



## Clinical trial results:

### 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)

#### Summary

EudraCT number	2022-002267-29
Trial protocol	NL IE BE
Global end of trial date	27 June 2023

#### Results information

Result version number	v1 (current)
This version publication date	18 April 2025
First version publication date	18 April 2025

#### Trial information

##### Trial identification

Sponsor protocol code	WVE-004-002
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05683860
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Wave Life Sciences UK Limited
Sponsor organisation address	1 Chamberlain Square CS, Birmingham, United Kingdom, B3 3AX
Public contact	Daniel Paulson, Wave Life Sciences, +1 617-949-2900, info@wavelifesci.com
Scientific contact	Daniel Paulson, Wave Life Sciences, +1 617-949-2900, info@wavelifesci.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2023
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of long-term treatment with WVE-004 in participants with amyotrophic lateral sclerosis (ALS) or frontotemporal dementia (FTD) with a documented mutation in the C9orf72 gene.

Protection of trial subjects:

The study was conducted according to the study protocol and standard operating procedures that meet the guidelines provided by the International Conference on Harmonisation for Good Clinical Practice in clinical studies, and any other applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Belgium: 2
Worldwide total number of subjects	8
EEA total number of subjects	8

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	4
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Following completion of WVE-004-001, eligible participants entered an open-label extension (OLE) study (WVE-004-002) regardless of whether they participated in only the single-dose phase, multiple-dose phase, or both parts of the study.

### Pre-assignment

Screening details:

A total of 8 participants were treated and none of the participants completed the study due to study termination by Sponsor.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	WVE-004 10 mg Q12W
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Arm description:

Eligible participants successfully completed the Phase 1b/2a WVE-004-001 study, met all inclusion criteria, and none of the exclusion criteria. Participants were administered 10 milligram (mg) of WVE-004 by intrathecal (IT) injection once every 12 weeks (Q12W) for 96 weeks.

Arm type	Experimental
Investigational medicinal product name	WVE-004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

WVE-004 10 mg was administered IT by direct lumbar injection using an atraumatic needle Q12W for 96 weeks.

Number of subjects in period 1	WVE-004 10 mg Q12W
Started	8
Completed	0
Not completed	8
Study terminated by sponsor	8

## Baseline characteristics

### Reporting groups

Reporting group title	WVE-004 10 mg Q12W
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Reporting group description:

Eligible participants successfully completed the Phase 1b/2a WVE-004-001 study, met all inclusion criteria, and none of the exclusion criteria. Participants were administered 10 milligram (mg) of WVE-004 by intrathecal (IT) injection once every 12 weeks (Q12W) for 96 weeks.

Reporting group values	WVE-004 10 mg Q12W	Total	
Number of subjects	8	8	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	4	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical			
Demographic data was not assessed for this study since all participants in Study WVE-004-002 rolled over from Study WVE-004-001.			
Units: Subjects			
Female	8	8	
Male	0	0	

## End points

### End points reporting groups

Reporting group title	WVE-004 10 mg Q12W
Reporting group description:	
Eligible participants successfully completed the Phase 1b/2a WVE-004-001 study, met all inclusion criteria, and none of the exclusion criteria. Participants were administered 10 milligram (mg) of WVE-004 by intrathecal (IT) injection once every 12 weeks (Q12W) for 96 weeks.	

### Primary: Number of Occurrences of Participants With Adverse Events (AEs), Severe AEs, Serious Adverse Events (SAEs), and Withdrawals Due to AEs

End point title	Number of Occurrences of Participants With Adverse Events (AEs), Severe AEs, Serious Adverse Events (SAEs), and Withdrawals Due to AEs <sup>[1]</sup>
End point description:	
A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment. The safety population included all enrolled participants who have received at least 1 dose of study medication in the OLE.	
End point type	Primary
End point timeframe:	
Day 1 to Week 120 (end of study)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistical analysis was performed for the primary end point.

<b>End point values</b>	WVE-004 10 mg Q12W			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants				
AEs	3			
severe AEs	0			
SAEs	0			
Withdrawals due to AEs	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Clinical Dementia Rating Plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration (CDR Plus NACC FTLD)

End point title	Change From Baseline in Clinical Dementia Rating Plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration (CDR Plus NACC FTLD)
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End point description:

Disease progression was measured using the CDR plus NACC FTLD scale. The evaluation included assessments of both cognitive and functional measures, including memory, orientation, judgment and

problem-solving, involvement in community affairs, home and hobbies, personal care, language and behavior, and comportment and personality. The rating for each domain was scored using a scale of 0 (none) to 3 (severe) based on the participant's function in relation to cognitive ability (not impairment due to other factors) and past performance (or baseline level of functioning). The overall rating for each domain was summed to provide a global clinical measure of the disease. The CDR plus NACC FTLD score ranges from 0 to 24, with a higher score indicating more severe impairment. Analysis of the CDR plus NACC FTLD and its sum of boxes score by Mixed Model for Repeated Measures (MMRM) analysis model was conducted in the WVE-004-001 study only.

End point type	Secondary
End point timeframe:	
Day 1 to Week 120 (end of study)	

<b>End point values</b>	WVE-004 10 mg Q12W			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: units on a scale				
arithmetic mean (standard deviation)	( )			

Notes:

[2] - No participants were analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in ALS Functional Rating Scale-Revised (ALSFRS-R)

End point title	Change From Baseline in ALS Functional Rating Scale-Revised (ALSFRS-R)
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End point description:

ALSFRS-R is an instrument to monitor the function of participants with ALS and their disease progression. The components of the scale are grouped into 4 factors or domains that encompass gross motor tasks, fine motor tasks, bulbar functions, and respiratory functions. These components measure speech, salivation, swallowing, writing, feeding, dressing, turning, walking, climbing, breathing, dyspnea, orthopnea, and respiratory insufficiency. Each component is scaled from 0 to 4, with 4 being normal, and a total score is calculated. ALSFRS-R was not assessed for Study WVE-004-002.

End point type	Secondary
End point timeframe:	
Day 1 to Week 120 (end of study)	

<b>End point values</b>	WVE-004 10 mg Q12W			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[3]</sup>			
Units: units on a scale				
arithmetic mean (standard deviation)	( )			

Notes:

[3] - No participants were analyzed.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Handheld Dynamometry (HHD)

End point title	Change From Baseline in Handheld Dynamometry (HHD)
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End point description:

The HHD was used to provide an objective quantitative measurement of strength, a key hallmark of decline in ALS disease progression. For the HHD assessment, participants would be sitting in a hard-backed chair with armrests or a wheelchair. Muscle strength was tested using the HHD device. Measurements were recorded in pounds. A value of 0 was assigned to a given muscle if a participant could not assume the testing position due to weakness. HHD was not assessed for Study WVE-004-002 due to the early termination of the study.

End point type	Secondary
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End point timeframe:

Day 1 to Week 120 (end of study)

<b>End point values</b>	WVE-004 10 mg Q12W			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[4]</sup>			
Units: pounds				
arithmetic mean (standard deviation)	( )			

Notes:

[4] - No participants were analyzed.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Pulmonary Function Testing Forced Vital Capacity (FVC)

End point title	Change From Baseline in Pulmonary Function Testing Forced Vital Capacity (FVC)
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End point description:

Pulmonary function tests are tests that show how well your lungs are working. The tests measure lung volume, capacity, rates of flow, and gas exchange. FVC analysis was conducted in the WVE-004-001 study only.

End point type	Secondary
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End point timeframe:

Day 1 to Week 120 (end of study)

<b>End point values</b>	WVE-004 10 mg Q12W			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[5]</sup>			
Units: liters				
arithmetic mean (standard deviation)	( )			

Notes:

[5] - No participants were analyzed.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ)-5

End point title	Change From Baseline in Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ)-5
End point description: The ALSAQ-5 is specifically used to provide a brief assessment of the impacts of ALS on participants. Participants were asked to think about the difficulties they have experienced during the reporting period and scale each event as never/rarely/sometimes/often/always or cannot do at all. ALSAQ-5 was not assessed for Study WVE-004-002 due to the early termination of the study.	
End point type	Secondary
End point timeframe: Day 1 to Week 120 (end of study)	

End point values	WVE-004 10 mg Q12W			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[6]</sup>			
Units: units on a scale				
arithmetic mean (standard deviation)	( )			

Notes:

[6] - No participants were analyzed.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Concentration of Poly-glycine-proline (Poly-GP) Levels in the Cerebrospinal Fluid (CSF)

End point title	Change From Baseline in the Concentration of Poly-glycine-proline (Poly-GP) Levels in the Cerebrospinal Fluid (CSF)
End point description: CSF samples were collected to determine the concentration of poly-GP levels in CSF. The safety population included all enrolled participants who had received at least 1 dose of study medication in the OLE.	
End point type	Secondary
End point timeframe: From Baseline to Week 12	



<b>End point values</b>	WVE-004 10 mg Q12W			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: picogram per milliliter				
arithmetic mean (standard deviation)				
Baseline (n=8)	19.321 (± 13.4362)			
Week 12 (n=3)	14.613 (± 12.0240)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

TEAE period in the OLE consisted of up to 96 weeks of treatment (at a maximum frequency of once every 4 weeks) followed by 24 weeks of follow-up.

Adverse event reporting additional description:

The Safety population included all participants who were enrolled in the OLE study.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	WVE-004 (Dose A)
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Reporting group description:

WVE-004 is a stereopure antisense oligonucleotide. It is administered via intrathecal injection.

Serious adverse events	WVE-004 (Dose A)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	WVE-004 (Dose A)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vision blurred			

subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Pneumonia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1  1 / 8 (12.50%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2022	Extended the duration of treatment from 12 weeks to 96 weeks.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to lack of clinical benefit, development of WVE-004 was stopped.

Notes: