An open-label, adaptive multiple-dose study to investigate the pharmacokinetics and pharmacodynamics of RO7234292 in csf and plasma, and safety and tolerability following intrathecal administration in patients with Huntington's disease.

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Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON49037

Source
ToetsingOnline

Brief title
BP40410

Condition

- Neurological disorders congenital
- Neuromuscular disorders

Synonym

Chronic Progressive Chorea, degenerative chorea

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Hoffmann-La Roche

Intervention

Keyword: Huntington's disease, Pharmacodynamics, Pharmacokinetics, RO7234292

Outcome measures

Primary outcome

The corresponding primary endpoints are as follows: 1. CSF and plasma concentrations of RO7234292 2. Change from baseline of mHTT concentrations in CSF 3. Relationship between plasma and/or CSF concentration or PK parameters and biomarker measures (mHTT in CSF)

Secondary outcome

The corresponding secondary endpoints are as follows: 1. Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale 2. Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory results 3. Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at visits indicated in the schedule of assessments, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct 4. Incidence of anti-drug antibodies (ADAs) at specified timelines relative to the prevalence of ADAs at baseline 5. Titer and antibody subtype, determined if ADAs are identified 6. Urine concentrations

of RO7234292 The exploratory objectives for this study would be to evaluate the effects of RO7234292 compared on the basis of the following endpoints: 1. Change from baseline in exploratory biomarkers in CSF (e.g. neurofilament light chain [NfL]) 2. Relationship between exploratory fluid biomarkers in CSF and blood (e.g. CSF and plasma NfL) 3. Relationship between biomarkers, safety (including Holter monitoring), PK, and immunogenicity 4. Relationship of biomarkers to clinical severity at baseline using the UHDRS and Clinical Global Impression

Study description

Background summary

To date, there are no approved treatments able to slow or stop the clinical progression of HD. Currently approved treatments aim to reduce the burden of symptoms, maximize function, and improve the patient's quality of life (Nance et al. 2011). Tetrabenazine and deutetrabenazine target abnormal involuntary movements (i.e., chorea) associated with HD, and these symptomatic therapies have a challenging benefit-risk profile. These drugs have been linked to many significant adverse events, including parkinsonism, akathisia, sedation, depression, and suicidal thoughts. They are contraindicated in patients who are actively suicidal and in patients with untreated or inadequately treated depression. Additionally, they may prolong the corrected QT interval (QTc), and caution is advised when used in combination with other drugs or medical conditions that potentially prolong the QTc. Other medications are utilized in HD to address particular symptoms, such as antidepressants (for depression, agitation, and irritability), anticonvulsants (for irritability and impulsive behavior), anxiolytics (for anxiety), cognitive-enhancing agents (for cognitive disturbances), and neuroleptics (for chorea) (Paulson and Albin 2011).

Study objective

To date, non-clinical and clinical data have been generated to support further investigation of RO7234292 in patients with early manifest HD. Building on the recently completed Phase I/IIa study and the ongoing OLE study, this Phase Ia study (BP40410) will collect clinical PK and pharmacodynamics (PD) data to characterize the magnitude and duration of CSF mHTT reduction after short-term

IT bolus dosing with RO7234292. This study will also further inform the semi-mechanistic population PK/PD model that has been developed on the basis of the currently available clinical and non-clinical data. Ultimately, this will guide clinical decision-making about optimal treatment regimens by providing information about the relationship between RO7234292 dosing and the time course of mHTT reduction, which could not be obtained any other way.

Study design

This study is open-label and will be conducted in an early manifest HD population over 8 months including an approximately 4-week screening period and an approximately 28-week study period. Patients will be admitted to the site in the afternoon/evening of Day -2 or in the morning of Day -1 to begin the first in-house period of the study. After completing the safety assessments, an IT catheter will be inserted to facilitate frequent CSF sampling and IT bolus dosing of RO7234292. After 24 hours of sampling, a single dose of RO7234292 will be given, after which sampling will continue for a further 72 hours before the catheter is removed. The patient will be discharged on Day 5 after all assessments have been completed. Patients will return to the site for the second in-house period in the afternoon/evening of Day 28 or in the morning on Day 29 and will be discharged on Day 29 after all assessments have been completed. The second dose of RO7234292 will occur via a lumbar puncture on Day 29. Patients will return to the site for daily visits on Days 30, 43, 71, 127, and the follow-up visit (6 months after the last study drug administration). After study completion, participants will be eligible to enroll in an OLE study (Study BN40955) with active RO7234292 compound, provided the data from the ongoing RO7234292 program support continued development, the patient meets the inclusion and exclusion criteria for the OLE, and the OLE is approved by the relevant competent authorities and Ethics Committees (ECs).

Intervention

Patients will receive two IT doses of the same dose strength of RO7234292 at an interval of 28 days during the treatment period (Day 1 and Day 29). Each dose of RO7234292 will be administered as a single IT bolus injection.

Study burden and risks

Risks: RO7234292 has had limited testing in humans. Next to the side effects mentioned in the Informed Consent Form, there may be side effects that are not known at this time. Burden: blood draws, lumbar punctures, questionnaires.

Contacts

Public
F. Hoffmann-La Roche Ltd

Grenzacherstrasse 124
Basel CH-4070
CH
Scientific
F. Hoffmann-La Roche Ltd

Grenzacherstrasse 124
Basel CH-4070
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed Informed Consent Form.
2. Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form.
3. Manifest HD diagnosis, defined as a Diagnostic Confidence Level (DCL) score of 4.
4. Independence Scale score of >= 70.
5. Genetically confirmed disease by direct DNA testing with a CAP score > 400 (Zhang et al. 2011), calculated as follows:
CAP = Age x (CAG repeat length - 33.66).
6. Ability to read the words "red", "blue" and "green" in the patient's native language.
7. Ability to walk unassisted without a cane or walker and move about without a wheelchair on a daily basis as reviewed at screening and baseline visit. Long

distance use of wheelchairs for convenience (e.g., greater than 50 meters) for transfer is permitted.
8. Body mass index >= 16 and <= 32 kg/m2; total body weight > 40 kg.
9. Ability to tolerate blood draws and lumbar punctures.
10. Estimated glomerular filtration rate >= 60 mL/min/1.73 m2 (Cockcroft-Gault formula).
11. Ability and willingness, in the Investigator's judgment, to comply with all aspects of the protocol including completion of interviews and assessments for the duration of the study.
12. Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment.
13. Signed study companion consent for participation if a study companion is available and fulfills the following criteria:
- Age >= 18 years.
- Reliable and competent, in the Investigator*s judgement.
- Sufficiently knowledgeable of the patient*s condition to complete study companion assessments of the patient, and likely to remain sufficiently knowledgeable throughout the study, in the Investigator*s judgement.
- Able to comment on the study participant*s symptoms and functioning experience, as required per Appendix 1.
Note: Companions with genetic confirmation of the mutant gene can only participate if they do not have confirmation of motor symptoms onset and, in the opinion of the Investigator, do not display any disease symptoms (i.e., the companion must have a DCL of < 4, as well as no cognitive or behavioral change that would question the validity of the acquired observer-reported data).
All effort should be made to retain the study companion; however, should this not be possible, a study companion can be replaced and new consent obtained.
14a. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods, and agreement to refrain from donating eggs.
Acceptable contraceptive methods have been listed in paragraph 4.1.1 of protocol v2.0.
14b. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm.
15. 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).

Exclusion criteria

1. 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 suicidal ideation is demonstrated by the C-SSRS per judgement 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. Mild passive suicidal ideation (i.e., occasional thoughts that life is not worth living or is hard) without history of attempts or hospitalization over the past 12 months is generally acceptable for study participation, but final decision on participation should be made carefully and in consultation with appropriately qualified mental health professional.
2. Current active psychosis, confusional state, or violent behavior.
3. Any serious medical condition or clinically significant laboratory, vital signs, or ECG abnormalities at screening that, in the Investigator's judgment, precludes the patient's safe participation in and completion of the study.
4. Increased QTc interval (QT interval corrected through use of Fridericia's formula [QTcF] > 470 ms), baseline resting bradycardia < 45 bpm, or baseline resting tachycardia > 100 bpm.
5. Family history of long QT syndrome or other risk factors for torsades de pointes.
6. 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.
7. Clinical diagnosis of chronic migraines or history of low pressure headache after lumbar puncture requiring hospitalization or blood patch.
8. Pregnant or breastfeeding, or intending to become pregnant during the study or until the follow-up visit (6 months ± 2 weeks after the last dose of study drug).
Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
9. Presence of implanted shunt for the drainage of CSF or an implanted CNS catheter.
10. Positive for hepatitis C virus antibody or hepatitis B surface antigen at screening.
11. Positive for human immunodeficiency virus (HIV)-1 or HIV-2 at screening.
12. Current or previous use of an ASO (including small interfering ribonucleic acid [RNA]).
13. Current or previous use of antipsychotics 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 of enrollment.
14. Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) 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.
15. Current use of tetrabenazine, valbenazine, or deutetrabenazine within 2 weeks prior to screening or within 6 x the elimination half-life of the medication prior to screening (whichever is longer) or anticipated use during the study.

16. 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.
17. Current use of 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.
18. Treatment with investigational therapy within 4 weeks prior to screening or 5 drug elimination half-lives of investigational therapy, whichever is longer.
19. Antiplatelet or anticoagulant therapy within the 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.
20. History of bleeding diathesis or coagulopathy.
21. 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.
22. History of gene therapy or cell transplantation or any other experimental brain surgery.
23. Concurrent or planned concurrent participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions. Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
24. Illicit drug (i.e., cannabis, opioid, stimulant, hallucinogen, designer) or alcohol abuse within 12 months prior to screening, in the Investigator's judgment.
25. Unable or unsafe to perform lumbar puncture on the patient.
26. Previous lumbar surgery that is likely, in the opinion of the Investigator or surgical team, to make IT catheter insertion or IT injection unduly difficult or hazardous.
27. Poor peripheral venous access.
28. Scoliosis or spinal deformity making IT injection not feasible in the outpatient setting.
29. Serious infection requiring oral or intravenous antibiotics within 14 days prior to screening.
30. Antiretroviral medications.
31. 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.
32. Preexisting intra-axial or extra-axial lesions (e.g., tumor, arterio-venous malformation, meningiomas) as assessed by a centrally read MRI scan during the screening period .

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-01-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RO7234292
Generic name:	RO7234292

Ethics review

Approved WMO Date:	09-09-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-11-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2020
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-07-2020
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:	25-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-12-2021
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	EUCTR2018-003010-40-NL
ClinicalTrials.gov	NCT04000594
CCMO	NL68965.000.19

Study results

Date completed:	18-02-2022
Results posted:	23-03-2023
Actual enrolment:	4

First publication
31-01-2023