A Multicenter, Open-label Extension (OLE) Study to Evaluate the Safety, Pharmacodynamics, and Clinical Effects of WVE-004 in Patients with C9orf72-associated Amyotrophic Lateral Sclerosis (ALS) and/or Frontotemporal Dementia (FTD)

Published: 29-07-2022
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Primaire Objective: - To evaluate the safety and tolerability of long-term treatment with the study drug in patients with ALS or FTD with a documented mutation in the C9orf72 geneSecondary Objective: - To evaluate the clinical and pharmacodynamic (...

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

Summary

ID

NL-OMON53682

Source
ToetsingOnline

Brief title
WVE-004-002

Condition

- Neuromuscular disorders
- Dementia and amnestic conditions

Synonym

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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

Primary Endpoint:

- Incidence of patients with adverse events (AEs), severe AEs, serious

adverse events (SAEs), withdrawals due to AEs

Secondary outcome

Secondary Endpoints:

Clinical Assessments:

- Clinical Dementia Rating plus National Alzheimer*s Coordinating Center

Frontotemporal Lobar Degeneration (CDR® plus NACC FTLD)

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

- Handheld dynamometry (HHD)

- Pulmonary function testing (forced vital capacity [FVC])

- Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ)-5

Pharmacodynamic Effects:

- Change from baseline in concentration of poly-glycine-proline (poly-GP)

levels in the cerebrospinal fluid (CSF)

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

Primaire Objective:
- To evaluate the safety and tolerability of long-term treatment with the study drug in patients with ALS or FTD with a documented mutation in the C9orf72 gene

Secondary Objective:
- To evaluate the clinical and pharmacodynamic (PD) effects of the study drug in patients with ALS or FTD with a documented mutation in the C9orf72 gene

Study design

All patients will receive intrathecal (IT) doses of WVE-004 starting at Week 0. Patients will continue to attend clinic visits every 12 weeks to undergo safety monitoring and assessment of clinical effects through Week 96. In addition, patients will receive monthly telephone calls for safety monitoring. Patients will return to the clinic for follow-up visits on Week 108 and Week 120.

Intervention

All patients will receive intrathecal (IT) doses of the study drug starting at Week 0.

The initial dose level is planned to be 10 mg of the study drug administered no more often than every 12 weeks. However, as the main study is ongoing and data are continuing to emerge, the Sponsor may decide to modify the dose level and frequency being evaluated in this study to ensure patients are receiving one that is optimized.

The dose level and frequency will not exceed the dose levels and associated frequencies evaluated in the WVE-004-001 study, which are recommended by the independent Data Safety Monitoring Board (DSMB) for that study. Dose modification will occur at the next dosing visit. If dosing occurs less often than every 12 weeks, dosing will still align with the currently planned visits (e.g., dosing may occur on some, but not all, of the planned visits on Weeks 12, 24, 36 etc.). If more than 1 dose level or dosing frequency combination is selected, patients will be randomized across the dosing cohorts using a fixed block size. The Sponsor is extending treatment with this amendment (Amendment 1.0) for up to 2 years. Patients will not be dosed beyond the 12-week duration specified in the original protocol until this protocol amendment and associated nonclinical data are approved.

Study burden and risks

While patients may receive treatments that are intended to help manage specific symptoms of ALS and FTD, none of these drugs are intended to address the underlying cause of these diseases. As such, a significant unmet medical need exists for effective treatments for ALS and FTD, particularly disease-modifying agents with the potential to impact the course of the disease.

The study drug has the potential to be a disease-modifying treatment to address the common genetic cause of C9orf72-associated ALS and FTD that gives rise to the devastating manifestations of both disorders. Initial clinical data following single doses of the study drug demonstrated a statistically significant reduction in poly-GP, supporting the potential benefit for patients. Nonclinical data available to date have not identified potential risks that would prevent the evaluation of the study drug in patients with ALS or FTD.

In nonclinical toxicity studies of study drug, impacts on motor function and neuroreflexes have been identified as potential risks and, in addition, ataxia resulting in the early euthanasia of several animals at the highest doses and frequencies administered. These potential risks should be monitored, as outlined in the study assessments.

Given the significant unmet need for treatments that slow or prevent the progression of disease in ALS and FTD patients, the risk/benefit profile of the study drug appears favorable for continued development.

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

1. Patient has the ability and is willing to provide informed consent prior to any study procedures. In instances where signed written informed consent is unable to be obtained it is acceptable for the patient to provide consent with legally authorized representative signing on the patient*s behalf.

2. Patient successfully completed the Phase 1b/2a study with WVE-004, WVE-004-001.

3. In the opinion of the Investigator, the patient is able to tolerate all study procedures, is willing to comply with all other protocol requirements, and tolerated study drug in the parent study.

4. Patient is willing to practice highly effective contraception for the duration of the study and for 5 months after the last dose of study drug if the patient or their partner 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 completion of the study.

5. Patient has identified a study partner(s) for the duration of the study.

Exclusion criteria

1. Patient has a clinically significant medical finding on the physical examination other than C9orf72-associated ALS or FTD that, in the judgment of the Investigator or Sponsor, will make the patient unsuitable for participation in and/or completion of the trial procedures.
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 renal insufficiency, which is defined as
creatinine clearance <40 mL/min.

2. Patient has a positive hepatitis B surface antigen or hepatitis C antibody test.

3. Patients who are pregnant (as determined by a serum pregnancy test) or breast feeding at the Screening visit or plans to become pregnant during the trial.

4. Patients deemed to be at significant risk for suicidal behavior based on Investigator assessment and/or active suicidal ideation.

5. Patient has a bone, spine, bleeding (e.g., hemophilia, Von Willebrand disease, or liver disease), or other disorder that exposes the patient to a risk of injury or unsuccessful LP.

6. Patient received prior treatment with viral or cellular-based gene therapy.

7. Patient received any other investigational drug, biological agent, or device within 1 month or 5 half-lives of study agent, whichever is longer.
Patient received an investigational oligonucleotide within the past 6 months or 5 half-lives of the drug, whichever is longer.

8. Patient 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.

9. Patient was noncompliant in the opinion of the Investigator or Sponsor when participating in study WVE-004-001.

10. 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

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-11-2022
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO

Date:	29-07-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	14-10-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-03-2023
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	EUCTR2022-002267-29-NL
CCMO	NL81832.000.22