A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRATHECALLY ADMINISTERED RO7234292 (RG6042) IN PATIENTS WITH MANIFEST HUNTINGTON'S DISEASE

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON55873

Source
ToetsingOnline

Brief title
BN40423 - GENERATION HD1

Condition

- Movement disorders (incl parkinsonism)

Synonym
Huntington's chorea, Huntington's disease

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman-La Roche

Intervention

Keyword: Antisense oligonucleotide, ASO, Huntington's Disease, Manifest disease

Outcome measures

Primary outcome

Efficacy: change from baseline in the composite Unified Huntington's Disease

Rating Scale (cUHDRS) score at Week 101.

Biomarker: change from baseline in CSF mHTT protein level at Week 101.

Secondary outcome

Efficacy:

Change from baseline in scores for the following individual scales at Week 101:

- TFC

- Total Motor Score (TMS)

- Symbol Digit Modalities Test (SDMT)

- Stroop Word Reading Test (SWR)

Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S)

score at Week 101:

- Proportion of patients with a decrease from baseline of > 1 point on the TFC

at Week 101

- Proportion of patients with a decline from baseline of > 1.2 points on the cUHDRS at Week 101

- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline at Week 101

Biomarker:

- Change from baseline in whole and regional brain volumes (caudate, whole brain, and ventricular), as determined by structural magnetic resonance imaging (MRI), at Week 101

- Change from baseline in CSF neurofilament light chain (NfL) protein level at Week 101

For exploratory, safety, PK and immunogenicity endpoints, please see protocol section 2.

Study description

Background summary

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by expansion of CAG repeats in exon 1 of the Huntingtin HTT gene on chromosome 4, which encodes for a mutant huntingtin (mHTT) protein. Based upon nonclinical and clinical evidence, mHTT is considered the primary driver of HD pathophysiology. Individuals who carry at least 40 CAG repeats inevitably experience progressive motor, cognitive, and functional decline usually in adult life, with a mean age of motor onset of 45 years. The average illness course post-motor onset is approximately 10-20 years, with pneumonia, heart failure, or other complications frequently cited as the cause of death. Individuals with end-stage disease have complete physical disability and

profound body wasting.

Currently approved treatments aim to reduce the burden of symptoms, maximize function, and improve the patient's quality of life. To date, there are no approved treatments able slow or stop the clinical progression of HD. The ASO RO7234292 is designed to target the cause of HD and offers the potential to meet this unmet medical need.

This study will evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of RO7234292 compared with placebo in patients with manifest HD.

Study objective

The primary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo.
The secondary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo.
The safety objective for this study is to evaluate the safety and tolerability of RO7234292 compared with placebo.
The PK objective for this study is to characterize the RO7234292 PK profile in plasma and trough CSF.
The immunogenicity objective for this study is to evaluate the immune response to RO7234292.
The biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo.

Study design

Study BN40423 is a Phase III, randomized, placebo-controlled, double-blind, multicenter clinical study to evaluate the efficacy, safety, PK, and biomarker effects of intrathecally administered RO7234292 in patients with manifest HD. Approximately 660 patients will be enrolled in the study.

Upon completion of the screening period, eligible patients will be randomly allocated in a 1:1:1 ratio to receive RO7234292 every 8 weeks (RO7234292 Q8W arm), RO7234292 every 16 weeks (RO7234292 Q16W arm), or placebo Q8W (placebo arm) by IT injection, as described in Table 1 of the protocol.

To maintain the study blind and integrity, patients in the RO7234292 Q16W arm will also receive placebo (i.e., alternating doses of active drug and placebo).

Patients will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, MoCA, C-SSRS, neuroimaging assessments (neurologic safety sequences), and adverse events including related concomitant medications, as detailed in Appendix 1 of

the protocol.

Patients who complete the treatment period will return to the clinic for an end-of-treatment visit at Week 101. Patients will then be given the option on an individual basis of receiving RO7234292 in an OLE study (BN40955) upon completion of Study BN40423, provided they meet eligibility criteria and the data from the ongoing RO7234292 program support continued development.

Intervention

Patients are randomized in one of the following three arms in a 1: 1: 1 ratio:

- RO7234292 (RO7234292 Q8W arm);
- RO7234292 (RO7234292 Q16W arm); or
- Q8W placebo (placebo arm)

Patients on the RO7234292 Q16W arm will also receive placebo (i.e., alternate doses of the active drug and placebo).

Note: no further study treatment will be administered in this study as of 22 March 2021.

Study burden and risks

RO7234292 has had limited testing in humans, with up to 9 months in 46 patients as of 30 January 2019. Patients have received a regimen of either every 4 weeks (Q4W) (23 patients) or every 8 weeks (Q8W) (23 patients). Adverse events or laboratory changes based on human and laboratory studies of RO7234292, knowledge of similar drugs, or theoretical risks are listed below. There may be side effects that are not known at this time.

* Pain after lumbar puncture (17 patients) and post-lumbar puncture events (for example, headache and nausea) (7 patients) (observed equally across the Q4W or Q8W treatment regimens)
* Falling at least once during study (observed in 12 Q4W and 8 Q8W patients)
* Increase in white blood cells in the fluid surrounding the spinal cord and brain*which may indicate inflammation from the lumbar puncture or the study drug (observed in 14 Q4W and 6 Q8W patients)
* Increase in proteins in the fluid surrounding the spinal cord and brain, which may indicate inflammation from the lumbar puncture or the study drug (observed in 15 Q4W and 5 Q8W patients)
* Inflammation of the lower back spinal nerve roots (radiculopathy/radiculitis), which may lead to changes in reflex responses, motor, or sensory symptoms (observed in 2 patients in the Q4W group who had ankle reflex loss without motor or sensory symptoms)
* Changes observed in muscle strength, ankle reflex changes, balance

difficulties, and some temporary changes in sensory function (1 patient in Q4W group)

In the patient information leaflet, additional theoretical risks are described. In addition, potential risks have been described for the unborn child, and for the study procedures.

In addition to the mentioned risks listed here, the study drug and the study procedures may come with other, unknown risks.

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

* Signed Informed Consent Form
* Age 25 to 65 years, inclusive
* Manifest HD diagnosis, defined as a diagnostic confidence level (DCL) score of 4
* Independence Scale (IS) score * 70
* Genetically confirmed disease by direct DNA testing with a CAP score >400, calculated as follows: CAP <= Age x (CAG repeat length - 33.66)
* Ability to read the words "red," "blue," and "green" in native language
* Ability to walk unassisted without a cane or walker and move about without a wheelchair on a daily basis as determined at screening and baseline visit
o Long-distance (e.g., > 50 meters) use of wheelchairs for convenience or transfer is permitted.
* Body mass index 16-32 kg/m2; total body weight > 40 kg
* Ability to undergo and tolerate MRI scans, to tolerate blood draws and lumbar punctures
* Creatinine Clearance (CrCl) * 60 mL/min (Cockcroft-Gault formula)
* Ability and willingness, in the investigator's judgment, to comply with all aspects of the protocol including completion of interviews and questionnaires for the duration of the study
* Ability and willingness, in the investigator's judgment, to carry a smartphone, wear a digital monitoring device, and complete smartphone-based tasks
* Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment
* Signed study companion consent for participation who fulfills all of the criteria as specified in protocol section 4.1.1.
* For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined in protocol section 4.1.1.
* For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined in protocol section 4.1.1.

Exclusion criteria

* History of attempted suicide or suicidal ideation with plan that required hospital visit and/or change in level of care within 12 months prior to screening
* Current suicidal ideation is demonstrated by the C-SSRS per judgment of the investigator. If suicidal ideation is present, a risk assessment should be done by an appropriately qualified mental health professional to assess whether it is safe for the patient to participate in the study.

* Current active psychosis, confusional state, or violent behavior
* Any serious medical condition or clinically significant laboratory, or vital sign abnormality or claustrophobia at screening that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
* History known to the investigator or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second-or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
* Lifetime clinical diagnosis of chronic migraines
* Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study drug
* Women of childbearing potential must have a negative serum pregnancy test result at baseline and a confirmatory urine pregnancy test prior to initiation of study drug.
* Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
* Positive for hepatitis C virus (HCV) antibody or hepatitis B surface antigen (HBsAg) at screening
* Known HIV infection
* Current or previous use of an antisense oligonucleotide (including small interfering RNA)
* Current or previous use of anti-psychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks from initiation of study treatment
* Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) and/or tetrabenazine, valbenazine, or deutetrabenazine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
* Current use of supplements (e.g., coenzyme Q10, vitamins, creatine) at a dose that has not been stable for at least 6 weeks prior to screening or is anticipated to change during the study
* Current use of an antidepressant or benzodiazepine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
* Treatment with investigational therapy within 4 weeks or 5 drug-elimination half-lives prior to screening, whichever is longer
* Antiplatelet or anticoagulant therapy within 14 days prior to screening or anticipated use during the study, including, but not limited to, aspirin (unless * 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
* History of bleeding diathesis or coagulopathy
* Platelet count less than the lower limit of normal
* Platelet counts between 125,000 and 150,000 mm3 are permissible as long as

the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.
* History of gene therapy, cell transplantation, or any experimental brain surgery
* Concurrent or planned participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions (e.g., lumbar puncture) Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
* Drug and/or alcohol abuse or psychological or physiological dependency within 12 months prior to screening, as per the investigator's judgment
* Poor peripheral venous access
* Scoliosis or spinal deformity or surgery making IT injection not feasible in an outpatient setting and potentially interfering with distribution of RO7234292 up the neuraxis
* An infection requiring oral or IV antibiotics within 14 days prior to screening and prior to randomization
* Antiretroviral medications, including antiretroviral medication taken as prophylaxis within 12 months of study enrollment
* Malignancy within 5 years prior to screening, except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
* Preexisting intra-axial or extra-axial (e.g., tumor, arterio-venous malformation) as assessed by a centrally read MRI scan during the screening period

Study design

Design

Study phase:	3
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):	04-08-2019
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	04-02-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-07-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	25-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2021
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	EUCTR2018-002987-14-NL
ClinicalTrials.gov	NCT03761849
CCMO	NL68007.000.19

Study results