AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG TERM SAFETY AND TOLERABILITY OF INTRATHECALLY ADMINISTERED RO7234292 (RG6042) IN PATIENTS WITH HUNTINGTON*S DISEASE

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This study will evaluate the long-term safety and tolerability of RO7234292 in patients with HD. In addition, the study will obtain long-term data on the efficacy, immunogenicity, exposure, and biomarkers of RO7234292. Specific objectives and...

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

Summary

ID

NL-OMON55276

Source
ToetsingOnline

Brief title
BN40955 - GEN-EXTEND

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

The safety objective for this study is to evaluate the safety and tolerability

of RO7234292 on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according

to the Adverse Event Severity Grading Scale (see Table 3)

- Change from baseline in targeted vital signs

- Change from baseline in physical findings

- Change from baseline in neurological findings

- Change from baseline in behavioral findings, as assessed by the

Columbia-Suicide Severity Rating Scale (C-SSRS)

- Change from baseline in cognition

- Change from baseline in targeted ECG results

- Change from baseline in targeted clinical laboratory test results

- Relationship between laboratory parameter change and safetytargeted endpoints

- Relationship between magnetic resonance imaging (MRI) parameter change and

safety-targeted endpoints

Secondary outcome

efficacy:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score as assessed every 16 weeks

- Change from baseline in scores for the following individual scales as assessed every 16 weeks:

* Total Functional Capacity Scale (TFC)

* Total Motor Score (TMS)

* Symbol Digit Modalities Test (SDMT)

* Stroop Word Reading (SWR) Test

- Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S) score as assessed every 16 weeks

- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline as assessed every 16 weeks

- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score as assessed every 16 weeks

- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) as assessed every 16 weeks

See protocol section 2.2 - 2.6 for details on the exploratory pharmacokinetic, immunogenicity, biomarker and health status utility objectives

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 gene (HTT) 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 (Wild and Tabrizi 2017). 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 (Sorensen and Fenger 1992). Individuals with end-stage disease have complete physical disability and profound body wasting.
To date, there are no approved treatments able to slow or stop the clinical progression of HD.
See section 1 of the protocol for more information

Study objective

This study will evaluate the long-term safety and tolerability of RO7234292 in patients with HD. In addition, the study will obtain long-term data on the efficacy, immunogenicity, exposure, and biomarkers of RO7234292. Specific objectives and corresponding endpoints for the study are outlined below. See section 2 of the protocol

Study design

Only patients with prior enrollment in a Roche-sponsored or Genentech-sponsored study in HD for the RO7234292 development program that made provision for entry into an OLE study will be eligible for this OLE study. Entry into the study should occur at the time the patient completes participation in one of the preceding studies. Upon completion of the inclusion visit, eligible patients will receive either 120 mg RO7234292 Q8W (RO7234292 Q8W arm) or 120 mg RO7234292 Q16W (RO7234292 Q16W arm) by bolus IT injection.
See section 3 of the protocol

Intervention

All patients in this study will have the opportunity to receive treatment with either 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W and will be assigned to treatment as described in Table 1 of the protocol.

Note: study treatment will be paused in this study as of 22 March 2021.

Study burden and risks

RO7234292 has had limited testing in humans, with up to 15 months in 46 patients as of 18 July 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.

* Falling at least once during study (observed in 18 Q4W and 10 Q8W patients)
* Pain after lumbar puncture (observed in 7 Q4W and 12 Q8W patients) and post-lumbar puncture syndrome events (for example, headache and nausea) (observed in 13 Q4W and 12 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 15 Q4W and 8 Q8W patients)
* Increased proteins in the fluid surrounding the spinal cord and brain, which may indicate inflammation from the lumbar puncture or the study drug (observed in 17 Q4W and 6 Q8W patients)
* Changes in gait or walking observed (in 6 Q4W patients) and none in Q8W patients)
* Inflammation of the spinal nerve roots (radiculopathy/radiculitis), which may lead to changes in reflex responses, motor, or sensory symptoms (lumbar radiculopathy 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)
* Speech and coordination difficulties (1 patient in Q4W group) which the study doctor considered as unrelated to RO7234292
* Excess build-up of fluid that surrounds the brain (ventricular enlargement) and that may potentially lead to changes in thinking, walking (1 Q4W patient), and/ or to urinary incontinence

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 ICF
- Prior enrollment in a Roche sponsored or Genentech-sponsored study in HD for the RO7234292 development program that made provision for entry into an OLE study
- Ability and willingness to comply with the study protocol including the visit schedule and all assessments, in the investigator's judgment
- Ability to undergo and tolerate MRI scans (e.g., no claustrophobia, no severe chorea or other condition that precludes MRI scans or renders scanning intolerable for the patient, no MRI-incompatible intrauterine devices, metallic dental braces, or other metal implants)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, during the treatment period and for 5 months after the final dose of study drug
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm during the treatment period and for 5 months after the final dose of study drug to avoid exposing the embryo

The following eligibility criteria only apply to patients who were eligible for Study BN40423 (GENERATION HD1) but were not randomized due to logistical challenges resulting from the COVID-19 pandemic

- Age 25 65 years, inclusive, at the time of signing of ICF and at the time of first dose administration
- 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 CAG-Age product (CAP) score >400
- 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
- Body mass index 16-32 kg/m2; total body weight >40 kg
- Ability to undergo and tolerate MRI scans
- Ability to tolerate blood draws and LPs
- Creatinine clearance (CrCl) ><=60 mL/min
- 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
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment

Exclusion criteria

- Withdrawal of consent from the preceding study
- Permanent discontinuation of RO7234292 for any drug-related safety concern during the preceding study or meeting of any study treatment discontinuation criteria specified in the preceding study at the time of enrollment into this study
- An ongoing, unresolved, clinically significant medical problem that in the judgment of the investigator would make it unsafe for the patient to participate in this study
- Antiplatelet or anticoagulant therapy within 14 days prior to inclusion 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
- Concurrent participation in any therapeutic clinical trial (other than the preceding study)
- Study treatment (RO7234292) is commercially marketed in the patient*s country for the patient-specific disease and is accessible to the patient
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study drug

The following exclusion criteria only apply to patients who were eligible for Study BN40423 (GENERATION HD1) but were not randomized due to logistical

challenges resulting from the COVID-19 pandemic:
- History of attempted suicide or suicidal ideation with plan (i.e., active suicidal ideation) that required hospital visit and/or change in level of care within 12 months prior to screening
- 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
- Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Positive for hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) at screening
- Known HIV infection
- Current or previous use of an ASO (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
- Treatment with investigational therapy within 4 weeks or 5 drug elimination half lives prior to screening, whichever is longer
- History of gene therapy, cell transplantation, or any experimental brain surgery
- Drug (i.e., cannabis, opioid, stimulant, hallucinogen, designer) 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 lesions (e.g., tumor, arteriovenous malformation, meningiomas, hydrocephalus, subdural haematoma) as assessed by a centrally read MRI scan during the screening period

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-02-2021
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO Date:	04-06-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-10-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2020

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:	19-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2021
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:	11-05-2021
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	EUCTR2018-003898-94-NL
ClinicalTrials.gov	NCT03842969
CCMO	NL73989.000.20

Study results