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

Published: 07-03-2022
Last updated: 17-01-2025

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...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON52367

Source
ToetsingOnline

Brief title
Illuminate

Condition

- Neurological disorders congenital

Synonym
ALSP

Research involving
Human

Sponsors and support

Primary sponsor: Vigil Neuroscience, Inc.

Source(s) of monetary or material Support: Biotech industrie

Intervention

Keyword: Observational, VGL101-01.002

Outcome measures

Primary outcome

Pharmacodynamic Endpoints

• Change from Baseline to Months 12, 24 and 36 in neurofilament light chain (NfL) in blood

• Change from Baseline to Months 12, 24 and 36 in NfL, cytokine panel, 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, 36 in structural and volumetric 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

• Clinical 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)

Secondary outcome

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Study description

Background summary

Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a fatal and rapidly progressing rare, genetic disease for which no definitive treatment options are available. 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). 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 may also be implicated in 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). 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). Currently used therapies for ALSP are targeted for temporary relief of motor and sensory symptoms and for the treatment of complications. These treatments provide limited supportive care and modest improvements in quality of life as the disorder progresses but do not address the most debilitating symptoms, such as cognitive decline. In addition, these treatments have no effects on the underlying disease process and do not slow the progression of the disorder. Hematopoietic stem cell transplantation (HSCT) has been investigated as a potential treatment for ALSP, with occasional success in sporadic cases (Eichler et al, 2016; Mochel et al, 2019; Gelfand et al, 2020). However, HSCT therapy is associated with major complications, has shown potential beneficial effects in only a small number of patients, and has not been evaluated in controlled trials. Thus, there is a significant unmet medical need for novel therapies to treat patients with ALSP (Balassa et al,

2019).
Vigil Neurosciences, Inc, is developing VGL101, a monoclonal antibody of triggering receptor on myeloid cells 2 (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 collect data to contribute to the development of future novel therapies, such as 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 objective

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 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 24 months.

Clinic visits to assess disease status will be conducted at Screening/Baseline and at Months 6, 12, 18, and 24. Each clinic visit will include clinical assessments (cognitive, motor, functional, psychiatric, severity of illness, and caregiver burden assessments) and imaging studies. Blood for biomarker analysis will be collected at Screening/Baseline and at Months 12 and 24. Adverse events (AEs) and concomitant medications and procedures will be recorded throughout the 24-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 and 24 from subjects who provide informed consent to participate in the optional CSF Biomarker Sub-study.

Study burden and risks

The participants of this study will make at least 5 visits for this study.
During these visits, subjects will be subjected to:
- Blood sampling (for biomarker analysis)
- Optional CSF Biomarker sample (sub-study)
- COVID-19 testing (per standard of care)
- Urine drug testing
- Pregnancy testing
- Measure weight and height
- Clinical outcome Assessments (cognition-, performance- and clinician-rated scales)
- Complete questionnaires
- MRI

The risks of participation in the study are primarily those associated with collection of blood and cerebrospinal fluid (CSF) samples for biomarker analyses.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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 caregiver 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: specially, 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: 7 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 caregiver who spends at least 4 hours per week with them. The caregiver 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 caregiver ICF.

Inclusion Criteria - 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 caregiver for subsequent visits who spends at least 4 hours per week with them unless otherwise approved by the sponsor and/or medical monitor. The caregiver 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 caregiver
ICF

Informed Consent
14. Subjects who are capable of providing written informed consent, including signing and dating the ICF, or who have a caregiver/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.

Exclusion criteria

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 prior to 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 of 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.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-12-2021
Enrollment:	4
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	07-03-2022
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-04-2022
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-01-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-08-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL78271.075.21