A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-004 Administered Intrathecally to Patients with C9orf72-associated Amyotrophic Lateral Sclerosis (ALS) or Frontotemporal Dementia (FTD)

Published: 09-03-2021
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Primary objective:• Evaluate the safety and tolerability of WVE-004 in patients with ALS or FTD with a documented mutation in the C9orf72 gene.Secondary objectives:• Characterize the pharmacokinetics (PK) of WVE-004 in plasma.• Characterize...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON52278

Source
ToetsingOnline

Brief title
WVE-004-001

Condition

- Neuromuscular disorders
- Dementia and amnestic conditions

Synonym
ALS, dementia

Research involving
Human

Sponsors and support

Primary sponsor: Wave Life Sciences UK Limited
Source(s) of monetary or material Support: Wave Life Sciences UK Limited

Intervention

Keyword: ALS, Amyotrophic Lateral Sclerosis, C9orf72, Frontotemporal Dementia

Outcome measures

Primary outcome

Incidence of patients with AEs, the incidence of patients with severe AEs,

incidence of patients with SAEs, and the incidence of patients who withdraw due

to AEs.

Secondary outcome

Secondary Endpoint(s)

• Pharmacokinetic parameters of WVE-004 in plasma

• CSF concentration of WVE-004

• Change from baseline in concentration of poly-GP levels in the CSF

Exploratory Endpoint(s)

Biomarker Assessments:

• Change from baseline in concentration of neurodegeneration markers

(including, but not limited to, neurofilament light chain in CSF and/or plasma,

or the extracellular domain of the P75 neurotrophin receptor [P75NTRECD] in

urine)

Laboratory Assessments of Clinical Effects:

• Change from baseline on electrocardiogram

• Change from baseline on pulmonary function tests

• Change from baseline in magnetic resonance imaging (MRI)

Clinical Assessments:

• Change from baseline in the following assessments of clinical signs and

symptoms:

Functional Assessments

* CDR® plus NACC FTLD

* ALS Functional Rating Scale-Revised (ALSFRS-R)

* Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40)

* Hand-held dynamometry (HHD)

* Neuropsychiatric Inventory Questionnaire (NPI-Q)©

Cognitive Assessments

* Trails Making A and B

* Stroop Test

* Verbal Fluency

* Symbol Digit Modalities Test (SDMT)

Study description

Background summary

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND) in some regions, is a progressive, fatal, motor neuropathy. Frontotemporal Dementia (FTD) is a degenerative disorder of the frontal and anterior temporal lobes. ALS and FTD are both associated with the G4C2 expansion in the C9orf72 gene. At this moment in the EU there is only 1 approved drug, Rilutek® (riluzole), for ALS which extends patient survival by 3 to 6 months. For FTD there is no disease-modifying drug, only the symptoms are currently treated. The study drug, WVE-004, is an antisense oligonucleotide (ASO) that promotes

RNase H-mediated degradation of C9orf72*s pathogenic mRNA variants. WVE-004 has the potential to reduce either RNA-based or protein-based toxicity and slow the progression of ALS or FTD.

Study objective

Primary objective:
• Evaluate the safety and tolerability of WVE-004 in patients with ALS or FTD with a documented mutation in the C9orf72 gene.
Secondary objectives:
• Characterize the pharmacokinetics (PK) of WVE-004 in plasma.
• Characterize cerebrospinal fluid (CSF) concentration of WVE-004.
• Evaluate the pharmacodynamic (PD) effect of WVE-004 via measurement of poly-GP in CSF.
Exploratory objectives:
• Evaluate the PD effects of WVE-004 via assessment of markers of neurodegeneration.
• Evaluate the effect of WVE-004 on signs and symptoms of ALS and FTD.
• Characterize changes in brain imaging in patients receiving WVE-004

Study design

Period 1: Up to 4 dose cohorts (P1C1, P1C2, P1C3, and P1C4) are planned. The planned initial dose in P1C1 is 10 mg. Patients will receive a single dose.
Period 2: Up to 4 dose cohorts (P2C1, P2C2, P2C3, and P2C4) are planned. The planned initial dose in P2C1 is 10 mg, administered at a maximum frequency of once monthly.

The maximum dose level in Period 1 and Period 2 and the maximum dose frequency in Period 2 will not exceed those currently recommended by the Dose Escalation Committee (DEC)/Data Safety Monitoring Board (DSMB).

Intervention

The study will include two distinct periods. Period 1 will evaluate single ascending doses (SAD), and Period 2 will evaluate multiple ascending doses (MAD) of WVE-004.

Period 2 cohorts will be based upon available clinical biomarker and safety data alongside nonclinical data. The maximum dose in Period 2 will not exceed a monthly dose of 11.2 mg, which is the human equivalent dose (HED) of the no observed adverse effect level (NOAEL) as established in the ongoing 13-week Good Laboratory Practice (GLP) study in cynomolgus monkeys. Dose escalation beyond the NOAEL established in the 13-week repeat dose toxicity study (11.2 mg monthly) will not occur until the supportive nonclinical data from subsequent chronic toxicity studies are submitted in a substantial amendment to the IMPD

and approved by the competent authorities.

Patients may participate in Period 1 (SAD) and Period 2 (MAD) or Period 2 only. All patients enrolled in Period 1 cohorts will have the opportunity to receive multiple doses in Period 2. All cohorts will include both ALS and FTD patients, and sentinel patients may be diagnosed with either ALS or FTD.
The Sponsor will continue to evaluate available nonclinical and clinical data to optimize the dose level and frequency for multiple dosing but intends to evaluate up to 4 dose levels in Period 1 and Period 2, and 2 dose frequencies in Period 2.

Cohorts in both Period 1 and Period 2 will be enrolled and dosed in a sequential manner. Cohorts that follow the initial dose cohort in Period 1 and Period 2 will not initiate until the requirements for dose escalation are met (as defined in the protocol on page 4-8). This study will utilize both a Dose Escalation Committee (DEC) and a Data Safety Monitoring Board (DSMB). WVE-004 will be administered IT in a volume of 20 mL of artificial cerebrospinal fluid (aCSF). Prior to administration, approximately 20 mL of CSF should be withdrawn.

Study burden and risks

Burden:
Period 1
Study visits 10x; 5x Phone visits, Genetic testing for C9orf72 gene 1x; Blood collection 15x; Screening questionnaire 1x; Lumbar puncture 7x, first lumbar puncture is to collect CSF and for study drug administration and the other lumber punctures are only for CSF collection; Questionnaires 10x; Physical examination 10x; Targeted postdose physical examination 6x; MRI 1x; Lungtest (forced vital capacity (FVC)) 10x; and ECG 6x

Sentinel subjects will have one extra visit on day 3. These subjects will have an extra: C-SSRS, FVC, physical examination, targeted postdose physical examination, blood collection, and ECG.

Period 2
Study visits 10x; Genetic testing for C9orf72 gene 1x; Blood collection 15x; Lumbar puncture 7x, up to 4 lumbar puncture for CSF collection and study drug administration and the other lumber punctures are only for CSF collection; Questionnaires 10x; Physical examination 9x; Targeted postdose physical examination 10x; MRI 1x; Lungtest (forced vital capacity (FVC)) 9x; Actipgraph wear 3 x 2 weeks, and ECG 11x.

Sentinel subjects will have one extra visit on day 3. These subjects will have an extra: C-SSRS, FVC, physical examination, targeted postdose physical examination, blood collection, and ECG.

IP related risks:
In studies in animals (rats and monkeys) using WVE-004, there were short-term effects on motor functioning (weakness of the legs, changes in mobility and walking), as well as slower neuro-reflexes. These effects resolved within 24-48 hours. Subjects will therefore remain 4 hours after each dose for careful monitoring by the investigator.

WVE-004 is a type of drug called an antisense oligonucleotide. Based on what we know about other, similar drugs, there may be a risk of potential damage to subject's liver or kidneys, changes in their blood (a decrease in platelets which are involved in clotting and an increase in the time it takes for their blood to clot), and immune reactions that can cause inflammation. An independent Data and Safety Monitoring Committee will review safety data from this
study. The subject will be made aware of any new risks if they arise.

Procedure related risks:
Subjects will be tested for hepatitis B, hepatitis C, HIV, and pregnancy and subjects will be updated about the outcome of these tests.

The subjects will undergo a lumbar puncture. This may include the following risks: mild to severe headache which may last for several days
, pain at the site where the needle entered the spinal canal, meningitis (an infection of the nervous system), bleeding, spinal fluid leakage, nerve damage, paralysis.

As mention above a blood collection will be performed this may include the following risks: pain and discomfort at the site where the needle enters the skin, fainting
bruising, swelling, an infection may develop at the site where the needle enters the skin (on rare occasions)

In addition a MRI will be performed and this may include the following risks: you be confined in a small, partially enclosed space, sound of the machine may be loud, people who are claustrophobic (fear of being in small spaces) can sometimes have anxiety during an MRI.

The subject will be asked to wear the Actigraph device for 2 weeks following the Period 2 Screening visit, and for 2 weeks prior to the Period 2 Day 85 (Week 12) and Day 169 (Week 24) visits. The Actigraph device measures how the subject moves throughout the day and is worn around the wrist like a watch. There are no known risk for wearing the device. If the device becomes uncomfortable to wear, hot, or causes skin irritation, it should be removed and the study doctor should be contacted immediately. Do not wear the device over any open wounds or irritated skin. The device does not capture or record the location. The device is designed and manufactured by Actigraph. Actigraph will receive data from the device, will analyse this data, and will provide this

analysis to the study Sponsor for assessment of changes in movement.

Finally, a ECG will be performed. Skin irritation, such as redness or itching, is rare, but could occur during an ECG from the electrodes or gel that is used. The ECG is painless and takes about 5 minutes.

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

ALS-Specific Inclusion Criteria:
1. Diagnosis of ALS based on clinical manifestations.
2. ALS: Clinically diagnosed possible, laboratory supported probable, probable, or definite criteria for diagnosing ALS according to the World Federation of Neurology revised El Escorial criteria.

3. Patients receiving riluzole have been on a stable dose for a minimum of 30 days.
4. Patients on edaravone have received a minimum of 1 cycle (28 days).
5. Patients discontinuing riluzole or edaravone had the last dose administered >=1 month prior to Screening.

FTD-Specific Inclusion Criteria:
6. FTD: Must have Global Clinical Dementia Rating - Frontotemporal Lobar Degeneration (CDR® plus NACC FTLD) score of 0.5 or 1.
7. FTD: Able to undergo periodic magnetic resonance imaging (MRI) of the brain. Patients with mixed phenotype (ALS and FTD) need not undergo MRI if their ALS symptoms prevent it.
Mixed Phenotype (ALS and FTD) Inclusion Criteria:
8. Patients who are mixed phenotype (ALS and FTD) must meet both the ALS-specific and FTD-specific criteria.

Inclusion Criteria Common to Both Diseases:
9. Patient must have the ability and be willing to provide written informed consent prior to any trial-related procedures.
10. Documented mutation (GGGGCC [G4C2] repeat expansion) in the first intronic region of the C9orf72 gene.
11. Body mass index (BMI) <=32 kg/m2.
12. Forced vital capacity (FVC) of >50% predicted.
13. Age of >=18 and <=80 years at Screening visit.
14. Willing and able to comply with scheduled visits, drug administration plan, laboratory tests, trial restrictions, and all trial procedures.
15. Willingness to practice highly effective contraception for the duration of the trial and for 5 months after the last dose of study drug if patients or their partners are of childbearing potential. Non-childbearing potential and highly effective methods of contraception are defined in the protocol. In addition, willingness to forego sperm or ova (egg) donation for the duration of the study and 5 months after the last dose.

Exclusion criteria

Exclusion Criteria:
1. Clinically significant medical finding on the physical examination other than C9orf72-associated ALS or FTD that, in the judgment of the Investigator, will make the patient unsuitable for participation in, and/or completion of the trial procedures, including, but not limited to:
a. Prior or ongoing medical conditions, including acute illness, within 28 days of Screening visit;
b. Clinically significant abnormality on laboratory testing at Screening, including but not limited to:
i. Renal insufficiency, which is defined creatinine clearance <40

mL/min
2. Positive hepatitis B surface antigen or hepatitis C antibody test.
3. Known to be positive for human immunodeficiency virus (HIV).
4. History of substance use disorder (except nicotine) within 6 months prior to the Screening Visit.
5. Significant cognitive impairment; or unstable psychiatric illness, including active psychosis, active suicidal ideation, recent suicide attempt, or untreated major depression, within the last 90 days, as determined by the Investigator. Mental status, psychiatric medical history, and eligibility for the study must be documented in the screening questionnaire.
6. Pregnant (as determined by a serum pregnancy test) or breast feeding at the Screening Visit, or plans to become pregnant during the trial.
7. Clinically significant abnormality on Screening electrocardiogram (ECG), including, but not limited to, a confirmed QT interval using Fridericia*s correction method (QTcF) of >=450 msec for males or >=470 msec for females.
8. Bone, spine, bleeding (e.g. hemophilia, Von Willenbrand diseas, liver disease), or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture.
9. Dementia due to a condition other than C9orf72-associated ALS or FTD, including, but not limited to, Alzheimer disease, Parkinson disease, dementia with Lewy bodies, Huntington's disease, or vascular dementia.

Prior or Concomitant Medications
10. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, and phencyclidine at the Screening Visit.
11. Changes in nutritional or herbal supplements or concomitant medications within 1 month prior to Screening visit or plans to modify dose or regimen during the trial.
12. Received prior treatment with viral or cellular-based gene therapy.
13. Received any other investigational drug, biological agent, or device within 1 month of 5 half-lives of study agent, whichever is longer. Received an investigational oligonucleotide, within the past 6 months or 5 half-lives of the drug, whichever is longer. Received prior treatment with investigational product BIIB078.
14. Anticipates using antiplatelet or anticoagulant therapy during the course of the study. Patients who received antiplatelet or anticoagulant therapy must complete one of the following washout periods before the Screening Visit:
a. A 7-day washout period for antiplatelet therapy,
b. A 1-day washout period for anticoagulants (except warfarin), or
c. A 5-day washout period for warfarin

Trial Compliance
15. Implantable central nervous system (CNS) device that may interfere with ability to administer trial drug via lumbar puncture or undergo MRI scan.
16. Deemed to be at significant risk for suicidal behavior based on Investigator assessment and/or active suicidal ideation.

17. Known hypersensitivity to any oligonucleotide, as demonstrated by a systemic allergic reaction, such as changes in pulse, blood pressure, breathing function, etc. or any other drug that in the opinion of the investigator may preclude study participation.
18. Patient is directly or indirectly involved in the conduct and administration of this trial as an Investigator, sub investigator, trial coordinator, or other trial staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the trial.

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:	Recruitment stopped
Start date (anticipated):	22-06-2021
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO

Date:	09-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	18-05-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2020-005193-94-NL
CCMO	NL76122.000.21