# Study to investigate the safety of VRG50635 in healthy volunteers and patients with motor neuron disease (amyotrophic lateral sclerosis)

Submission date	Recruitment status	Prospectively registered
20/09/2022	No longer recruiting	[] Protocol
Registration date	Overall study status	Statistical analysis plan
26/09/2022	Completed	[] Results
Last Edited	Condition category	Individual participant data
26/09/2022	Nervous System Diseases	[_] Record updated in last year

## Plain English summary of protocol

#### Background and study aims

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder that results from the loss of motor neurons in the brain and spinal cord causing paralysis of voluntary muscles. Like most neurodegenerative disorders, ALS is thought to be caused by abnormal protein aggregation and the derailing of cell pathways that are protective and essential for the correct functioning, development, and formation of new neurons in the brain. Thus, repair and/or preservation of the integrity of the neuronal protein quality control system is an attractive and emerging therapeutic target. In this study, the safety and tolerability of PIKfyve inhibitor VRG50635 will be investigated.

Who can participate? Healthy men and women and adult ALS patients

What does the study involve?

In part 1, participants will be given a single dose of VRG50635 or placebo. There will also be a food effect cohort who will receive single doses of VRG50635 or placebo. In part 2, participants will be given multiple doses of VRG50635 or a placebo and in part 3, VRG50635 and placebo for 28 days in a cross-over assignment. Participants will be monitored throughout the study for adverse events, vital signs, electrocardiography, physical signs, suicidal ideation and with laboratory safety tests.

What are the possible benefits and risks of participating?

No benefit from participating in this research is anticipated. There might be side effects or adverse effects of the study drug, for example, cases of anemia, weight loss and a rare case of acute myeloid leukemia have been encountered in preclinical studies.

Where is the study run from? Centre for Human Drug Research (The Netherlands) When is the study starting and how long is it expected to run for? April 2022 to October 2023

Who is funding the study? Verge Genomics (USA)

Who is the main contact? Dr Lars Smits (Project Leader) (The Netherlands) lsmits@chdr.nl

# **Contact information**

**Type(s)** Public

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# Additional identifiers

EudraCT/CTIS number 2022-002747-22

**IRAS number** 

**ClinicalTrials.gov number** Nil known

Secondary identifying numbers CHDR2219

# Study information

## Scientific Title

A randomised, double-blind, placebo-controlled, single- and multiple-, ascending-dose study of the safety, tolerability, and pharmacokinetics and pharmacodynamics of VRG50635 and food effect in healthy volunteers (phase Ia) and multiple-dose study in subjects with amyotrophic lateral sclerosis

#### Study objectives

VRG50635 is hypothesized in improving motor neuron health and survival, has exposures in the central nervous system (CNS), has effects on the relevant target, pathway, and disease biomarkers supporting translatability, and has a favorable safety profile in non-human models. Furthermore, the active metabolite VRG50468 can reduce amyotrophic lateral sclerosis (ALS) patient motor neuron death in vitro across multiple genetic subtypes with efficacy that surpasses current approved ALS drugs.

#### Ethics approval required

Old ethics approval format

#### Ethics approval(s)

Approved 06/09/2022, Stichting Beoordeling Ethiek Biomedisch Onderzoek (stichting BEBO, Dr. Nassaulaan 109401 HK ASSEN, The Netherlands; +31592405871; info@stbebo.nl), ref: NL81735. 056.22

#### Study design

Three-part first-in-human single-centre randomized double-blind placebo-controlled parallelgroup dose-ranging study with healthy subjects (parts 1 and 2) and a patient crossover cohort (part 3)

## Primary study design

Interventional

#### Secondary study design

Randomised parallel trial

**Study setting(s)** Other

## Study type(s)

Treatment

#### Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

#### Health condition(s) or problem(s) studied

Amyotrophic lateral sclerosis

#### Interventions

VRG50635 is a PIKfyve inhibitor. In each cohort in part 1, 6 subjects will receive VRG50635 and 2 subjects will receive a placebo. In part 2, 8 subjects will receive VRG50635 and 2 subjects will receive a placebo. Part 3 is a crossover design; each subject will receive a placebo and VRG50635 for 28 days with a washout of 2 weeks in between. Dose range Part 1: Cohort 1: 60mg Cohort 2: 120mg

Cohort 3: 240mg

Cohort 4: 600mg Cohort 5: 1200mg Cohort 6: 1800mg

Part 2 and 3: The dose levels will be determined based on results from parts 1 and 2.

#### Intervention Type

Drug

#### Phase

Phase I

## Drug/device/biological/vaccine name(s)

VRG50635

## Primary outcome measure

Part 1 Single ascending dose:

1. Assessment of:

1.1. Adverse events (AEs) measured by collecting the number of AEs, the intensity, relationship with the study drug and chronicity, continuously throughout the study

1.2. Vital signs, evaluations of systolic and diastolic blood pressure, pulse rate, respiratory rate (only predose, 0.5h, 1.5h, 24h) and temperature at screening, Day -1, predose and postdose at 0.5 h, 1.5h, 2h, 24h, 48h and at follow-up (FU)

1.3. Electrocardiograms (ECGs) measured in triplicate at screening, predose and postdose at 0.5 h, 1.5h, 4h, 7h, 24h, 48h and at FU. The ECG parameters assessed will include heart rate, PR, QRS, QT and QTcF.

1.4 Physical examinations, including neurological examination, at screening predose, 48h postdose and at FU

1.5. Suicidal ideation and behaviour measured using the Columbia Suicide Severity Rating Scale (C-SSRS) at screening, Day -1, and 48h postdose

1.6. Laboratory safety tests, including chemistry, hematology, coagulation and glucose at screening, Day-1, 24h (no Coagulation), 48h, at FU

Part 2 Multiple ascending doses

2. Assessment of:

2.1. Adverse events (AEs) measured by collecting the number of AEs, the intensity, relationship with the study drug and chronicity, continuously throughout the study

2.2. Vital signs, evaluations of systolic and diastolic blood pressure, pulse rate, respiratory rate (only predose, Day 2 and Day 4) and temperature at screening, Day -1, predose and postdose on Day 1 (2h and 5h), Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, Day 9 and at FU

2.3. ECGs measured in triplicate at screening, Day -1, predose and postdose on Day 1 (2h and 5h), Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 9 and at FU. The ECG parameters assessed will include heart rate, PR, QRS, QT and QTcF.

2.4. Physical examinations, including neurological examination, screening, predose and postdose on Day 1, Day 3, Day 5, Day 7, Day 9 and FU

2.5. Suicidal ideation and behaviour measured using the Columbia Suicide Severity Rating Scale (C-SSRS) at screening, Day -1, and postdose on Day 9

2.6. Laboratory safety tests, including chemistry, hematology, coagulation and glucose at screening, Day -1 (no coagulation) and postdose on Day 1 (no coagulation), Day 3, Day 5 (no coagulation), Day 7 (no coagulation), Day 9 and at FU

Part 3 ALS

3. Assessment of:

3.1. AEs measured by collecting the number of AEs, the intensity, relationship with the study drug and chronicity, continuously throughout the study

3.2. Vital signs, evaluations of systolic and diastolic blood pressure, pulse rate, respiratory rate (only predose, 0.5h, 1.5h, 24h) and temperature at screening, predose, and postdose on Day 1, Day 2, Day 7, Day 14, Day 28 (both occasions), and FU

3.3. ECGs measured in triplicate at screening, predose, and post-dose on Day 1, Day 2, Day 7, Day 14, Day 28 (both occasions) and FU. The ECG parameters assessed will include heart rate, PR, QRS, QT and QTcF.

3.4. Physical examinations, including neurological examination, at screening, predose, and postdose on Day 1, Day 7, Day 14, Day 28 and Day 29 (both occasions) and FU

3.5 Suicidal ideation and behaviour measured using the Columbia Suicide Severity Rating Scale (C-SSRS) at screening, predose and postdose on Day 1, Day 7, Day 14, and Day 28 (both occasions).

3.6. Laboratory safety tests, including chemistry, hematology, coagulation and glucose at screening, predose and postdose on Day 7 (no coagulation), Day 14, (no coagulation), Day 28 (both occasions) and FU (no coagulation)

### Secondary outcome measures

Part 1 Single ascending dose:

Characterize plasma and urine pharmacokinetics (PK) of VRG50635 and active metabolite VRG50648. PK parameters include Tmax, Tlag, Cmax AUC(0-last), AUC (0-inf) and T1/2. Urine PK parameters include cumulative total amount excreted in urine and cumulative percentage of dose in urine. Plasma PK timepoints: predose and postdose: 0.5h, 1h, 1,5h, 2h, 4h, 7h, 10h, 24h, 34h, 48h; Urine PK timepoints: Predose, 0-6h, 6-24h, 24-36 hours, 36-48 hours (cohorts 2, 3, 4, 5 and 6)

Characterize plasma PK of VRG50635 and VRG50648 after high-fat meal. PK parameters include Tmax, Tlag, Cmax AUC(0-last), AUC (0-inf) and T1/2. Plasma PK timepoints: predose and postdose: 0.5h, 1h, 1,5h, 2h, 4h, 7h, 10h, 24h, 34h, 48h.

## Part 2 Multiple ascending doses

Characterize plasma and cerebrospinal fluid (CSF) PK of VRG50635 and VRG50648. PK parameters include Tmax, Tlag, Cmax AUC(0-last), AUC (0-inf) and T1/2. CSF PK parameters include concentrations and plasma/CSF ratio. Plasma PK timepoints: pre-dose and 0.5, 1, 1.5, 2, 4, 7, 10 h post-dose; pre-dose sample on Days 2, 3, on Day 4 prior to CSF sample, 5; on Day 6 predose and on Day 7, pre-dose, 0.5, 1, 1.5, 2, 4, 7 and 10 h following the last dose; on Day 8, 24h after the last dose; on Days 9 and 10, 48 and 72 h after the last dose. CSF sample timepoint: Day 4, 2 hours post-dose.

#### Part 3 ALS

Characterize plasma and CSF PK of VRG50635 and VRG50648. PK parameters include Tmax, Tlag, Cmax AUC(0-last), AUC (0-inf) and T1/2. CSF PK parameters include concentrations and plasma /CSF ratio. Plasma PK timepoints: pre-dose and 0.5, 1, 1.5, 2, 4, 9, 12 h post-dose; predose on Day 2 (44); pre-dose sample on Days 7 (50), 14 (57) and 28 (71); and 0.5, 1, 1.5, 2, 4, 9, 12 hours post-dose on Day 28 (71) and a 24 hours post-dose sample on Day 29 (72). On days -1, 28 and 71 a PK sample will be taken directly after CSF sampling. CSF sample timepoints: Day -1, 28 and 71, 2 hours post-dose.

## Overall study start date

01/04/2022

Completion date 01/10/2023

# Eligibility

## Key inclusion criteria

Inclusion criteria for Parts 1 and 2:

1. Healthy male or female aged between 18 to 65 years old at screening (inclusive) 2. For male and female subjects of childbearing potential: Subjects and their spouse/partners who are of childbearing potential must use highly effective contraception when engaging in sexual activity consisting of 2 forms of birth control (1 of which must be a barrier method such as latex or polyurethane condoms) starting at screening and continue throughout the clinical study period, and for 90 days after the final study drug administration.

3. For males: Subject must not donate sperm starting at screening and throughout the clinical study period, and for 90 days after the final study drug administration.

Inclusion criteria for Part 3:

1. Diagnosis of laboratory-supported probable, probable, or definite (sporadic) amyotrophic lateral sclerosis (ALS) according to the El Escorial World Federation of Neurology revised research diagnostic criteria (Ludolph et al. 2015)

2. Aged between 18 and 80 years old

3. 5 years or less since the onset of ALS symptoms

4. Forced vital capacity (FVC) ≥50% predicted value

5. Able to swallow medication for the duration of the study (in the opinion of the investigator)

## Participant type(s)

Mixed

Age group

Adult

**Lower age limit** 18 Years

**Upper age limit** 65 Years

**Sex** Both

**Target number of participants** 93

#### Key exclusion criteria

Exclusion criteria for Parts 1 and 2:

1. History of clinically significant hematological, renal, neurologic, pancreatic, gastrointestinal, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, immunological, allergic disease, or other major disorders

2. Current significant medical or psychiatric condition

3. Evidence of clinically significant hepatic or renal impairment in the opinion of the investigator, including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 the upper limit of normal (ULN) or bilirubin > 1.5ULN. Patients with Gilbert syndrome without evidence of hepatic impairment may be enrolled.

4. Poor peripheral venous access

5. A lifetime history of suicidal behavior or suicidal ideation as determined by a positive response ("Yes") to either question 4 or question 5 of the C-SSRS at screening

6. For part 2 only: Subjects not eligible for lumbar puncture (anti-coagulation, anti-aggregation or blood coagulation pathologies, recent spine surgery, acquired or congenital spine malformation, clinical signs of intracranial hypertension, cutaneous infection at the punction site)

Exclusion criteria for Part 3:

1. Amyotrophic lateral sclerosis (ALS) patients with a known mutation in the SOD1 or C9orf72 gene

2. Tracheotomy and/or ventilator-dependent (or daily use of non-invasive ventilation ≥ 22 hours for 7 consecutive days)

3. After percutaneous gastrostomy (PEG) operation

4. Subjects not eligible for lumbar puncture (anti-coagulation, anti-aggregation or blood coagulation pathologies, recent spine surgery, acquired or congenital spine malformation, clinical signs of intracranial hypertension, cutaneous infection at the punction site)

Date of first enrolment

23/09/2022

Date of final enrolment 20/09/2023

## Locations

**Countries of recruitment** Netherlands

**Study participating centre Centre for Human Drug Research** Zernikedreef 8 Leiden Netherlands 2333 CL

## Sponsor information

**Organisation** Verge Genomics

Sponsor details

Two Tower Place Suite 950 South San Francisco United States of America 94080 + 1 650 906 9841 sujata@vergegenomics.com

**Sponsor type** Industry

## Funder(s)

**Funder type** Not defined

# Funder Name

Verge Genomics

# **Results and Publications**

## Publication and dissemination plan

Planned publication in a high-impact peer-reviewed journal

# Intention to publish date

20/10/2024

## Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date.

**IPD sharing plan summary** Data sharing statement to be made available at a later date