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 1a)

Published: 23-08-2022
Last updated: 07-04-2024

Part 1; Single ascending dose (main objective)• To investigate the safety and tolerability of single oral doses of VRG50635 in healthy adult subjectsPart 1; Single ascending dose (secondary objective)• To characterize the plasma and urine...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON56052

Source
ToetsingOnline

Brief title
SAD MAD of VRG50635 in HV

Condition

- Spinal cord and nerve root disorders

Synonym
Amyotrophic lateral sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Verge Genomics
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: ALS, Pharmacodynamic, Pharmacokinetic, Safety

Outcome measures

Primary outcome

Part 1; Single ascending dose:

• Assessment of adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations, Columbia Suicide Severity Rating Scale (C-SSRS) and laboratory safety tests

Part 2; Multiple ascending dose

• Assessment of AEs, vital signs, ECGs, physical examinations, C-SSRS and laboratory safety tests

Secondary outcome

Part 1 Single ascending dose Food effect

•VRG50635 and VRG50468 measured by LC-MS/MS in plasma samples following single oral doses of VRG50635. The pharmacokinetic parameters include: Tmax, tlag, Cmax, AUC(0-last), AUC(0-inf) and T1/2

•Urine PK parameters: cumulative total amount excreted in urine and cumulative percentage of dose in urine

Food Effect part 1

•PK of VRG50635 and VRG50468 following single oral dose to healthy adult subjects in the fed and fasted states, based on the following parameters where possible and appropriate: Tmax, tlag, Cmax, AUC(0-last), AUC(0-inf) and T1/2

Part 2; Multiple ascending dose

• VRG50635 and VRG50468 measured by LC-MS/MS in plasma samples and CSF following multiple oral doses of VRG50635. The pharmacokinetic parameters include: Tmax, tlag, Cmax, AUC(0-tau), Ctrough, Cavg, T1/2 and ARAUC

• VRG50635 and VRG50468 concentrations measured by LC-MS/MS in CSF and plasma/CSF ratio

Study description

Background summary

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 perturbation of the autophagy pathway that is neuroprotective and essential for synaptic plasticity, glial neuroinflammation, oligodendrocyte development, and neurogenesis 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.

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

Study objective

Part 1; Single ascending dose (main objective)
• To investigate the safety and tolerability of single oral doses of VRG50635 in healthy adult subjects

Part 1; Single ascending dose (secondary objective)
• To characterize the plasma and urine pharmacokinetic (PK) profile of Prodrug VRG50635 and Parent VRG50468 following single oral doses of VRG-50635 in healthy adult subjects

Part 1 Single ascending dose Food effect (secondary objective)
• To characterize the effect of food (high fat meal) on the plasma PK of Prodrug VRG50635 and Parent VRG50468 following a single oral dose of VRG50635 in the fed state, when administered to healthy adult subjects

Part 2; Multiple ascending dose (main objective)
• To investigate the safety and tolerability of multiple oral doses of VRG50635 in healthy adult subjects

Study design

This is a two-part first in human, single centre, randomized, double blind, placebo-controlled, parallel group, dose-ranging study in healthy subjects (parts 1 and 2) to investigate the safety, tolerability, pharmacokinetics and target engagement of VRG50635.

Intervention

VRG50635 or placebo oral administration of capsules

Part 1: single dose of VRG50635 or placebo (Food effect cohort 3 : 2 single doses of VRG50635 or placebo)
Part 2: multiple dose of VRG50635 or placebo

Study burden and risks

For this first-in-human study, the population will be healthy volunteers.

Contacts

Public
Verge Genomics

Two Tower Place, Suite 950
South San Francisco 94080
US
Scientific
Verge Genomics

Two Tower Place, Suite 950
South San Francisco 94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion criteria - Parts 1 and 2
1. Healthy male or female between 18 to 65 years of age at screening (inclusive).
4. 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.
5. 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.

Exclusion criteria

Exclusion criteria - 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.
4. 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 > 1.5 ULN. Patients with Gilbert syndrome without evidence of hepatic impairment may be enrolled.
14. Poor peripheral venous access.
21. 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.
26. 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)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-09-2022
Enrollment:	84
Type:	Actual

Medical products/devices used

Registration:	No

Product type:	Medicine
Brand name:	VRG50635
Generic name:	Not applicable

Ethics review

Approved WMO Date:	23-08-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	12-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EudraCT	EUCTR2022-002747-22-NL
CCMO	NL81735.056.22
Other	T.b.d.