm enlarged ventricles consistent with white matter lesions and cerebral atrophy. Although atypical, MRI with diffusion-weighted imaging (DWI) has shown high signaling in the bipyramidal tracts that connect brain to spinal cord in a patient with ALSP (Li et al, 2020). Magnetic resonance imaging scans will be obtained throughout the study to monitor disease progression.

4.2.3 Clinical Outcome Assessments

The structural, genetic, and neuropathophysiological abnormalities of ALSP lead to the onset of neurologic symptoms, such as moderate to severe motor and neuropsychiatric impairments (Sundal & Wszolek, 2017; Konno et al, 2018; Oosterhoff et al, 2018; Tian et al, 2019; Kempthorne et al, 2020; Zhan et al, 2020; Zhou et al, 2020). The battery of cognitive, motor, and psychiatric scales that will be used in this study have been selected to assess the effects of ALSP on the core symptoms of the disease over time.

4.3 Definition of End of Study

The end of the study is defined as the last date on which the last subject completes the Month 36/ET Visit.

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects who meet all of the following criteria are eligible for the study:

General and Administrative

1. Male or female subjects aged ≥18 years on the day the informed consent form (ICF) is signed.
2. Subjects who are able, in the opinion of the investigator, to understand the nature of the study and to comply with the protocol requirements, including scheduled visits, blood sampling, and other study procedures, or who have a study partner or legal guardian who can understand and assist the subject in complying with the protocol requirements.
3. Subjects who are willing and able to refrain from use of any prohibited medication/treatments that are not permitted by the protocol throughout the study period.
4. Subjects who receive approval of sponsor medical personnel as to final suitability for the study.

Inclusion Criteria – Subjects with "Definitive ALSP"

5. Subjects who have documentation of a gene mutation in the *CSF1R* gene (prior to enrollment).
6. Subjects who fulfill both of the following criteria (a and b):
    a. More than two findings of clinical signs or symptoms in any of the following categories:
        i. Cognitive impairment or psychiatric problem
        ii. Pyramidal signs on neurological examination
        iii. Extrapyramidal signs, such as rigidity, tremor, abnormal gait, or bradykinesia
        iv. Epilepsy
    b. MRI findings consistent with ALSP: specifically, bilateral cerebral white matter lesions with or without thinning of the corpus callosum (Konno et al, 2018; Appendix 3, Section 10.3).

    NOTE: Subjects with other causes of leukoencephalopathy, including vascular dementia, multiple sclerosis, or leukodystrophy (e.g., adrenoleukodystrophy, Krabbe disease, metachromatic leukodystrophy), will be excluded.
7. Subjects who, in the investigator's opinion, have demonstrated clinical progression of their ALSP within the past year.
8. Subjects who have a score of ≥12 on the MoCA.
9. Subjects who are ambulatory with or without aids (cane, crutches, etc.) or, if restricted to a wheelchair, are still able to wheel self, transfer in and out of wheelchair, and walk up to 5 meters with or without aid.

NOTE: Subjects that are non-ambulatory for reasons other than progression of ALSP may be enrolled.

10. Subjects who meet the criteria for definitive ALSP must have a designated study partner (i.e. caregiver) who spends at least 4 hours per week with them. The study partner must be able and willing to assist the subject in complying with the study requirements, be able to provide information during study visits, and be willing to sign a study partner ICF. Subjects who do not have a study partner may be enrolled at the investigator's discretion if they are able to comply with protocol requirements.

Inclusion Criterion – Subjects with "Prodromal ALSP"

11. Subjects who have documentation of a gene mutation in *CSF1R* gene (prior to enrollment).
12. MRI findings consistent with ALSP: specifically, bilateral cerebral white matter lesions with or without thinning of the corpus callosum (Konno et al, 2018; Appendix 3, Section 10.3). Prodromal subjects may have none or up to and including 2 ALSP-related clinical signs or symptoms (i.e., they do not meet the clinical criteria outlined in 6a as "more than two").
13. Subjects who meet the criteria for prodromal ALSP and who, at later study visits, meet the criteria for definitive ALSP should have a designated study partner for subsequent study visits who spends at least 4 hours per week with them unless otherwise approved by the sponsor and/or medical monitor. The study partner must be able and willing to assist the subject in complying with the study requirements, be able to provide information during study visits, and be willing to sign a study partner ICF. Subjects who do not have a study partner may continue the study at the investigator's discretion if they are able to comply with protocol requirements.

Informed Consent

14. Subjects who are capable of providing written informed consent, including signing and dating the ICF, or who have a study partner/legal guardian who can provide written informed consent (with subject assent).

Screening Assessments

15. Woman of childbearing potential must have a negative urine pregnancy test at Screening/Baseline.

5.2 Exclusion Criteria

Subjects will be excluded from the study for any of the following reasons:

Medical Conditions

1. Subjects with any neurological or psychiatric diseases that can produce cognitive, motor, or behavioral impairment similar to ALSP, including, but not limited to, Alzheimer's disease, frontotemporal dementia, ALS, stroke, Huntington disease, multiple sclerosis, Parkinson's disease, and Down syndrome, or with active alcohol/drug abuse.
2. Subjects with any concurrent diagnosis that may confound neuropsychological testing (e.g., hearing impairment, visual impairment).

3. Subjects with any concurrent diagnosis that may confound ambulation measurements (e.g., amputee).
4. Subjects with contraindications for undergoing a lumbar puncture, such as bleeding disorders, increased intracranial pressure, or abnormal spinal anatomy. NOTE: Only for subjects who participate in the optional CSF Biomarker Sub-study.
5. Subjects who are unable to undergo MRI (e.g., implants not compatible for MRI, claustrophobia, inability to remain still that will prevent acquisition of a good quality scan).
6. Female subjects who are pregnant, planning pregnancy in the next 12 months, or breastfeeding.
7. Subjects who are at significant risk of suicidal or violent behavior, in the opinion of the investigator. If a subject answers "yes" to the Question 4 or 5 on the C-SSRS, a risk assessment should be done by a qualified healthcare professional to assess whether it is safe for the subject to participate in the study.
8. Subjects with a current history of major medical illness, such as renal failure, congestive heart failure, or advanced pulmonary disease, that could put the subject at additional risk if participating in the study.
9. Subjects with a history of cancer that required active treatment in the last 5 years, with the exception of in situ cervical cancer and basal cell carcinoma of the skin.
10. Subjects with any condition or situation that, in the opinion of the investigator or sponsor medical personnel, may place the subject at significant risk, confound the study results, or interfere significantly with the subject's participation in the study.
11. Subjects who have previously undergone HSCT or plan to undergo HSCT within 12 months of the Screening/Baseline visit.

Prior/Current Clinical Study Experience

12. Subjects who are concurrently enrolled in an investigational drug or device study or who received an investigational product within 30 days or 5 half-lives before signing the ICF.

    Note: Subjects who are receiving VGL101 in a clinical study may enroll after conclusion of their participation in the VGL101 clinical study.

Other Exclusion Criteria

13. Subjects who are involved, directly or indirectly, in the conduct or administration of this study as an investigator, sub-investigator, study coordinator, or other study staff member.

5.3 Lifestyle Considerations

No lifestyle restrictions will be imposed.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to

ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). If additional study procedures were performed during screening, information from these procedures should be recorded in the electronic case report form (eCRF).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after discussion with the medical monitor and resolution of the issue that led to initial screen failure.

6 INVESTIGATIONAL MEDICINAL PRODUCT(S) AND CONCOMITANT THERAPY

6.1 Investigational Medicinal Product

No intervention will be administered. Subjects will receive their usual treatments for ASLP, as prescribed by their physicians.

6.2 Concomitant Therapy

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 recorded in the eCRFs, along with the following: reason for use, dates of administration (including start and stop dates), dose, and frequency of administration. A complete history of medications for the treatment of ALSP will be recorded.

7 SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal from the Study

Subjects may withdraw from the study at any time or may be withdrawn at any time, at the discretion of the investigator, for safety, behavioral, or compliance reasons. When a subject wishes to withdraw consent, it is important to distinguish between withdrawing his/her consent for a particular study procedure or visit versus withdrawing his/her consent from the study entirely (i.e., premature discontinuation). Reasons for premature discontinuation from the study include, but are not limited to, the following:

- Withdrawal of consent
- Death
- Intercurrent illness
- Unacceptable AEs
- Protocol violation or noncompliance
- Lost to follow-up
- Investigator discretion
- At request of the sponsor, regulatory agencies, or institutional review board/independent ethics committee (IRB/IEC)

An ET Visit (as shown for the Month 36 Visit in the Schedule of Assessments in Table 1) should be conducted at the time of study discontinuation.

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.

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.

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.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data that are collected before withdrawal of consent.

Subjects who withdraw from the study may request destruction of any samples that have been taken and not tested, and the investigator must document this in the site study records.

7.2 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigative site. The site must attempt to contact the subject and reschedule the missed visit as soon as possible and must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls). These contact attempts should be documented in the subject's medical record. Subjects who continue to be unreachable will be considered to have withdrawn from the study.

Attempts will be made to determine the survival status (alive or deceased) of any subjects who fail to return for their study visit or who discontinue 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 study partner 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.

Discontinuation of specific sites or of the study as a whole is described in Appendix 1 (Section 10.1.6).

8 STUDY ASSESSMENTS AND PROCEDURES

Adherence to the study design requirements, including those specified in the Schedule of Assessments (Table 1), is essential and is required for study conduct. Protocol waivers or exemptions are not allowed.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects that are screened and to confirm eligibility or to record reasons for screen failure, as applicable.

Procedures that are conducted as part of the subject's routine clinical management, within the screening period, that are obtained before the ICF is signed may be used for screening or baseline purposes provided that the procedures meet the protocol-specified criteria and were performed within the timeframe that is defined in the Schedule of Assessments.

8.1 Screening Assessments

8.1.1 Informed Consent

The investigator or designated member of the investigational site staff is responsible for providing each subject with adequate explanations of the aims, methods, anticipated benefits, and potential risks of the study and for obtaining written informed consent from each subject (as detailed in Section 10.1.2 before any study-related procedures are performed.

Subjects who meet the criteria for definitive ALSP must have a designated study partner (i.e. caregiver) who spends at least 4 hours per week with them. The study partner must be able and willing to assist the subject in complying with the study requirements, be able to provide information during study visits, and be willing to sign a study partner ICF. Subjects who do not have a study partner may be enrolled at the investigator's discretion if they are able to comply with protocol requirements.

Subjects who meet the criteria for prodromal ALSP and who, at later study visits, meet the criteria for definitive ALSP should have a designated study partner for subsequent study visits who spends at least 4 hours per week with them unless otherwise approved by the sponsor and/or medical monitor. The study partner must be able and willing to assist the subject in complying with the study requirements, be able to provide information during study visits, and be willing to sign a study partner ICF. Subjects who do not have a study partner may continue the study at the investigator's discretion if they are able to comply with protocol requirements.

8.1.2 Medical/Family History and Demographic Information

Relevant medical history (including surgical history) will be documented during Screening to assess subject eligibility. Any medical conditions should be captured with at

least a start date and an indication of whether the condition is ongoing or resolved. Detailed information related to family/subject history of ALSP will be recorded.

Date of birth, sex, ethnicity, and race will be recorded.

8.1.3 Retrospective Pre-Screening MRI (Optional)

Retrospective pre-screening MRI scans obtained prior to participation in this study may be collected if available from the medical history of each consenting subject. This information will be used to explore the pre-study trajectory of MRI findings.

8.1.4 Prior and Concomitant Medications/Procedures

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 medical procedures will also be recorded.

8.1.5 Documentation of CSF1R Gene Mutation

Documentation of a *CSF1R* mutation is required for all subjects before enrollment in the study.

8.1.6 Clinical Global Impression – Severity of Illness (GGI-S)

The Clinical Global Impressions – Severity of Illness (CGI-S) (Guy, 1976) scale is a 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.

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

The Patient Global Impression – Severity of Illness (PGI-S) is the patient-reported counterpoint to the CGI-S (Guy, 1976). The PGI-S is a 1-item questionnaire that is designed to assess patient's impression of disease severity. The PGI-S item asks the respondents to best describe how their symptoms are now on the following 4-point scale: 1 = normal, 2 = mild, 3 = moderate, or 4 = severe.

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

8.1.8 Urine Drug Screen

Subjects will undergo urine drug screening for the presence of phencyclidine (PCP), cocaine, cannabinoids, opiates/barbiturates, benzodiazepines, amphetamines, methadone, and MDMA (3,4 methylenedioxymethamphetamine/Ecstasy/Molly) at Screening/ Baseline. Subjects with a positive urine drug screen will be excluded, unless explained by use of an approved prescription medication.

8.2 Pharmacodynamic (Biomarker) Assessments

8.2.1 Blood for NfL Analysis

Blood samples for NfL will be obtained at Screening/ Baseline and at Months 6, 12, 18, 24, 30, and 36/ET to provide further insight into the onset and progression of ALSP. The completion of these investigations will be based on the results of this or other exploratory work.

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.

Detailed instructions regarding sample collection, processing, and shipping will be provided to the sites in a study laboratory manual.

8.2.2 Magnetic Resonance Imaging

MRI scans, including, but not limited to T1-weighted, T2-weighted, FLAIR, and diffusion-weighted MRI scans, will be obtained at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET. The MRI scans may be obtained ±2 days before the scheduled visit. 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.

Detailed instructions regarding the MRI collection protocol will be provided in a separate set of image acquisition guidelines.

Please note that subjects may be given light sedation (e.g., short acting benzodiazepine) if they are unable to lie still during scanning or have involuntary movements; this is not a protocol requirement and can be based on PI discretion. For those subjects receiving light sedation, if the MRI is scheduled on the same day as their cognitive assessments then the sedation and scan should occur after the cognitive assessments have been completed.

8.3 Clinical Outcome Assessments

The schedule of assessments is shown in Table 1. 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.

Detailed instructions regarding the collection and assessment of the clinical outcome assessments will be provided in a separate manual.

8.3.1 Cognitive Assessments

8.3.1.1 Montreal Cognitive Assessment Scale (MoCA)

The MoCA is a brief 30-question test that is used to evaluate cognitive abilities and dementia (Smith et al, 2007; Chou et al, 2010). The MoCA evaluates different types of cognitive domains, including orientation, short-term memory, delayed recall, abstraction, visuospatial, and executive functioning; language; and attention. The scale, which is available in 35 languages, takes 10 to 12 minutes to complete. Scores range from zero to 30; scores of ≥26 are generally considered normal.

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

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

The CDR®+NACC-FTLD (Miyagawa et al, 2020) is a semi-structured global assessment measure that was developed to measure the severity of dementia symptoms in Alzheimer's disease and related dementias. The scale measures the following 6 domains: Memory; Orientation; Judgement and Problem Solving; Community Affairs Engagement; Home and Hobbies; Behavior; Language; and Personal Care. The first 7 domains are rated on a 5-point scale as follows: 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 sum total of the ratings of the 8 individual domains is calculated to create the clinical dementia rating (CDR®+NACC-FTLD) sum of boxes (CDR®+NACC-FTLD-SB).

The global CDR®+NACC-FTLD score is calculated from the 8 domains and is rated on a 5-point scale (0/0.5/1/2/3; see below). The CDR®+NACC-FTLD-SB exhibits good correlation with frontotemporal cerebral blood hypoperfusion in patients with FTLD patients and is useful in the characterization of the non-amnestic symptoms in patients with dementia. CDR®+NACC-FTLD was selected as an outcome measure in this trial because frontal lobes are often affected by the disease process of ALSP, and behavioral symptoms are common in patients with ALSP.

Global CDR®+NACC-FTLD score ranges from 0 to 3 (the lower the better) and is calculated using the following criteria:

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 study partner who has provided informed consent for this study.

8.3.1.3 Brief Assessment of Cognition (BAC)

The BAC (https://littlegreensoftware.com/work/bacbacs) is a tablet-based version of the paper-based BAC instrument that was developed for use in schizophrenia and other conditions that affect cognition. The BAC can be administered as a full battery or as a customized smaller selection of subsets of tests. The following test subsets are included: verbal memory, digit sequencing, verbal fluency, and symbol coding. All tests in the BAC are completed under the supervision of a trained rater.

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

8.3.2 Motor Assessments (Ambulatory Subjects)

8.3.2.1 Two-Minute Walk Test (2MWT)

The 2MWT (Witherspoon et al, 2019) 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.

8.3.2.2 Timed Up and Go (TUG) Test

The TUG (Ibrahim et al, 2017) is used to determine the time 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 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 patient 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.

8.3.3 Severity of Illness Assessments

8.3.3.1 Clinical Global Impression – Change (CGI-C)

The CGI-C (Guy, 1976) is a 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.

8.3.3.2 Patient Global Impression – Change (PGI-C)

The PGI-C is the patient-reported outcome counterpoint to the CGI-C (Guy, 1976). 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.

8.3.4 Other Functional and Psychiatric Assessments

8.3.4.1 Functional Assessment Questionnaire (FAQ)

The FAQ (Pfeffer et al, 1982) 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 patients with mild dementia and has been used in clinical trials of patients with mild cognitive impairment and in patients 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.

The FAQ will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET. The FAQ will only be completed if the subject has a study partner who has provided informed consent for the study.

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

The NPI-12 (Cummings et al, 1994) is an abbreviated 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 study partner. The study partner is usually a family member who is involved in the daily care of the patient 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 study partner as it is written. After reading the screening question, the study partner 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.

The NPI-12 will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET. The NPI-12 will only be completed if the subject has a study partner who has provided informed consent for the study.

8.3.4.3 Cortical Basal ganglia Functional Scale (CBFS)

The CBFS (Lang et al, 2020) is a novel rating scale that evaluates experiences in daily living (EDL) and behavioral, language, and cognitive impairments in patients with 4 repeat tauopathies. The CBFS consists of 14 questions on motor EDLs (Motor Component) and 17 questions on nonmotor EDLs (Nonmotor Component), 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 patient but should be answered by the patient and study partner working together. Responses are to be based on the usual or average function over the past 2 weeks.

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

8.3.4.4 Zarit Burden Interview

The Zarit Burden Interview (Knight et al, 2000) is a caregiver self-report measure that is used to assess the burden of the disease on the primary caregiver. The revised version contains 22 items; each item on the interview is a statement that the study partner is asked to rate using a 5-point scale that ranges from 0 (“never”) to 4 (“nearly always”). Translations of the Zarit Burden Inventory are available in many languages. The 22-item questionnaire will be used in this study to assess the impact of ALSP on study partners.

The Zarit Burden Interview will be completed at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET. The Zarit Burden Interview will only be completed if the subject has a study partner who has provided informed consent for the study.

8.4 Safety Assessments

Safety assessments include AEs, physical and neurological examinations, the C-SSRS, and pregnancy testing for women of childbearing potential.

8.4.1 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 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 the ET Visit will be recorded. All

AEs/SAEs will be monitored until resolution or stabilization. Adverse event reporting procedures are summarized in Appendix 2 (Section 10.2).

8.4.2 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.

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

The C-SSRS (Posner et al, 2011) is a semi-structured interview that was designed to quantify the severity of suicidal ideation and behavior. The C-SSRS, which is available in over l00 languages, requires approximately 5 minutes to complete. Interviewers are not required to have mental health training and can be trained on administration of the questionnaire if they have no prior experience with it. The "Baseline/Screening" (lifetime and last 6 months) and "Since Last Visit" versions of the scale will be used.

The "Baseline/Screening" (lifetime and last 6 months) version, which assesses the lifetime experience of the subject with suicide events and suicidal ideation and the occurrence of suicide events or ideation within a specified time period prior to entry into the study, will be completed for all subjects at Screening/Baseline to determine eligibility. For subjects with a positive response on Question 4 or 5 of the C-SSRS at Screening/Baseline, a risk assessment should be done by a qualified healthcare professional to assess whether it is safe for the subject to participate in the study.

The "Since Last Visit" C-SSRS form will be completed at Months 6, 12, 18, 24, 30, and 36/ET. If a subject demonstrates potential suicidal ideation associated with actual intent or method or plan as indicated by "YES" answers on Question 4 or 5 of the C-SSRS, the investigator will evaluate whether a risk assessment by a qualified mental health professional (or the investigator alone if the investigator is a qualified mental health professional) is needed and whether the subject should continue in or be discontinued from the trial.

8.4.4 COVID-19 Assessments and Testing

COVID-19 assessments (temperature and symptom assessment) and testing will be performed per local guidelines and standard of care at the site.

If a subject develops an active COVID-19 infection (whether confirmed or suspected) during the study, the investigator must consult with the sponsor medical monitor to determine the best course of action.

8.4.5 Pregnancy Testing

A urine pregnancy test will be performed for women of childbearing potential at Screening/Baseline and at Months 6, 12, 18, 24, 30, and 36/ET. Female subjects of childbearing potential must have a negative urine pregnancy test at Screening/Baseline for entry into the study. If a subject becomes pregnant during the study, the investigator must consult the sponsor medical monitor to determine the best course of action.

8.5 Optional CSF Biomarker Sub-study

Cerebrospinal fluid samples for NfL, cytokine(s), soluble TREM2, and soluble CSF1R analysis 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. The completion of these investigations will be based on the results of this or other exploratory work.

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.

Detailed instructions regarding sample collection, processing, and shipping will be provided to sites in a study laboratory manual.

8.6 Survival Assessment

Attempts will be made to determine the survival status (alive or deceased) of any subject who fails to return for the vial visit 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 study partner 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.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

The sample size of approximately 60 subjects was determined empirically and is expected to provide sufficient information to address the study objectives in this rare disease.

9.2 Analysis Sets

Data will be analyzed for all subjects who have data available at Screening/Baseline and at least 1 post-baseline timepoint.

9.3 Statistical Analysis

The Statistical Analysis Plan will be finalized before database lock and will include a more technical and detailed description of the statistical analyses that are described in this section.

9.3.1 Disposition and Demographics

The number of subjects who were enrolled, completed the study, and discontinued from the study, along with the reason for discontinuation, will be summarized. Descriptive statistics will be presented for continuous demographic and baseline characteristics; counts and percentages will be presented for categorical variables.

9.3.2 Prior and Concomitant Medications

Prior and concomitant medications will be mapped to a World Health Organization (WHO) Drug Dictionary preferred term and drug classification. The number and percent of subjects taking medications will be summarized using preferred terms and drug classifications.

9.3.3 Clinical Outcome and Biomarker Analyses

Descriptive statistics will be presented for the observed and change from baseline values for clinical, biomarker, and safety assessments. Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. Ninety-five percent (95%) confidence intervals will be presented as appropriate.

The association between phenotypic heterogeneity and phenotype/genotype and clinical outcomes/disease progression and between biomarkers and clinical outcomes/disease progression may be assessed.

9.3.4 Safety Analyses

Adverse events will be mapped to a MedDRA (Medical Dictionary for Regulatory Activities) preferred term and system organ classification. Severity will be assessed by investigator. All AEs will be listed for individual subjects showing both verbatim and preferred terms. Separate summaries of AEs, adverse events of interest (AESIs), SAEs, and AEs leading to discontinuation from the study will be prepared.

Categorial safety data (e.g., C-SSRS) will be summarized with frequency counts and percentages.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2 Informed Consent Process

The investigator or designee will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (with subject assent) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

Subjects who meet the criteria for definitive ALSP must have a designated study partner (i.e. caregiver) who spends at least 4 hours per week with them. The study partner must be able and willing to assist the subject in complying with the study requirements, be able to provide information during study visits, and be willing to sign a study partner ICF. Subjects who do not have a study partner may be enrolled at the investigator's discretion if they are able to comply with protocol requirements.

Subjects who meet the criteria for prodromal ALSP and who, at later study visits, meet the criteria for definitive ALSP should have a designated study partner for subsequent study visits who spends at least 4 hours per week with them unless otherwise approved by the sponsor and/or medical monitor. The study partner must be able and willing to assist the subject in complying with the study requirements, be able to provide information during study visits, and be willing to sign a study partner ICF. Subjects who do not have a study partner may continue the study at the investigator's discretion if they are able to comply with protocol requirements.

The medical record must include a statement that informed consent was obtained before the subject was enrolled in the study and the date consent was obtained. The authorized person who obtains the informed consent must also sign the ICF.

Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Individuals who do not meet the criteria for participation in this study at initial screening (screen failure) may be rescreened at the discretion of the investigator, after discussion with the medical monitor, and after resolution of the issue that led to initial screen failure. Rescreened subjects do not need to sign another ICF but will be assigned a new subject number.

10.1.3 Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

Subjects must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

Subjects must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4 Dissemination of Clinical Study Data

The sponsor will fulfill its commitment to publicly disclose clinical study results through posting study results on ClinicalTrials.gov and other public registries in accordance with

applicable local laws/regulations. Study results will be reported in an objective, accurate, balanced, and complete manner and will be reported regardless of study outcome or the country in which the study was conducted.

10.1.5 Source Documents

Source documents, defined as original documents, data, and records, provide evidence for the existence of the subject, and substantiate the integrity of the data that are collected. Source documents are filed at the investigator's site and should contain all information in original records and certified copies of original records of clinical findings, observations, or other activities in the clinical trial that are necessary for the reconstruction and evaluation of the trial. Data collected during this study must be recorded on the appropriate source documents.

Data that are transcribed from source documents onto the eCRFs must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current medical records must also be available.

In some instances, the initial entry of data will be made by subjects and site personnel onto a hand-held device or tablet at the site and will be considered the source, e.g. eSource. This system is fully compliant with 21 CFR Part 11 regulations.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data documents.

10.1.6 Study and Site Closure

The sponsor designee reserves the right to close the investigative site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigative sites will be closed upon study completion. An investigative site is considered to be closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate investigative site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigative site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, sponsor procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further investigational medicinal product development.

10.1.7 Publication Policy

The publication policy is outlined in the Clinical Trial Agreement. The data generated in this clinical trial are the exclusive property of Vigil Neuroscience, Inc, and are confidential. Written approval from Vigil Neuroscience, Inc, is required before disclosing any information related to this clinical trial is disclosed.

The clinical study report will be prepared and provided to the regulatory agencies as required by the applicable regulatory requirement(s).

10.2 Appendix 2: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events and Serious Adverse Events

10.2.1 Definition of Adverse Event

Definition of an Adverse Event

- An AE is any untoward medical occurrence in a clinical study subject.
- An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated).

Events Meeting the Definition of an Adverse Event

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital sign measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition, including an increase in frequency and/or severity of the condition.
- New conditions that are detected or diagnosed after administration of the investigational medicinal product even though the condition may have been present before the start of the study.

Events Not Meeting the Definition of an Adverse Event

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder that is being studied or expected progression, signs, or symptoms of the disease/disorder that is being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) that are present or detected at the start of the study and that do not worsen.

10.2.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death.**

b. **Is life-threatening.**
The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongs existing hospitalization.**
In general, hospitalization signifies that the subject is admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity.**
The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect.**

f. **Other situations**
Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.2.3 Recording and Follow-up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information on the Serious Adverse Event Form in the eCRFs.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the AE/SAE eCRF form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

- The investigator will make an assessment of severity for each AE and SAE that is reported during the study and will assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category that is used for rating the intensity/severity of an event. Both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator will make every effort to assess the relationship of the AE, if any, to the study procedures. Causality will be assessed using the ICH-recommended categories as presented below:
    - Not Related: An AE will be considered "not related" to the study procedures if there is not a reasonable possibility (defined below) that the event has been caused by the study procedures required by the study.
    - Related: An AE will be considered "related" to the use of the study procedures if there is a reasonable possibility (defined below) that the event may have been caused by the study procedures required by the study.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship (e.g., reasonable temporal association) rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study procedures, will be considered and investigated.
- For each AE/SAE, the investigator **must** document that he/she has reviewed the AE/SAE and has provided an assessment of causality in the medical note.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, **it is important that the investigator always makes an assessment of causality for each event before the initial transmission of the SAE data to the sponsor or designee**.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings, including histopathology.

- New or updated information should be recorded on the Serious Adverse Event Form and marked as follow-up, as well as in the eCRFs.

- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.2.4 Reporting of Serious Adverse Events

Serious Adverse Event Reporting to Sponsor/Designee Via Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor or designee will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.

- Contacts for SAE reporting are provided in the Safety Reporting Plan.

Serious Adverse Event Reporting to Sponsor/Designee Via Paper Case Report Form

- Email transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts for SAE reporting are provided in the Safety Reporting Plan

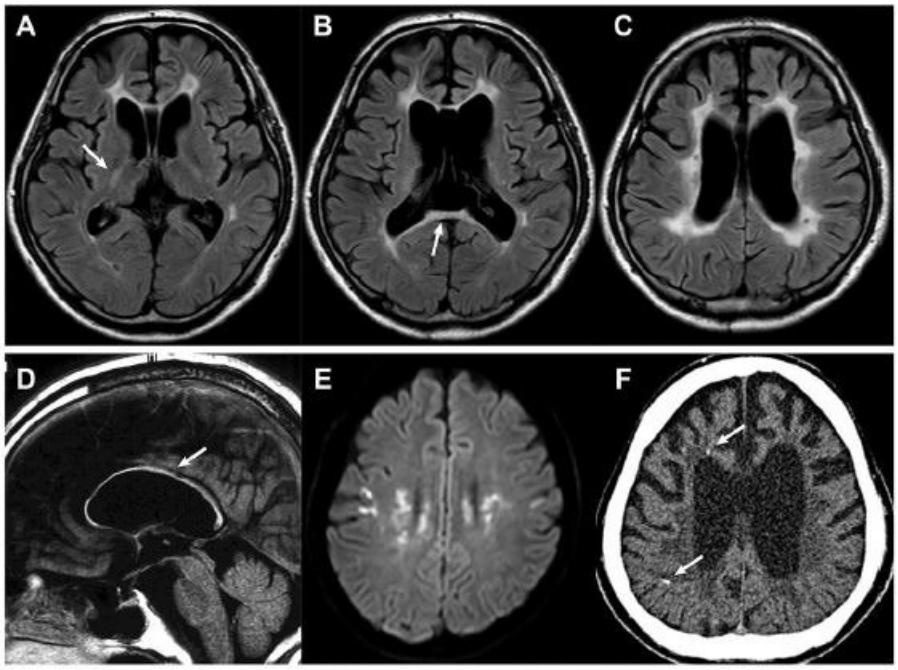
10.3 Appendix 3: Criteria for ALSP Based on Magnetic Resonance Imaging (MRI)/Computed Tomography (CT)

Brain MRI/CT findings (Konno et al, 2018**)**:

1. Bilateral cerebral white matter lesions
2. Thinning of the corpus callosum

Characteristic brain MRI findings of ALSP are shown in Figure 2.

Figure 2 Characteristic Brain Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) Findings in Patients With adult-Onset Leukoencephalopathy With Axonal Spheroids and Pigmented Glia (ALSP)



(A–E,MRI; F, CT). Fluid attenuated inversion recovery imaging of a 43-year-old case with p.Ile794Thr mutation in colony-stimulating factor 1 receptor (*CSF1R*) (A–C, axial; D, sagittal). Abnormal signals are observed in frontal white matter around anterior horn of the lateral ventricles, in the posterior limb of the internal capsule (arrow, A), and in the splenium of the corpus callosum (arrow, B). A thinning of the corpus callosum is shown (arrow, D). (E) Diffusion-restricted lesions in a 22-year-old case with the splice site mutation (c.2442+1G>A) in *CSF1R*. (F) Calcifications are revealed by thin-slice CT of the 43-year-old case with p.Ile794Thr mutation (arrows).
Source: Konno et al, 2018.

Additional Diagnostic Criteria:

On brain MRI scans, the white matter lesions without gadolinium enhancement can be scattered and asymmetric during the initial stages of the disease but later become confluent, diffuse, and more symmetric. Frontal and parietal lobe predominance is

observed with involvement of the periventricular deep white matter and dilation of the lateral ventricles.

Thinning of the corpus callosum with signal abnormalities is observed even in the early stages of the disease (Sundal et al, 2012; Konno et al, 2017a). Fluid attenuated inversion recovery sagittal imaging is recommended to evaluate changes in the corpus callosum. Abnormal signaling in the pyramidal tracts and diffusion-restricted lesions are observed in some cases (Konno et al, 2017a; Konno et al, 2017b).

None of ALSP cases showed middle cerebellar peduncle lesions, which are known as a characteristic finding of some leukoencephalopathies (Konno et al, 2018).

10.4 Appendix 4: Abbreviations and Definitions

Abbreviation	Definition
2MWT	2-Minute Walk Test
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALSP	Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia
BAC	Brief Assessment of Cognition
CBFS	Cortical Basal ganglia Functional Scale
CDR	Clinical dementia rating
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
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression - Change
CGI-S	Clinical Global Impression – Severity of Illness
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CSF	Cerebrospinal fluid
CSF1R	Colony-stimulating factor 1 receptor
C-SSRS	Columbia-Suicide Severity Rating Scale
CVA	Cerebrovascular accident
ET	Early Termination
eCRF	Electronic case report form
EDL	Experiences in daily living
FAQ	Functional Activities Questionnaire
FLAIR	Fluid-attenuated inversion recovery
FTD	Frontotemporal dementia
GCP	Good Clinical Practice
HSCT	Hematopoietic stem cell transplant
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IRB	Institutional review board

Abbreviation	Definition
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NfL	Neurofilament light chain
NPI-12	Neuropsychiatric Inventory – 12 Item Version
PGI-C	Patient Global Impression - Change
PGI-S	Patient Global Impression – Severity of Illness
SAE	Serious adverse event
TREM2	Triggering receptor on myeloid cells 2
TUG	Timed Up and go

10.5 Appendix 5: Protocol Amendment History

The summary of changes for the current amendment (Amendment 4; protocol version 5.0) is located before the Table of Contents.

10.5.1 Amendment 1: Protocol Version 2.0 (29 Jul 2021)

Overall Rationale for Amendment

The overall rationale for this amendment is to revise the Schedule of Assessments to exclude some of the previously planned clinical outcome measures to reduce burden on the study participants and to revise the study entry criteria to exclude kindred individuals and individuals who had previously received a hemopoietic stem cell transplant (HSCT), as recommended by the US Food and Drug Administration (FDA).

Section No. and Title	Description of Change	Brief Rationale
1.1, Study Endpoints, Pharmacodynamic (Biomarker) Endpoints 3.2.1, Pharmacodynamic (Biomarker) Endpoints	Revised the first endpoint to exclude measurement of cytokines and soluble TREM2 in blood	Only to be evaluated in CSF
	Revised the second endpoint to indicate that biomarkers in CSF will only be determined in subjects who provide informed consent to participate in an optional CSF Biomarker Sub-study	Reduce subject burden
	Revised third endpoint to remove the types of MRIs that will be performed	Remove excessive detail from objective
1.1, Study Endpoints, Clinical Outcome Endpoints 3.2.2, Clinical Outcome Endpoints	Revised the clinical outcome measures to exclude the following assessments: MDS-UPDRS – Part III, TFC, CIBIC+, MINT, SF-36, Aural Analytics Speech Assessment, and Real-World Experience of ADL (PAMSys sensor)	Reduce subject burden
	Reordered clinical outcome endpoints into the following categories: 1) cognitive assessments, 2) motor assessments, 3) severity of illness assessments, and 4)functional, psychiatric, and other assessments	Categorize scales by purpose rather than by the individual who completes the assessment
1.1, Brief Summary 4.1, Overall Design	Revised paragraph 1 to remove references to “kindred”	Limit relevant patient population for this natural history study to carriers of the

Section No. and Title	Description of Change	Brief Rationale
		CSF1R mutation (symptomatic or asymptomatic)
1.1, Brief Summary 4.1, Overall Design	Revised paragraph 2 to remove biomarkers in CSF, and to remove references to testing for COVID-19	Consistency with changes in the Schedule of Assessments
	Added a paragraph about the optional CSF Biomarker Sub-study	Consistency with changes in the Schedule of Assessments
1.1, Treatment Groups and Duration	Revised duration of follow-up from "24 months" to "up to 24 months"	Account for potential early discontinuations
1.1, Number of Subjects 9.1, Sample Size Determination	Changed planned sample size from up to 50 subjects (approximately 38 with ALSP and 12 carriers [asymptomatic or kindred]) to up to 36 subjects (approximately 30 subjects with symptomatic ALSP and 6 asymptomatic carriers of the *CSF1R* gene mutation)	Reduction in sample size due to change in study population (i.e., exclusion of kindred subjects)
1.2, Schema	Revised Figure 1	Consistency with changes in study design and Schedule of Assessments
1.3, Schedule of Assessments	Revised wording to 1) specify that, whenever feasible, cognitive and motor assessments should be prioritized, and 2) remove recommendations for timing of other assessments	Clarify study procedures
1.3, Schedule of Assessments	Reorganized assessments	Clarify study procedures
1.3, Schedule of Assessments 8.1, Screening Assessments	Removed the MMSE as a screening tool; removed the optional skin biopsy	Reduce subject burden
1.3, Schedule of Assessments 8.3, Clinical Outcome Assessments	Removed the following assessments: MDS-UPDRS – Part III, TFC, CIBIC+, MINT, SF-36, Aural Analytics Speech Assessment, Real-World Experience of ADL (PAMSys sensor)	Reduce subject burden
	Added the CBFS as a clinical outcome measure	Obtain additional information on experiences in daily living and on behavioral, language, and cognitive impairments

Section No. and Title	Description of Change	Brief Rationale
1.3, Schedule of Assessments 8.3.9, Gait and Balance Assessments (BioSensics Wearable Sensors) in Ambulatory Subjects at Selected Sites	Removed specification that only subjects who are enrolled at US sites would be eligible to participate in the digital biomarker assessment	Provide flexibility
1.3, Schedule of Assessments 4.4, Safety Assessments 8.4.4, COVID-19 Assessments and Testing	Changed COVID-19 assessments and testing to be in line with local guidelines and standard of care at each site	Study will be conducted across multiple geographies which may have differing COVID-19 guidelines
1.3, Schedule of Assessments 7.2, Lost to Follow-up 8.6, Survival Assessment	Added an assessment (telephone call) of survival at 24 months after the date of the Screening Visit for subjects who fail to return for the Month 24 Visit or who discontinue from the study before completing the 24-month observation period	Obtain additional information on the outcome of ALSP
1.3, Schedule of Assessments	Reclassified collection of CSF for biomarker evaluation as an optional CSF Biomarker Sub-study	Reduce subject burden
2.3, Benefit/Risk Assessment	Modified the last sentence related to the risk of CSF sampling	Clarify that the risk of CSF sampling (lumbar puncture) only applies to those who participate in the optional CSF Biomarker Sub-study
4.2.2, Pharmacodynamic (Biomarker) Endpoints	Removed paragraph 2 (rationale for measurement of cytokines in in blood)	Not relevant (cytokines will only be measured in CSF)
	Revised several sentences to indicate that biomarkers in CSF will be determined only in subjects who consent to participate in the optional CSF Biomarker Sub-study	Clarify study procedures
	Added interferon gamma-inducible protein 10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1)	Provide potential biomarkers for evaluation based on emerging nonclinical and transitional work
4.3, Definition of End of Study	Revised definition to include the Early Termination (ET) Visit	Clarify study procedures

Section No. and Title	Description of Change	Brief Rationale
5.1, Inclusion Criteria	Removed reference to CSF sampling (i.e., the subject must be willing to adhere to the CSF sampling schedule) from inclusion #2	Consistency with designation of CSF sampling as only required for those who agree to participate in the optional CSF Biomarker Sub-study
	Revised inclusion #7 from "subjects who are in stable medical condition" to "subjects who, in the investigator's opinion, have demonstrated clinical progression of their ALSP within the past year"	Clarify inclusion criterion
	Revised inclusion #8 from "a score of ≥20 on the MMSE" to "a score ≥12 on the MoCA" and to allow subjects with a score >7 to be enrolled with sponsor approval	The MMSE scale was removed; therefore, the entry criterion was amended to use the MoCA assessment (which was retained)
	Deleted inclusion criterion related to kindred subjects (previously inclusion #12)	Change in study population
	Deleted inclusion criterion related to a negative COVID-19 test within 72 hours before Baseline (previously inclusion #14)	Consistency with removal of mandatory COVID-19 testing from Schedule of Assessments
5.2, Exclusion Criteria	Added a note that exclusion #4 (contraindications for undergoing a lumbar puncture) only applies to subjects who agree to participate in the optional CSF Biomarker Sub-study	Clarify exclusion criterion
	Added "previous HSCT within 12 months prior to Screening/Baseline" as exclusion criterion #11	Change in study population
7.1, Subject Discontinuation/ Withdrawal from the Study	Added information pertaining to withdrawal of consent	Clarify study procedures
8.1.2, Medical/Family History and Demographic Information	Revised section to indicate that "relevant" medical history would be recorded	Clarify study procedures
8.1.4, Documentation of *CSF1R* Gene Mutation	Removed second sentence (kindred subjects must have a first degree relative with ALSP and *CSF1R* mutation)	Change in study population
8.2.1, Blood for NFLs and Soluble CSF1R Analysis	Removed references to cytokine panel and TREM2	Only to be evaluated in CSF

Section No. and Title	Description of Change	Brief Rationale
8.2.2, Magnetic Resonance Imagining	Revised types of MRIs that will be collected to include FLAIR	Changed to align with imaging acquisition guidelines
8.4.3, Columbia-Suicide Severity Rating Scale (C-SSRS)	Clarified that the Screening/Baseline evaluation should be conducted by a qualified healthcare professional to assess whether it is safe for the subject to participate in the study	Clarify study procedures
10.1.2, Financial Disclosure	Removed section	Information will be included in the Clinical Trial Agreement
10.1.6, Data Quality Assurance	Removed section	Information will be included in the Clinical Trial Agreement
10.2, Appendix 2, Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of Adverse Events and Serious Adverse Events	Minor wording changes	Reflect process at Vigil
Overall	Minor grammatical corrections and editorial changes	Correct minor errors, unrelated to content, in previous protocol or for consistency with the changes summarized above

Abbreviations: ADL = activities of daily living, ALSP = adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, CSF = cerebrospinal fluid, *CSF1R* = colony-stimulating factor 1 receptor, CIBIC+ = Clinician Interview Based Impression of Change + Caregiver Input, FLAIR = fluid-attenuated inversion recovery, HSCT = hemopoietic stem cell transplant, MDS-UPDRS = Movement Disorders – Unified Parkinson's Disease Rating Scale, MINT = Multilingual Naming Test, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, SF-36 = 36-Item Short Form Health Survey, TFC = Total Functional Capacity, TREM2 = triggering receptor on myeloid cells 2.

10.5.2 Amendment 2: Protocol Version 3.0 (22 Mar 2022)

Overall Rationale for Amendment

The overall rationale for this amendment is to revise the classification of the subjects to be enrolled in the study to reflect the ALSP patient population.

Section No. and Title	Description of Change	Brief Rationale
1.1, Study Endpoints, Pharmacodynamic (Biomarker) Endpoints 3.2.1, Pharmacodynamic (Biomarker) Endpoints 8.2.1 Blood for NfL Analysis	Revised the first bullet in the pharmacodynamic (biomarker) endpoints to remove references to soluble colony stimulating factor 1 receptor (CSF1R) in blood.	Only to be evaluated in CSF

Section No. and Title	Description of Change	Brief Rationale
1.1, Number of Subjects 9.1, Sample Size Determination	Changed planned sample size from up to 36 subjects (approximately 30 subjects with symptomatic ALSP and 6 asymptomatic carriers of the *CSF1R* gene mutation) to up to 50 subjects are planned for enrollment (of which approximately 20% of subjects will be classified as 'Prodromal ALSP' and the remaining subjects will have 'Definitive ALSP'. Prodromal ALSP is defined as ALSP meeting radiologic but not full clinical criteria.	Increase in sample size due to change in study population
1.1, Number of Subjects	Clarified that if a subject that has been classified as a 'Prodromal ALSP' patient progresses while on study such that they meet the definition of a 'Definitive ALSP' patient, the subject will be reclassified as 'Definitive ALSP' and another 'Prodromal ALSP' spot will open for enrollment.	Clarification on how subjects will be classified on study if they progress from 'Prodromal ALSP' to 'Definitive ALSP' while on study.
1.2, Schema 1.3, Schedule of Assessments	Revised Figure 1 and Schedule of Assessments to include biomarkers in blood collection at the Month 6 visit.	Consistency with changes in study design and Schedule of Assessments
1.3, Schedule of Assessments	Added Urine pregnancy test at each visit.	Ensure consistency between the Schedule of Assessments and Section 8.4.5.
1.3, Schedule of Assessments	Added Coagulation at the Screening/Baseline and Month 12 Visits for the Optional CSF Biomarker Sub-study participants.	Ensure that the site can safely proceed with CSF biomarker collection at each visit.
5.1, Inclusion Criteria	Changed classification of Symptomatic ALSP to Definitive ALSP	Change in study population.

Section No. and Title	Description of Change	Brief Rationale
	Revised inclusion criteria #6 to have more than two findings of clinical signs or symptoms and further defined MRI findings needing to have bilateral cerebral white matter lesions with or without thinning of the corpus callosum.	Change inclusion criteria 6 to align with "Definitive ALSP" per Konno et, 2018.
	Revised inclusion #8 to not allow subjects with a score >7 and <12 to be enrolled with sponsor approval	Change in study population
	Revised inclusion criteria #9 to only allow for non-ambulatory subjects that were not related to ALSP progression.	Change in study population
	Changed classification of Asymptomatic ALSP to Prodromal ALSP	Change in study population.
	Added inclusion criteria #12 to ensure that subjects with Prodromal ALSP have MRI findings consistent with ALSP.	Change in study population.
5.2, Exclusion Criteria	Added examples for exclusion #5 for examples of what subjects should be excluded from the study for not being able to undergo an MRI and that patients with renal impairment and contraindication for the use of MRI contrast agent may be enrolled and have non-contrast MRI exams.(e.g., implants not compatible for MRI, claustrophobia, inability to remain still that will prevent acquisition of a good quality scan)	Clarify exclusion criterion
	Revised inclusion criteria #11 to allow for the inclusion of subjects who have had HSCT longer than 6 months from baseline visit.	Change in study population

Section No. and Title	Description of Change	Brief Rationale
8.2.2, Magnetic Resonance Imagining	Revised types of MRIs to T1 (with or without contrast).	Changed to align with imaging acquisition guidelines
	Included note that subjects may be given light sedation if they are unable to lie still during scanning.	Clarify study procedures
Overall	Minor grammatical corrections and editorial changes	Correct minor errors, unrelated to content, in previous protocol or for consistency with the changes summarized above

Abbreviations: ALSP = adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, CSF = cerebrospinal fluid, *CSF1R* = colony-stimulating factor 1 receptor, HSCT= hematopoietic stem cell therapy, MRI = magnetic resonance imaging, NfL = neurofilament light chain.

10.5.3 Amendment 3: Protocol Version 4.0 (03-Oct-2023)

Overall Rationale for Amendment

The overall rationale for this amendment is to expand the observation period of the study from 24 months to 36 months to allow for the collection of additional data on the natural history of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) and to extend the window to capture disease progression from prodromal ALSP to definitive ALSP. Additional revisions to clarify study procedures were also incorporated.

Section No. and Title	Description of Change	Brief Rationale
Cover Page, Short Title Synopsis, Short Title	Changed short title *from* Natural History Study in ALSP *to* Illuminate.	Administrative change to provide additional study identifier.
Sponsor Signatories	Changed Vigil signatory *from* Spyros Papapetropoulos, MD, PhD *to* Christopher Silber, MD.	Change in sponsor personnel.
1.1, Protocol Synopsis, Study Endpoints 3.2, Study Endpoints	Revised the study endpoints to include the change from baseline to Months 30 and/or 36	Change in study design to extend the study from 24 to 36 months and to add visits at Months 30 and 36.
1.1, Protocol Synopsis, Study Endpoints, Clinical Outcome Endpoints, Cognitive Assessments 3.2.2, Clinical Outcome Endpoints; 3.2.2.1, Cognitive Assessments	Changed CDR® + NACC-FTD to CDR® + NACC-FTLD.	Correct previous error.
1.1, Protocol Synopsis, Study Endpoints, Clinical Outcome Endpoints, Motor Assessments (Ambulatory Subjects) 3.2.2, Clinical Outcome Endpoints; 3.2.2.2, Motor Assessments (Ambulatory Subjects)	Removed “change from Baseline to Months 6 and 12 in gait and balance assessments (BioSensics wearable sensors) in ambulatory subjects at selected sites” as a study endpoint.	Removed as an assessment to reduce subject burden.

Section No. and Title	Description of Change	Brief Rationale
1.1, Protocol Synopsis, Brief Summary 4.1, Study Design	Revised the duration of the study *from* 24 months *to* 36 months and modified the study visits and assessments to reflect the addition of visits at Months 30 and 36.	Change in study design to extend the study from 24 to 36 months and to add visits at Months 30 and 36.
	Added a provision for discontinuation from this study to enter a VGL101 clinical study and information related to the ET Visit for such subjects.	Clarify study procedures.
1.1, Protocol Synopsis, Number of Subjects 9.1, Sample Size Determination	Changed the number of subjects *from* up to 50 subjects *to* approximately 60 subjects.	Provide flexibility for dropouts and simultaneous enrollment at sites at the end of subject recruitment.
1.1, Protocol Synopsis, Treatment Groups and Duration	Revised the duration of subject follow-up *from* 24 months *to* 36 months.	Change in study design.
1.2, Schema	Revised the schematic to include additional visits at Months 30 and 36.	Change in study design.
1.3, Schedule of Assessments	Added visits at Months 30 and 36.	Collect additional data on the natural history of ALSP and extend the window to capture disease progression from prodromal to definitive ALSP.
	Added a blood draw for biomarkers at Month 18.	Correct previous omission.
	Removed Month 24 as the ET visit and revised the schedule of assessments at the Month 24 visit to match the schedule of assessments at the Month 12 visit.	Change in study design to change the ET visit from Month 24 to Month 36.
	Removed sensor-based gait and balance assessments at selected sites for the schedule of assessments.	Reduce subject burden.
	Revised several footnotes to reflect the addition of the Month 30 and Month 36 visits and the change in the ET visit from Month 24 to Month 36.	Change in study design.
	Added a footnote to state that, at the discretion of the investigator, 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.	Clarify study procedures.

Section No. and Title	Description of Change	Brief Rationale
	Added that 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.	Clarify study procedures.
	Added a footnote to state that, 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.	Clarify study procedures.
	Added a footnote to state that, 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 study and will be analyzed as part of both studies.	Clarify study procedures.
	Added a footnote to state 1) that, 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, and 2) that 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.	Clarify study procedures.
4.3, Definition of End of Study	Changed the end of study *from* Month 24/Early Termination (ET) *to* Month 36/Early Termination (ET).	Change in study design.
5.1, Inclusion Criteria	Revised inclusion #10 to require subjects who meet the criteria for definitive ALSP to have a caregiver.	Ensure that a caregiver is available to complete the scales for subjects with definitive ALSP.
	Added exclusion #13 to state that subjects who meet the criteria for prodromal ALSP and who later meet the criteria for definitive ALSP must have a caregiver to assist them.	Ensure that a caregiver is available to complete the scales for the subjects once they progress to definitive ALSP.
5.2, Exclusion Criteria	Removed reference to MRI contrast agents from exclusion #5.	Contrast MRIs will no longer be done in this study as available data suggest that there is insufficient evidence to pursue contrast-enhanced MRI as a biomarker for ALSP.

Section No. and Title	Description of Change	Brief Rationale
	Revised exclusion #11 *from* subjects who have previously undergone HSCT within 6 months prior to Screening/Baseline *to* subjects who have previously undergone HSCT or plan to undergo HSCT within 12 months of the Screening/Baseline visit.	Ensure that subjects who enter the study will not undergo HSCT for the first 12 months, which could confound the assessment of the natural history of ALSP.
	Added a note to exclusion #12 to state that subjects who are receiving VGL101 in a clinical study may enroll in this study after conclusion of their participation in the VGL101 clinical study.	Allow subjects who are treated with VGL101 in therapeutic studies to enroll in this study.
7.1, Subject Discontinuation/ Withdrawal from the Study	Changed the ET visit *from* Month 24 *to* Month 36.	Change in study design.
7.1, Subject Discontinuation/ Withdrawal from the Study 8.2; Pharmacodynamic (Biomarker Assessments); 8.2.1, Blood for NfL Analysis	Added that, 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.	Clarify study procedures.
7.1, Subject Discontinuation/ Withdrawal from the Study 8.2; Pharmacodynamic (Biomarker Assessments); 8.2.2, Magnetic Resonance Imagining	Added that, 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.	Clarify study procedures.
7.1, Subject Discontinuation/ Withdrawal from the Study 8.4, Safety Assessments; 8.4.1, Adverse Events	Revised the time period for collection of adverse events to through Month 24 (*for subjects who complete the study before implementation of Amendment 3)*, *Month 36 (for subjects who complete the study after implementation of Amendment 3*), or the ET Visit.	Clarify procedures as a result of the change in study duration.

Section No. and Title	Description of Change	Brief Rationale
7.1, Subject Discontinuation/ Withdrawal from the Study 8.5, Optional CSF Biomarker Sub-study	Added that 1) 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, and 2) 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.	Clarify study procedures.
7.2, Lost to Follow-up 8.6, Survival Assessment	Revised the timing of the contact to assess survival to 24 months (*for subjects who withdraw from the study before implementation of Amendment 3)* and 36 months *(for subjects who withdraw from the study after implementation of Amendment 3)* after the date of the subject's Screening Visit.	Clarify procedures as a result of the change in study duration.
8.1.1, Informed Consent 10.1.2, Informed Consent Process	Revised section to indicate that subjects who meet the criteria for definitive ALSP must have a caregiver who is willing to provide informed consent and that subjects who meet the criteria for prodromal ALSP and later develop definitive ALSP must have a caregiver who is willing to provide informed consent.	Consistency with changes in inclusion criteria #10 and #13, respectively.
8.2, Pharmacodynamic (Biomarker) Assessments 8.3, Clinical Outcome Assessments 8.4, Safety Assessments	Revised the text throughout each section to include the Month 30 and Month 36 visits and to match the Schedule of Assessments (Table 1).	Change in study design.
8.3.1.2, Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center-Frontotemporal Lobar Degeneration (CDR®+NACC-FTLD)	Changed previous scale (CDR® + NACC-FTD) to CDR® + NACC-FTLD.	Correct previous error.
	Added a statement that, at the discretion of the investigator, 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.	Clarify study procedures.
8.3.1.3, Brief Assessment of Cognition (BAC)	Revised description of scale.	Correct previous errors.

Section No. and Title	Description of Change	Brief Rationale
8.3.4.1, Functional Assessment Questionnaire (FAQ) 8.3.4.2, Neuropsychiatric Inventory – 12 Item Version (NPI-12) 8.3.4.4, Zarit Burden Inventory	Added a statement in each section to say that the scales will only be completed if the subject has a caregiver who has provided informed consent to participate in the study.	Clarify study procedures.
8.3, Clinical Outcome Assessments; 8.3.2.3, Gait and Balance Assessments (BioSensics Wearable Sensors) in Ambulatory Subjects at Selected Sites	Removed section.	Removed as an assessment to reduce subject burden.
8.4, Safety Assessments; 8.4.1, Adverse Events	Revised the time period for collection of adverse events to through Month 24 (*for subjects who complete the study before implementation of Amendment 3)*, *Month 36 (for subjects who complete the study after implementation of Amendment 3*), or the ET Visit.	Clarify procedures as a result of the change in study duration.
8.5, Optional CSF Biomarker Sub-study	Added a footnote to state 1) that, 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, and 2) that 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.	Clarify study procedures.
9.1, Sample Size Determination	Removed reference to the percentage of subjects with prodromal ALSP.	Allow enrollment of individuals with prodromal ALSP to be discontinued at sponsor discretion.

Abbreviations: ALSP = adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, CTD® + NACC-FTD = Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center-Frontotemporal Dementia, CTD® + NACC-FTLD = Clinical Dementia Rating Scale plus National Alzheimer's Coordinating Center-Frontotemporal Lobar Degeneration, ET = early termination, FAQ = Functional Assessment Questionnaire, HSCT= hematopoietic stem cell therapy, MoCA = Montreal Cognitive Assessment, MRI = magnetic resonance imaging, NPI-12 = Neuropsychiatric Inventory – 12-Itrem Version.

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INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A Natural History Study of Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP)
Protocol Number:	VGL101-01.002
Version:	5.0
Date:	02 Oct 2024

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with all consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), and applicable laws and regulations.

Signed:_____ Date:_____