

# A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-003 Administered Intrathecally in Patients With Huntington\*s Disease

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Primary objective:x To evaluate the safety and tolerability of WVE-003 in patients with Huntington's disease (HD)Secondary objectives:x To characterize the pharmacokinetics (PK) of WVE-003 in plasma x To characterize the concentration of WVE-...

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Pending
<b>Health condition type</b>	Congenital and hereditary disorders NEC
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON53854

### Source

ToetsingOnline

### Brief title

Phase 1b/2a Study of WVE-003 in Patients with Huntington's Disease

### Condition

- Congenital and hereditary disorders NEC

### Synonym

Huntington's Disease

### Research involving

Human

### Sponsors and support

**Primary sponsor:** Wave Life Sciences UK Limited

**Source(s) of monetary or material Support:** betaald door de verrichter Wave Life Science

## Intervention

**Keyword:** Huntington's Disease, Phase 1b/2a, WVE-003

## Outcome measures

### Primary outcome

Safety:

Adverse events, concomitant medications, physical examinations including detailed neurological examination, vital signs, weight, 12-lead ECGs, clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis), CSF safety evaluations, MRI of the brain, and C-SSRS

### Secondary outcome

Pharmacokinetics:

- x Pharmacokinetic parameters of WVE-003 in plasma
- x Concentration of WVE-003 in CSF

Pharmacodynamics:

- x Change from baseline in the level of mHTT protein in CSF
- x Change from baseline in the level of wtHTT protein in CSF
- x Change from baseline in the level of tHTT protein in CSF
- x Change from baseline in the level of NfL in CSF
- x Change from baseline in the level of exploratory biomarkers in CSF, plasma, and/or PBMC's

## Clinical Effects Endpoint(s):

- x Change from baseline in the UHDRS TFC
- x Change from baseline in UHDRS total motor score
- x Change from baseline in the UHDRS independence scale
- x Change from baseline in Symbol Digit Modalities Test
- x Change from baseline in Stroop word reading test
- x Change from baseline in the composite UHDRS
- x Change from baseline in the PBA-s
- x Changes from baseline in MRI of the brain

## Study description

### Background summary

This is a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of WVE-003 in adult patients with early-manifest HD who carry the targeted single nucleotide polymorphism (SNP) rs362273 (SNP3)

### Study objective

Primary objective:

- x To evaluate the safety and tolerability of WVE-003 in patients with Huntington's disease (HD)

Secondary objectives:

- x To characterize the pharmacokinetics (PK) of WVE-003 in plasma
- x To characterize the concentration of WVE-003 in cerebrospinal fluid (CSF)

Exploratory objectives:

- x To evaluate the pharmacodynamic (PD) effect of WVE-003 on the levels of mutant huntingtin (mHTT) protein in CSF
- x To evaluate the effect of WVE-003 on clinical measures of disease including the Unified Huntington's Disease Rating Scale (UHDRS) and Short Problem Behaviors Assessment (PBA-s)
- x To evaluate the PD effect of WVE-003 on other measures of PD activity, e.g.,

levels of wild type huntingtin (wtHTT) protein, total huntingtin (tHTT) protein, and neurofilament light (NfL) in CSF  
x To evaluate changes from baseline in magnetic resonance imaging (MRI) of the brain

## **Study design**

To participate in the study, patients must undergo prescreening to confirm they are heterozygous for SNP3 with the A variant on the same allele as the cytosine-adenine-guanine (CAG) triplet expansion. Prescreening can happen any time before Screening. The prescreening testing process to confirm the presence of SNP3 is expected to take up to 6 weeks. If patients meet these criteria, they will continue to the Screening visit. The prescreening assessment will have a separate informed consent form (ICF).

The study will include 2 distinct periods: Period 1 to evaluate single ascending dose (SAD) cohorts and Period 2 to evaluate multiple ascending dose (MAD) cohorts of WVE-003. Period 2 will not be initiated until nonclinical data supportive of multiple dosing are approved by the local regulatory authorities. Following this approval, the Sponsor intends to initiate Period 2. Patients may participate in Period 1 (SAD) and Period 2 (MAD) or Period 2 (MAD) only. All patients enrolled in Period 1 cohorts will have the opportunity to receive multiple doses in Period 2.

Cohorts in both Period 1 and Period 2 will be enrolled, randomized, and dosed in a sequential manner. Subsequent cohorts will not initiate until the requirements for dose escalation are met (as defined below). This study will utilize both a Dose Escalation Committee (DEC) and a Safety Monitoring Committee (SMC). The DEC will be responsible for making recommendations regarding dose escalation in Period 1, initiation of multiple dosing in Period 2, and subsequent dose escalation in Period 2. Decisions made by the DEC will be reviewed by the SMC.

WVE-003 will be administered intrathecally in a volume of 20 mL of artificial CSF (aCSF).

Period 1: This period will consist of a single dose and a minimum of 12 weeks of postdose follow-up.

Period 2: This period will consist of up to 12 weeks of treatment and 12 weeks of follow-up.

## **Intervention**

The currently planned starting dose level in Period 1 is 30 mg. The dose levels in subsequent Period 1 cohorts and Period 2 will be determined based on the findings in Period 1 and pending repeat-dose toxicity data from the GLP

studies. The dose levels will not exceed a maximum dose of 168 mg in Period 1 or the HED of the NOAEL from the 13-week GLP study in cynomolgus monkeys in Period 2, unless addressed by a protocol amendment. In Period 2, doses will be administered on Weeks 0, 2, and 4, and monthly thereafter (5 total doses).

WVE-003 will be provided as lyophilized powder for reconstitution and dilution for IT injection. WVE-003 for injection will be prepared by reconstituting and diluting the lyophilized powder with aCSF supplied by the Sponsor.

Placebo will be aCSF provided by the Sponsor. It will be a sterile, preservative-free solution. Placebo will be visually identical in appearance to the WVE-003 injection solution and administered intrathecally in order to maintain the blind. Placebo will be administered in a volume of 20 mL.

## **Study burden and risks**

Participation in the study requires amongst other the following of the subject:

- Visits: Prescreening, screening visit, period 1 (5 visits, including 1 overnight stay) and period 2 (8 visits)
- Possible side effects or adverse effects of the study drug, as described in Section E9. WVE-003 has never been used in humans before.
- Experience discomfort from the measurements during the study, as described in E9, like the lumbar puncture to draw CSF and administer the study drug
- Women should not get pregnant during the study or within 6 months following the last dose of administration of WVE-003. Males should not conceive a child.

Huntington's disease is a rare, progressive neurological disease. Currently available treatments for HD only mitigate symptoms and do not affect the underlying HD pathology, the disease course, or life expectancy after diagnosis of HD. No approved treatments exist that can cure, slow, or reverse the course of HD. Based on the results of the nonclinical studies, WVE-003 has promise as a disease-modifying agent for the treatment of patients with HD.

## **Contacts**

### **Public**

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### **Scientific**

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

### Inclusion criteria

1. Documented ability to understand the written study ICF(s) and consent, and has provided signed written informed consent prior to any study procedures.
2. Ambulatory male or female
3. Age  $\geq 25$  to  $\leq 60$  years old
4. Body mass index (BMI)  $\leq 32$  kg/m<sup>2</sup>
5. Documented CAG triplet repeats  $\geq 36$  in the HTT gene
6. Documented heterozygosity at SNP3
7. Documented presence of the A variant of SNP3 on the same allele as the pathogenic CAG triplet expansion
8. Clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4
9. UHDRS Total Functional Capacity (TFC) scores  $\geq 9$  and  $\leq 13$
10. In the opinion of the Investigator, the patient is able to tolerate all study procedures, and is willing to comply with all other protocol requirements.
11. Willingness to practice highly effective contraception for the duration of the study and for 5 months (i.e., 5 elimination half-lives) 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 completion of the study.

## Exclusion criteria

1. Malignancy or received treatment for malignancy, other than treated basal cell or squamous cell carcinoma of the skin, within the previous 5 years.
2. Positive for Hepatitis B virus (HBV) or Hepatitis C virus (HCV).
3. Known to be positive for human immunodeficiency virus (HIV).
4. Clinically significant medical finding on the physical examination other than HD that, in the judgment of the Investigator, will make the patient unsuitable for participation in and/or completion of the study procedures.
5. Previously received tominersen.
6. Received prior treatment with viral or cellular-based gene therapy.
7. Received any other study drug, including an investigational oligonucleotide, within the past 1 year or 5 half-lives of the drug, whichever is longer, with the exception of the following:
  - a. Received WVE-120101 within the last 3 months (i.e., 5 half-lives); or
  - b. Received WVE-120102 within the last 3 months (i.e., 5 half-lives)
8. Implantable central nervous system device that may interfere with ability to administer study drug via lumbar puncture or undergo MRI scan.
9. History of substance abuse disorder (except nicotine) within 6 months prior to the Screening Visit.
10. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit.
11. Started or changed dose for concomitant medication for the treatment of HD symptoms or psychiatric disorders within 30 days prior to the Screening Visit (concomitant medications that have been administered on a stable regimen for  $\geq 30$  days are permitted).
12. Pregnant (as determined by a serum pregnancy test) or breast feeding at the Screening Visit, or plans to become pregnant during the course of the study.
13. Clinically significant laboratory abnormality at Screening.
14. Clinically significant abnormality at Screening electrocardiogram (ECG), including but not necessarily limited to a confirmed QT interval corrected for heart rate (QTc)  $\geq 450$  msec for males or  $\geq 470$  msec for females.
15. Clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal, neurologic, malignant, metabolic, psychiatric, or other condition that, in the opinion of the Investigator, precludes the patient's safe participation in the study or would interfere with the study assessments. Mental status, psychiatric medical history, and eligibility for the study must be documented in the screening questionnaire.
16. Bone, spine, bleeding, or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture.
17. Inability to undergo brain MRI (with or without sedation).
18. Deemed to be at significant risk for suicidal behavior based on any of the following criteria:
  - a. The opinion of the Investigator; or
  - b. Answers \*yes\* to Actual Suicide Attempts or Suicidal Behaviors in the Suicidal Behaviors section of the Columbia-Suicide Severity Rating

Scale (C-SSRS) with reference to a 2 year period prior to the Screening Visit;  
or  
c. Answers \*yes\* on any items in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to the Screening Visit; or  
d. Answers \*yes\* on any items in the Suicidal Ideation section of the C-SSRS at the Baseline Visit since the last visit (Screening Visit).

19. Involved directly or indirectly in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study 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 study.

20. History of hypersensitivity to other antisense oligonucleotides and any other drug that, in the opinion of the investigator, may preclude study participation.

## 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:	Pending
Start date (anticipated):	15-07-2023
Enrollment:	4
Type:	Anticipated

## Ethics review

Approved WMO	
Date:	08-02-2022



Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	18-08-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	14-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	
Date:	15-06-2023
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	EUCTR2020-004556-15-NL
ClinicalTrials.gov	NCT05032196
CCMO	NL79700.000.22