PROTOCOL

TITLE:	**AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF INTRATHECALLY ADMINISTERED RO7234292 (RG6042) IN PATIENTS WITH HUNTINGTON'S DISEASE**
PROTOCOL NUMBER:	BN40955
VERSION NUMBER:	7
EUDRACT NUMBER:	2018-003898-94
NCT NUMBER	NCT03842969
IND NUMBER:	137873
TEST PRODUCT:	Tominersen (RO7234292)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
02-Apr-2021 18:15:14	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
7	See electronic date stamp on title page			
6 [a]	16 March 2021	—	—	—
5	3 September 2020	—	—	—
4	13 February 2020	—	—	—
3	16 April 2019	—	—	—
1	20 November 2018	Germany	2	14 February 2019

[a] Version 6 was finalized but not distributed to sites or Health Authorities and is superseded by Version 7.

PROTOCOL AMENDMENT, VERSION 7:
RATIONALE

Protocol BN40955 has been amended to pause study treatments based on sponsor decision. The GENERATION HD1 phase III study, BN40423, has been amended in accordance with the Urgent Safety Measure Dear Investigator Letter issued on 22 March 2021. A pre-planned review of safety and efficacy data from Study BN40423, as well as available open-label data, was conducted by the BN40423 independent Data Monitoring Committee (iDMC). Following review of the data, the iDMC has recommended that all dosing (120 mg Q8W and Q16W and placebo) in Study BN40423 be permanently stopped. This iDMC recommendation was not based on any new emergent safety concerns, but on a totality of evidence indicating that the treatment arms demonstrated unfavorable safety and efficacy trends compared to the placebo arm over time. The iDMC has also made a recommendation for the ongoing patients in the Study BN40423 to be followed for safety and efficacy outcomes until study completion as per protocol, without study drug administration. Study BN40955 (open-label extension [OLE]) is exploring the same dosing regimens (i.e., tominersen [RO7234292] 120 mg Q8W and Q16W); therefore, the Sponsor has made a decision to pause dosing in the OLE until further data assessments can be conducted.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Language has been added to indicate effective 22 March 2021 study treatment will be paused. Patients already on the study will continue to be followed for safety and efficacy outcomes until study completion (Sections 1.3, 3.1.1, 3.3.1, and 4.5, and Appendices 1a, 1b, and 2a).
- It has been clarified that neurologic examinations should continue to be performed at each clinic visit and before the lumbar puncture, if there is no study treatment administration (Section 4.5.3 and Appendices 1a, 1b, and 12).
- It has been clarified that patients should not perform any activity that is associated with a change in the ambient air pressure for at least 24 hours post lumbar procedure, irrespective if study treatment is administered or not (Section 4.5.5, Appendix 1a and 1b).
- Wording in Section 5.1.1 and Section 5.1.2 has been amended to be consistent with the latest available risk data as per the RO7234292 Investigator's Brochure Version 7.
- Plasma and cerebral spinal fluid (CSF) sample collection for pharmacokinetics (PK) analysis has been stopped (Appendices 1a and 1b).
- Plasma samples for immunogenicity analysis will continue to be collected while study treatment is paused (Appendix 1a).

- The schedules of activities have been modified to indicate the pause in study treatment administration and to clarify the frequency of safety and biomarker assessments (Appendices 1a, 1b , 2b, 3, 4, and 7)
  - Neurological examinations, C-SSRS, EQ-5D-5L will continue to be performed as per the original schedule
  - In order to reduce patient burden and continue to monitor safety, the LP will be performed every 16 weeks for both treatment arms. CSF (for safety and biomarkers), and local PT and/or INR, aPTT and platelet count will continue to be collected at every LP visit

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**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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MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**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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TEST PRODUCT:	Tominersen (RO7234292)
PHASE:	Phase III
INDICATION:	Huntington's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the long-term safety and tolerability of RO7234292 in patients with Huntington's disease (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.

Objectives will be achieved primarily by using data collected in this open-label extension (OLE) study, but may also be informed by using previously collected data from participants of the preceding Roche studies. Data may be linked and, if appropriate, may be analyzed by pooling data.

Safety Objective

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 (AEs), with severity determined according to the Adverse Event Severity Grading Scale
- 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 safety-targeted endpoints
- Relationship between MRI parameter change and safety-targeted endpoints

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of RO7234292 on the basis of the following endpoints:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale score as assessed every 16 weeks (Q16W)
- Change from baseline in scores for the following individual scales as assessed Q16W:
  - Total Functional Capacity Scale.
  - Total Motor Score.
  - Symbol Digit Modalities Test.
  - Stroop Word Reading Test.
- Change from baseline in the Clinical Global Impression, Severity Scale score as assessed Q16W
- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale score from baseline as assessed Q16W
- Change from baseline in the Huntington's Disease Daily Activities Scale score as assessed Q16W
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (smartphone and wrist-worn wearable) as assessed Q16W

Exploratory Pharmacokinetic/Pharmacodynamic Objectives

The exploratory pharmacokinetic (PK) objective for this study is to characterize the RO7234292 PK trough plasma and trough cerebrospinal fluid (CSF) samples on the basis of the following endpoints:

- Trough concentration of RO7234292 in plasma at specified timepoints
- Trough concentration of RO7234292 in CSF at specified timepoints

The exploratory PK/pharmacodynamic (PK/PD) objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of RO7234292 on the basis of the following endpoints:

- Relationship between trough plasma and/or trough CSF concentrations of PK parameters for RO7234292 and efficacy endpoints
- Relationship between trough plasma and/or trough CSF concentrations of PK parameters for RO7234292 and safety endpoints

Exploratory Immunogenicity Objective

The exploratory immunogenicity objectives for this study are as follows:

- To evaluate the immune response to RO7234292 on the basis of the following endpoints:
  - Incidence of anti-drug antibodies (ADAs) at specified timepoints relative to the prevalence of ADAs at baseline.
  - Determination of the ADA specificity followed by assessments of the magnitude (titer) of the ADA response.
- To evaluate potential effects of ADAs on the basis of the following endpoint:
  - Relationship between ADA status and efficacy, safety, or PK endpoints.

Exploratory Biomarkers Objective

The exploratory biomarker objective for this study is to identify biomarkers that are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to RO7234292, are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), can provide evidence of RO7234292 activity (i.e., PD

biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers (e.g., tau and neurofilament light chain protein [NfL]) in plasma and CSF efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with RO7234292 on the basis of the following endpoint:

- Change from baseline in patient-reported EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index and Visual Analog Scale (VAS) scores at specified timepoints

Study Design

Description of Study

This OLE study will evaluate the long-term safety and tolerability of RO7234292 administered intrathecally (IT) to patients with HD. In addition, the study will obtain long-term data on the efficacy, immunogenicity, exposure, and biomarkers of RO7234292.

Effective 22 March 2021, dosing is paused, including enrollment. Patients already on the study will continue to be followed for safety and efficacy outcomes until study completion.

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. The preceding Roche-sponsored or Genentech-sponsored study must have been approved by the relevant national competent authority and applicable Institutional Review Board/Ethics Committee in a country in order for a patient from that country to be included in the OLE.

For patients who have participated in previous Roche studies, entry into this long-term, open-label extension study will occur at an inclusion visit. This inclusion visit is a combined visit with the preceding study's last applicable visit where patients are due for their end of treatment visit, last CSF collection, or safety follow-up unless otherwise specified, and serves as the baseline visit for the long-term, open-label extension study. For participants who have not participated in a previous Roche study, a separate screening visit will occur to determine eligibility into the long-term, open-label extension study. Patients who successfully meet eligibility criteria will then enter the study and attend the baseline study visit. Patients who were enrolled in Study BN40423 before implementation of Version 4 of that protocol will be prematurely discontinued by the Sponsor from Study BN40423 and offered treatment in this study (Study BN40955) when it is available at sites.

If dosing at the inclusion visit is not possible, the Medical Monitor should be consulted and a short treatment interruption may be permitted. For patients entering from Study BN40423 prior to implementation of protocol Version 4, the inclusion visit should occur at the end-of-treatment visit for Study BN40423.

Patients Impacted by Covid-19 during Study BN40423 Screening

Patients who were screened and eligible for the placebo-controlled Phase III Study BN40423 (Generation-HD1) but were not randomized prior to the close of Study BN40423 enrollment due to logistical challenges resulting from the COVID-19 pandemic, will be offered open-label RO7234292 as part of this study, Study BN40955. Participation can occur once approved and available at sites and so long as the patient meets Study BN40955 eligibility. These patients will undergo screening assessments during a 4-week screening period. A maximum of 1 re-screening will be allowed within 8 weeks of an initial screening failure in Study BN40955.

The CAG repeat length testing from Q2 Solutions will be accepted for this study. If re-screening is required, the CAG repeat length testing from Q2 Solutions does not need to be repeated. The screening MRI and viral serology from the initial screening, including from other Roche RO7234292 studies, may be acceptable as part of the screening assessments if performed within 12 weeks of the inclusion visit.

For patients entering from Study BN40697, in the event of any delay in start-up activities where it is not possible to conduct the inclusion visit at the time of the last applicable visit in Study BN40697, a separate inclusion visit should be scheduled. For patients entering from Study ML41885, the inclusion visit will take place at the safety follow-up visit of Study ML41885 (i.e., SFU1).

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. Patients will be assigned to treatment groups as described below:

Preceding Study Treatment	Treatment Regimen
Open-label 120 mg RO7234292 Q4W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Open-label 120 mg RO7234292 Q8W	120 mg RO7234292 Q8W
No treatment or ≤4 doses of 120 mg or less RO7234292 with a treatment-free follow-up period	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Blinded placebo Q8W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Blinded 120 mg RO7234292 Q8W	120 mg RO7234292 Q8W
Blinded 120 mg RO7234292 Q16W	120 mg RO7234292 Q16W
For Patients enrolled into Study BN40423 prior to implementation of Study BN40423 Protocol Version 4:	
Blinded 120 mg RO7234292 Q4W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Blinded 120 mg RO7234292 Q8W	120 mg RO7234292 Q8W
Blinded Placebo Q4W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Open-label 120 mg RO7234292 Q16W	120 mg RO7234292 Q16W

Q4W=every 4 weeks; Q8W=every 8 weeks; Q16W=every 16 weeks.

For patients who did not previously receive treatment with RO7234292 (e.g., from a natural history study) or received short-term treatment (≤4 doses), the end of study visit for the preceding study will serve as the inclusion visit for Study BN40955. For patients who completed the full treatment course in the preceding study, the inclusion visit for Study BN40955 will take place at the visit at which the last dose was administered. For patients enrolled in Study BN40423 prior to implementation of Protocol Version 4 who were prematurely discontinued, the inclusion visit for Study BN40955 will take place at the end-of-treatment visit for Study BN40423. For patients entering from Study BN40697, in the event of any delay in start-up activities where is not possible to conduct the inclusion visit for Study BN40955 at the time of last applicable visit in Study BN40697, a separate inclusion visit should be scheduled. At the inclusion visit for Study BN40955, clinical ratings and assessments that are common between the preceding study and Study BN40955 will be completed once and will serve both studies. Clinical ratings and assessments required in Study BN40955 that were not completed as part of the preceding study will also need to be completed at the inclusion visit. Patients who were eligible for Study BN40423 (GENERATION-HD1) but were not randomized due to logistical challenges resulting from the COVID-19 pandemic will undergo screening and inclusion visits.

Patients will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, Montreal Cognitive Assessment (MoCA), C-SSRS, neuroimaging assessments and reporting of AEs and concomitant medications. Patients enrolling from Study BN40697 will have an optional MRI of brain and spine with contrast media, in addition to the other brain neuroimaging assessments.

In case of a failed IT bolus dosing procedure (e.g., due to an inadequate establishment of access to the IT space), a second dosing attempt may occur up to 7 days after the originally scheduled dosing attempt. For this additional visit, safety and tolerability evaluations on the day of lumbar puncture (LP) administration will be performed as detailed in Appendix 1a and Appendix 1b, including neurological examination (predose and postdose), vital signs, and a review of AEs and concomitant medication. If the second dosing attempt occurs more than 72 hours after the last coagulation panel and platelets test, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets need to be conducted again and results reviewed prior to the LP attempt.

Telephone safety follow-up calls will be conducted between dosing visits to check for any change in patient status (i.e., AEs, concomitant medications) since last visit. Depending on the patient's health status, an unscheduled clinic visit may be arranged. If a patient is due for a telephone safety call and they are in-clinic then this telephone safety follow-up call can be completed in-clinic at the site's discretion. As a result of the COVID-19 pandemic, only where sites are impacted, these telephone safety calls can be conducted instead of an in-clinic visit.

Number of Patients

Up to approximately 1100 patients with HD will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)

  If capacity to consent is in question, formal capacity assessment by an appropriately qualified professional should be obtained. In cases where capacity to consent is not fully present, but the participant is known previously to have favored participation in an open-label study and is able to assent, consent may be obtained by a legally authorized representative. (Note: Patients in Germany who are not fully capable of providing informed consent are not eligible for inclusion).
- 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
- For women of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  Women must remain abstinent or use 2 methods of contraception, including at least one method with a failure rate of $<$1% per year, during the treatment period and for 5 months after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. A vasectomized man must undergo a medical assessment that confirms the success of the surgery before he can be considered surgically sterile.

  Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 5 months after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

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.

Patients must meet the following criteria for study entry during screening (some will be reassessed at the inclusion visit prior to randomization and study drug dosing):

- Signed ICF
- Age 25−65 years, inclusive, at the time of signing the 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 $\geq$70
- Genetically confirmed disease by direct DNA testing with a CAG-Age product (CAP) score $>$400 (Zhang et al. 2011), calculated as follows:

  CAP=Age $\times$ (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

  Long-distance (e.g., $>$50 meters) use of wheelchairs for convenience or transfer is permitted.
- Body mass index 16−32 kg/m^2; total body weight $>$40 kg
- 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)
- Ability to tolerate blood draws and LPs
- Creatinine clearance (CrCl) $\geq$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
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

- 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

  Platelet counts between 125,000 and 150,000 mm^3 are permissible as long as the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.
- 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

  Women of childbearing potential must have a negative urine pregnancy test at the inclusion visit (obtained as part of the preceding study assessments).

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.

Patients who meet any of the following criteria will be excluded from study entry:

- 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 judgment of the investigator. If suicidal ideation is present, a risk assessment should be completed 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 an appropriately qualified mental health professional.
- 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 central nervous system (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 antisense oligonucleotide (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

  Abuse is defined as a maladaptive pattern of use that leads to failure to fulfill major work or social obligations or use in situations where it leads to physical danger or legal problems, and may be the focus of clinical attention.
- 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 intravenous (IV) antibiotics within 14 days prior to and during 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, arterio-venous malformation, meningiomas, hydrocephalus, subdural haematoma) as assessed by a centrally read MRI scan during the screening period

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur a minimum of 6 months after the last patient is enrolled.

Length of Study

The total length of the study, from enrollment of the first patient to the end of the study, is expected to be approximately 6 years. It is expected that patients may *participate for* a minimum of 6 months and a maximum of approximately 6 years in Study BN40955.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is RO7234292.

Statistical Methods

Primary Analysis

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

All verbatim AE terms will be mapped to Medical Dictionary of Regulatory Activities (MedDRA) thesaurus terms. The Adverse Event Severity Grading Scale will be used for assessing AE severity. Laboratory values determined as an AE should be graded as detailed in the protocol and based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

All safety data, including AEs, laboratory tests, neurologic examination, C-SSRS, MoCA, ECG, and vital signs, will be reported in individual listings and summarized by treatment for each assessment time using descriptive statistics. For continuous variables, both the original value as well as the change from baseline will be reported.

The incidence of AEs will be summarized on the basis of body systems and dictionary preferred terms. The incidence of AEs by severity and relationship to study drug or study procedure and incidence of marked abnormal laboratory test results will be provided.

Determination of Sample Size

The sample size for this study is determined by the number of patients from preceding studies who may be eligible for enrollment in this study and is estimated to be up to approximately 1100 patients.

Optional Interim Analyses

The Sponsor may choose to conduct one or more interim analyses including safety, PK, PD biomarkers and clinical endpoints as relevant. Details of each interim analysis will be described in a dedicated Statistical Analysis Plan (SAP), which will be finalized before the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
app	application
ASO	antisense oligonucleotide
CAG	cytosine, adenine, guanine
CAP	CAG-Age Product
CGI-C	Clinical Global Impression, Change
CGI-S	Clinical Global Impression, Severity
ClinRO	clinician-reported outcome
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
cUHDRS	composite Unified Huntington's Disease Rating Scale
DCL	diagnostic confidence level
DIL	*Dear Investigator Letter*
EC	Ethics Committee
Ecrf	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
FDA	Food and Drug Administration
HA	health authority
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HD	Huntington's disease
HD-DAS	Huntington's Disease Daily Activities Scale
HDID	Huntington's Disease Identification Number
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
HTT	huntingtin (gene)
HTT	huntingtin (protein)
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iDMC	*independent Data Monitoring Committee*
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board

Abbreviation	Definition
IS	Independence Scale
IT	intrathecal
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LP	lumbar puncture
MAD	multiple ascending dose
mHTT	mutant huntingtin (protein)
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NfL	neurofilament light chain (protein)
OLE	open-label extension
PD	pharmacodynamic
PerfO	performance outcome
PK	pharmacokinetic
PRO	patient-reported outcome
Q4W	every 4 weeks
Q8W	every 8 weeks
Q16W	every 16 weeks
QTc	corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities Test
SWR	Stroop Word Reading
TFC	Total Functional Capacity Scale
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
USM	*Urgent Safety Measure*
VAS	Visual Analog Scale
WPAI	Work Productivity and Activity impairment
wtHTT	wild-type huntingtin (protein)

1. BACKGROUND

1.1 BACKGROUND ON HUNTINGTON'S DISEASE

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by expansion of cytosine, adenine, and guanine (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.

The estimated prevalence of HD in North America, northwestern Europe, and Australia ranges from 5.96–13.17 cases per 100,000 (Baig et al. 2016). Although genetic testing can be used to identify individuals who will develop the disease, the diagnosis of HD is clinical through neurologic examination of the motor system. The clinical diagnosis of HD is made when the patient exhibits ″unequivocal presence of an otherwise unexplained extrapyramidal movement disorder″ (e.g., chorea, dystonia, bradykinesia, rigidity) or ″motor onset″ (Huntington Study Group 1996; Hogarth et al. 2005).

The manifest disease period can be subdivided into 5 stages based on functional capacity (Ross et al. 2014). Stage 1 represents the highest level of capacity and is characterized by mild or no incapacity in terms of independence in daily activities. Stage 5 represents severe disability and dependence on full-time care (Shoulson and Fahn 1979). The 5 clinical stages are defined by the score on the Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) Scale, with Stage 1 corresponding to TFC scores of 11–13, Stage 2 to scores of 7–10, Stage 3 to scores of 3–6, Stage 4 to scores of 1–2, and Stage 5 to a score of 0 (Shoulson and Fahn 1979).

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 (AEs), including parkinsonism, akathisia, sedation, and 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, irritability), anticonvulsants (for irritability, impulsive behavior), anxiolytics (for anxiety), cognitive-enhancing agents (for cognitive disturbances), and neuroleptics (for chorea; Paulson and Albin 2011).

1.2 BACKGROUND ON RO7234292

Neuropathological abnormalities in HD appear to be the consequence of a toxic gain-of-function of the mHTT protein (Wexler et al. 1987; Walker 2007; Moumné et al. 2013). Therefore, a therapy that reduces synthesis of the toxic mHTT protein should directly target the primary disease mechanism. As the genetic origin of HD is localized to just one gene, inhibiting the expression of this *HTT* gene is a promising therapeutic option (Stanek et al. 2013).

RO7234292 (RG6042) was originally developed by Ionis Pharmaceuticals, Inc. and was formerly known as ISIS 443139 and IONIS-HTT_{Rx}. This antisense oligonucleotide (ASO) is being developed to reduce the synthesis of all forms of the HTT protein by targeting the *HTT* mRNA from both the wild-type and the mutant alleles and directing its catalytic degradation through the action of ribonuclease H1, an endogenous enzyme present in most mammalian cells (Cerritelli and Crouch 2009; Crooke and Bennett 1996), including cells of interest in the CNS (e.g., neurons and neuroglia). Reduction of the *HTT* gene mRNA could potentially inhibit downstream toxic effects of mHTT and lead to a sustained reversal in HD symptoms.

Pharmacology data support selective targeting of *HTT* mRNA transcripts from both alleles as a potentially safe and effective mechanism for the treatment of HD. Using ASOs targeting human *HTT* mRNA in rodents, significant reduction of mutant *HTT* mRNA transcripts, wild-type HTT mRNA transcripts, and mHTT protein has been achieved throughout most brain regions (Kordasiewicz et al. 2012). Furthermore, transient delivery of these ASOs in transgenic mouse models of HD delayed disease progression and mediated a sustained reversal of disease phenotype that persisted longer than *HTT* mRNA knockdown (Kordasiewiecz et al. 2012; Stanek et al. 2013).

Nonclinical proof-of-concept studies with ASOs targeting *HTT* have been conducted in three models of HD, including YAC128 mice expressing the full-length mutant human *HTT* transgene with a 128 CAG repeat expansion, BACHD mice expressing the full-length mutant human HTT genomic sequence with 97 CAG/CAA repeats, and R6/2 mice expressing exon 1 of the mutant human *HTT* gene with 110–135 CAG repeats. These studies demonstrate that ASOs targeting human *HTT* mRNA improve motor function and protect against human HTT transgene expression in YAC128 mice; improve motor function, hypoactivity, and stress response in BACHD mice; and preserve striatal volume and increase survival in R6/2 mice.

The pharmacokinetics (PK) and toxicity of intrathecal (IT) administration of RO7234292, an ASO that targets human *HTT* mRNA, were assessed in cynomolgus monkeys for 13 weeks (biweekly for the first month, then monthly thereafter) at dose levels up to 50 mg/dose (5 bolus administrations, for a total dose of 250 mg) and chronically for 9 months, up to 35 mg/dose (10 bolus monthly administrations for a total dose of 350 mg). The drug was safe and well-tolerated in these studies.

In a first-in-human, Phase I/IIa double-blind, placebo-controlled, dose-escalation study (Clinicaltrials.gov Identifier NCT02519036) (ISIS 443139-CS1) 4 doses of RO7234292 (ranging from 10 mg to 120 mg) were well-tolerated and achieved significant dose-dependent lowering of cerebrospinal fluid (CSF) mHTT protein when administered IT every 4 weeks (Q4W; monthly) to 46 patients with early manifest HD. Exploratory analyses identified a relationship between lowering of mHTT protein and improvement in some clinical measures. Taken together, these data supported further clinical testing to demonstrate definitive clinical benefit of mHTT protein reduction in the CNS. The data from this study also supported the initiation of Study ISIS 443139-CS2 (Study BN40697; Clinicaltrials.gov Identifier NCT03342053), a 15-month, Phase II open-label extension (OLE) study for patients who participated in Study ISIS 443139-CS1.

Preliminary data from analysis conducted when all individuals in Study BN40967 had reached 9 months of treatment showed that a 120 mg every-8-week (Q8W; every 2 months) dosing regimen of RO7234292 achieved a 47% median CSF mHTT lowering at trough (i.e., sample taken immediately before the next dose) and the 120 mg Q4W dosing regimen achieved a 66% median lowering at trough. Both results exceed the 20%–40% target for CSF mHTT lowering at trough and steady state based upon efficacy data from nonclinical models, and exceed the result of approximately 40% median lowering observed in the completed Phase I/IIa study. Details on the most recent information from nonclinical and clinical studies can be found in the RO7234292 Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study is designed to assess the long-term safety and tolerability of IT administered RO7234292 in patients who have completed or have participated in other F. Hoffmann-La Roche, Ltd.–sponsored (hereafter referred to as Roche) and/or Genentech-sponsored studies in HD in the development program for RO7234292. Presently, there are no therapies available to stop or slow the clinical progression of HD, which is relentless until patients experience premature death. The ASO RO7234292 is designed to target the cause of HD and offers the potential to meet this unmet medical need.

To date, nonclinical and clinical data support further investigation of RO7234292 in patients with HD. Current planned or ongoing studies in the RO7234292 clinical development plan are designed for durations of up to approximately 2 years. This study is designed to collect safety data in a larger number of patients and will also study the

benefit and potential risks of RO7234292 when administered by IT bolus injection Q8W or every 16 weeks (Q16W) over a longer period.

Review of preliminary 9-month safety and tolerability data for RO7234292 from the Phase II OLE (Study BN40697) suggested that, relative to the Q4W treatment regimen, the Q8W treatment regimen may be more suitable for chronic IT dosing, as evidenced by improved adherence to the less frequent regimen. This is supported by observations of fewer overall AEs, decreased proportion of patients with moderate AEs, and fewer AEs considered possibly related to study drug in the Q8W regimen compared to the Q4W regimen (for details see the RO7234292 Investigator's Brochure).

There were no acute safety concerns meriting a change to the ongoing Phase II OLE study protocol (Study BN40697). However, given the 9-month CSF mHTT results, which suggested a longer than anticipated duration of effect of RO7234292 on CSF mHTT lowering, it is not necessary to use a Q4W paradigm to test the dose rationale. As a result, the results from OLE Study BN40697 justified a change in Study BN40955 to explore less frequent dosing regimens by continuing the Q8W RO7234292 arm and replacing the Q4W arm with a Q16W arm.

The existing dose rationale tests a more frequent dosing regimen (i.e., 120 mg Q8W), which from present data is anticipated to maintain trough CSF mHTT reduction of at least approximately 40%, and a less frequent regimen (i.e., 120 mg Q16W), which is still anticipated to lower mHTT acutely, but will allow greater recovery of HTT levels between doses. From present data, trough CSF mHTT reduction of approximately 25% is predicted to be maintained in a 120 mg Q16W paradigm.

A pre-planned review of safety and efficacy data from the GENERATION HD1 phase III Study BN40423, as well as available open-label data, was conducted by the BN40423 independent Data Monitoring Committee (iDMC). Following review of the data, the iDMC recommended that all dosing (120 mg Q8W and Q16W and placebo) in Study BN40423 be permanently stopped. This iDMC recommendation was not based on any new emergent safety concerns, but on a totality of evidence indicating that the treatment arms demonstrated unfavorable safety and efficacy trends compared to the placebo arm over time. The iDMC also made a recommendation for the ongoing patients in the Study BN40423 to be followed for safety and efficacy outcomes until study completion as per protocol, without study drug administration. Study BN40955 (open-label extension [OLE]) is exploring the same dosing regimens (i.e., tominersen [RO7234292] 120 mg Q8W and Q16W); therefore, the Sponsor made a decision to pause dosing in the OLE until further data assessments can be conducted.

The known potential risks associated with RO7234292 and additional risks related to lumbar punctures (LPs), along with mitigation measures, are elaborated in Section 5.1.

2. OBJECTIVES AND ENDPOINTS

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.

Objectives will be achieved primarily by using data collected in this OLE study, but may also be informed by using previously collected data from participants of the preceding Roche studies. Data may be linked and, if appropriate, may be analyzed by pooling data.

2.1 SAFETY OBJECTIVE

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 AEs, 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 safety-targeted endpoints
- Relationship between magnetic resonance imaging (MRI) parameter change and safety-targeted endpoints

2.2 EXPLORATORY EFFICACY OBJECTIVES

The exploratory efficacy objective for this study is to evaluate the efficacy of RO7234292 on the basis of the following endpoints:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score as assessed Q16W
- Change from baseline in scores for the following individual scales as assessed Q16W:
  - Total Functional Capacity Scale.
  - 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 Q16W
- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline as assessed Q16W
- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score as assessed Q16W
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) as assessed Q16W

2.3 EXPLORATORY PHARMACOKINETIC/PHARMACODYNAMIC OBJECTIVES

The exploratory PK objective for this study is to characterize the RO7234292 PK trough plasma and trough CSF samples on the basis of the following endpoints:

- Trough concentration of RO7234292 in plasma at specified timepoints
- Trough concentration of RO7234292 in CSF at specified timepoints

The exploratory PK/pharmacodynamic (PK/PD) objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of RO7234292 on the basis of the following endpoints:

- Relationship between trough plasma and/or trough CSF concentrations of PK parameters for RO7234292 and efficacy endpoints
- Relationship between trough plasma and/or trough CSF concentrations of PK parameters for RO7234292 and safety endpoints

2.4 EXPLORATORY IMMUNOGENICITY OBJECTIVES

The exploratory immunogenicity objectives for this study are as follows:

- To evaluate the immune response to RO7234292 on the basis of the following endpoints:
  - Incidence of anti-drug antibodies (ADAs) at specified timepoints relative to the prevalence of ADAs at baseline.
  - Determination of the ADA specificity followed by assessments of the magnitude (titer) of the ADA response.
- To evaluate potential effects of ADAs on the basis of the following endpoint:
  - Relationship between ADA status and efficacy, safety, or PK endpoints.

2.5 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify biomarkers that are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to RO7234292, are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation (i.e., safety biomarkers), can provide evidence of RO7234292 activity

(i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers (e.g., tau and neurofilament light chain protein [NfL]) in plasma and CSF (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with RO7234292 on the basis of the following endpoint:

- Change from baseline in patient-reported EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index and Visual Analog Scale (VAS) scores at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This OLE study will evaluate the long-term safety and tolerability of RO7234292 administered IT to patients with HD. In addition, the study will obtain long-term data on the efficacy, immunogenicity, exposure, and biomarkers of RO7234292.

Effective 22 March 2021, dosing is paused, including enrollment. Patients already on the study will continue to be followed for safety and efficacy outcomes until study completion (see Appendix 1a, Appendix 1b, and Appendix 2b).

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. The preceding Roche-sponsored or Genentech-sponsored study must have been approved by the relevant national competent authority and applicable Institutional Review Board (IRB)/Ethics Committee (EC) in a country in order for a patient from that country to be included in the OLE.

For patients who have participated in previous Roche studies, entry into this long-term, open-label extension study will occur at an inclusion visit. This inclusion visit is a combined visit with the preceding study's last applicable visit where patients are due for their end of treatment visit, last CSF collection, or safety follow-up unless otherwise specified, and serves as the baseline visit for the long-term, open-label extension study. For participants who have not participated in a previous Roche study, a separate screening visit will occur to determine eligibility into the long-term, open-label extension study. Patients who successfully meet eligibility criteria will then enter the study and attend the baseline study visit. Patients who were enrolled in Study BN40423 before implementation of Version 4 of that protocol will be prematurely discontinued by the

Sponsor from Study BN40423 and offered treatment in this study (Study BN40955) when it is available at sites.

If dosing at the inclusion visit is not possible, the Medical Monitor should be consulted and a short treatment interruption may be permitted. For patients entering from Study BN40423 prior to implementation of Protocol Version 4, the inclusion visit should occur at the end-of-treatment visit for Study BN40423.

Patients who were screened and eligible for the placebo-controlled Phase III Study BN40423 (Generation-HD1) but were not randomized prior to the close of Study BN40423 enrollment due to logistical challenges resulting from the COVID-19 pandemic, will be offered open-label RO7234292 as part of this study, Study BN40955. Participation can occur once approved and available at sites and so long as the patient meets Study BN40955 eligibility. These patients will undergo screening assessments during a 4-week screening period. A maximum of 1 re-screening will be allowed within 8 weeks of an initial screening failure in Study BN40955.

The CAG repeat length testing from Q2 Solutions will be accepted for this study. If re-screening is required, the CAG repeat length testing from Q2 Solutions does not need to be repeated. The screening MRI and viral serology from the initial screening, including from other Roche RO7234292 studies, may be acceptable as part of the screening assessments if performed within 12 weeks of the inclusion visit.

For patients entering from Study BN40697, in the event of any delay in start-up activities where it is not possible to conduct the inclusion visit at the time of the last applicable visit in Study BN40697, a separate inclusion visit should be scheduled (see Appendix 1a).

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. Patients will be assigned to treatment groups as described below and in Table 1:

- Patients who previously received open-label 120 mg RO7234292 Q4W in a preceding study or who are currently receiving open-label 120 mg RO7234292 Q4W in Study BN40955 will be randomly allocated to receive 120 mg of RO7234292 Q8W or 120 mg of RO7234292 Q16W.

  Patients who previously received open-label 120 mg of RO7234292 Q8W in a preceding study or are currently receiving open-label 120 mg RO7234292 Q8W in Study BN40955 will receive 120 mg of RO7234292 Q8W.

  Patients who previously received placebo in a preceding study will be randomly allocated to receive either 120 mg of RO7234292 Q8W or RO7234292 Q16W.

  The drug administered at the inclusion visit will be the last dose or at the last CSF collection of the preceding study (if the inclusion visit is at the last visit in

the preceding study) or will be the first dose in Study BN40955 if a separate inclusion visit is required (see Appendix 1a).

- After implementation of Study BN40955 Protocol Version 3, patients who are already enrolled in Study BN40955 will sign the amended Informed Consent Form (ICF) at or before their next clinic visit, and will be assigned to either the 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W arm, and then follow the schedule of activities for Protocol Version 3 (see Appendix 1a)—matching treatment week according to Appendix 2—at the clinic visit and going forward.
- Patients who did not previously receive treatment with RO7234292 (e.g., from a natural history study, eligible patients from Study BN40423 study who were not randomized due to logistical challenges resulting from the COVID-19 pandemic) or received short-term treatment (≤4 doses) with a treatment-free follow-up period will be randomly allocated to receive 120 mg of RO7234292 Q8W or 120 mg of RO7234292 Q16W. The first dose in Study BN40955 will take place at the inclusion visit.
- Patients who previously received blinded placebo Q8W will be randomly allocated to receive 120 mg of RO7234292 Q8W or 120 mg of RO7234292 Q16W. The first dose in Study BN40955 will take place at the inclusion visit.
- Patients who previously received blinded 120 mg of RO7234292 Q8W will receive open-label 120 mg of RO7234292 Q8W.
- Patients who previously received blinded 120 mg of RO7234292 Q16W will receive open-label 120 mg of RO7234292 Q16W.

For patients who enrolled from Study ML41885, the inclusion visit will take place at the first safety follow-up visit of Study ML41885 (i.e., safety follow-up [SFU1]). The drug administered at the inclusion visit will be the first dose in Study BN40955. Patients who consent to be enrolled into this study (Study BN40955) will be assigned to a treatment group as shown below:

- Patients who received open-label 120 mg of RO7234292 Q16W will receive open-label 120 mg of RO7234292 Q16W.

Patients enrolled in Study BN40423 prior to implementation of Protocol Version 4 will be prematurely discontinued from that study. Patients who consent to be enrolled into this study (Study BN40955) will be assigned to treatment groups as shown below:

- Patients who received blinded 120 mg of RO7234292 Q4W will be randomly allocated to receive open-label 120 mg of RO7234292 Q8W or 120 mg of RO7234292 Q16W.
- Patients who received blinded 120 mg of RO7234292 Q8W will receive open-label 120 mg of RO7234292 Q8W.
- Patients who received blinded placebo Q4W will be randomly allocated to receive open-label 120 mg of RO7234292 Q8W or 120 mg of RO7234292 Q16W.

Table 1 Treatment Regimen in Study BN40955 Based on Previous Study Treatment

Preceding Study Treatment	Treatment Regimen
Open-label 120 mg RO7234292 Q4W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Open-label 120 mg RO7234292 Q8W	120 mg RO7234292 Q8W
No treatment or ≤4 doses of 120 mg or less RO7234292 with a treatment-free follow-up period	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Blinded placebo Q8W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Blinded 120 mg RO7234292 Q8W	120 mg RO7234292 Q8W
Blinded 120 mg RO7234292 Q16W	120 mg RO7234292 Q16W

Table 1 Treatment Regimen in Study BN40955 Based on Previous Study Treatment (cont.)

Preceding Study Treatment	Treatment Regimen
For Patients enrolled into Study BN40423 prior to implementation of Study BN40423 Protocol Version 4:	
Blinded 120 mg RO7234292 Q4W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Blinded 120 mg RO7234292 Q8W	120 mg RO7234292 Q8W
Blinded Placebo Q4W	Randomized 1:1 to 120 mg RO7234292 Q8W or 120 mg RO7234292 Q16W
Open-label 120 mg RO7234292 Q16W	120 mg RO7234292 Q16W

Q4W=every 4 weeks; Q8W=every 8 weeks; Q16W=every 16 weeks.

For patients who did not previously receive treatment with RO7234292 (e.g., from a natural history study) or received short-term treatment (≤4 doses), the end of study visit for the preceding study will serve as the inclusion visit for Study BN40955. For patients who completed the full treatment course in the preceding study, the inclusion visit for Study BN40955 will take place at the visit at which the last dose was administered. For patients enrolled in Study BN40423 prior to implementation of Protocol Version 4 who were prematurely discontinued, the inclusion visit for Study BN40955 will take place at the end-of-treatment visit for Study BN40423. For patients entering from Study BN40697, in the event of any delay in start-up activities where is not possible to conduct the inclusion visit for Study BN40955 at the time of last applicable visit in Study BN40697, a separate inclusion visit should be scheduled (see Appendix 1a). At the inclusion visit for Study BN40955, clinical ratings and assessments that are common between the preceding study and Study BN40955 will be completed once and will serve both studies. Clinical ratings and assessments required in Study BN40955 that were not completed as part of the preceding study will also need to be completed at the inclusion visit. Patients who were eligible for Study BN40423 (GENERATION-HD1) but were not randomized due to logistical challenges resulting from the COVID-19 pandemic will undergo screening and inclusion visits, see details of assessments in Appendix 1b and Appendix 5.

Patients will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, Montreal Cognitive Assessment (MoCA), C-SSRS, neuroimaging assessments and reporting of AEs and concomitant medications, as detailed in Appendix 1a and Appendix 1b. Patients enrolling from Study BN40697 will have an optional MRI of brain and spine with contrast media, in addition to the other brain neuroimaging assessments.

In case of a failed IT bolus dosing procedure (e.g., due to an inadequate establishment of access to the IT space), a second dosing attempt may occur up to 7 days after the originally scheduled dosing attempt. For this additional visit, safety and tolerability evaluations on the day of LP administration will be performed as detailed in Appendix 1a and Appendix 1b, including neurological examination (predose and postdose), vital signs, and a review of AEs and concomitant medication. If the second dosing attempt occurs more than 72 hours after the last coagulation panel and platelets test, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets need to be conducted again and results reviewed prior to the LP attempt (see Appendix 1a and Appendix 1b).

Telephone safety follow-up calls will be conducted between dosing visits to check for any change in patient status (i.e., AEs, concomitant medications) since last visit (see Appendix 2). Depending on the patient's health status, an unscheduled clinic visit may be arranged. If a patient is due for a telephone safety call and they are in-clinic then this telephone safety follow-up call can be completed in-clinic at the site's discretion. As a result of the COVID-19 pandemic, only where sites are impacted, these telephone safety calls can be conducted instead of an in-clinic visit.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur a minimum of 6 months after the last patient is enrolled.

The total length of the study, from enrollment of the first patient to the end of the study, is expected to be approximately 6 years. It is expected that patients may *participate for* a minimum of 6 months and a maximum of approximately 6 years in Study BN40955.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for RO7234292 Dose and Schedule

Effective 22 March 2021 dosing in this study (BN40955) is paused. On 18 Mar 2021, the BN40423 iDMC recommended that dosing be stopped in the Phase III randomized controlled trial. Because the OLE is exploring the same dosing regimens (i.e., RO7234292 120 mg Q8W and Q16W) the Sponsor made a decision to pause dosing in the OLE until further data assessments can be conducted.

In this study, RO7234292 will be administered either Q8W (RO7234292 Q8W arm) or Q16W (RO7234292 Q16W arm) by IT injection. The dose and dosing regimen administered in this study was initially the same as the dose and dosing regimen selected for the Phase III Study BN40423, a double-blind, placebo-controlled study of RO7234292 administered Q4W and Q8W by IT injection over 25 months in patients with manifest HD. However, based on preliminary 9-month data from the open-label Study BN40697, the Phase III Study BN40423 was amended to replace the

120 mg Q4W regimen with a 120 mg Q16W regimen. The same change was made to this study.

Until completion of Phase III Study BN40423, the magnitude and duration of mHTT protein lowering that is required for clinical efficacy is unknown. Specifically, it is unknown whether acute mHTT protein lowering alone with full recovery of protein levels between dosing will be sufficient for clinical efficacy, or whether more sustained suppression of protein levels will be required for clinical efficacy. Data from transgenic animal models suggest that brain tissue lowering of mHTT protein in the range of 30%–60% is associated with beneficial effects on the disease phenotype, which corresponds to a trough CSF lowering range of 20%–40% based on a non-human primate PK/PD model.

Because of this uncertainty, 2 active dosing regimens will be used in this study: RO7234292 Q8W (RO7234292 Q8W arm) and RO7234292 Q16W (RO7234292 Q16W arm), by IT injection.

The 120-mg dose has been chosen for the Q8W dosing group based on the following:

- In the chronic toxicology study in cynomolgus monkeys, the no-observed-adverse-effect level was determined to be at least 35 mg/dose (the highest dose tested). Conservatively correcting for differences in CSF volume between cynomolgus monkeys (≤15 mL) and humans (≥150 mL) with a scaling factor of 10, the human equivalent dose corresponds to 350 mg, representing a 3-fold safety margin to the proposed 120-mg clinical dose.
- Both the 90-mg and 120-mg RO7234292 Q4W groups in the Phase I/IIa study (ISIS 443139-CS1) resulted in a median CSF mHTT protein reduction of approximately 40%, with individual cases reaching approximately 60% reduction at trough, well above the described nonclinical threshold for efficacy. The 120-mg dose group exhibited a more consistent decline compared with the 90-mg dose group.
- In the same Phase I/IIa study, 120 mg of RO7234292 administered IT Q4W for 4 doses was safe and well-tolerated compared with placebo. See additional details in the RO7234292 Investigator's Brochure.
- In approximately 70% of patients (23 of 34 patients) assigned to receive RO7234292 in the Phase I/IIa study, CSF mHTT protein was declining at the last trough measurement (either Day 113 or 141), suggesting sustained reduction of CSF mHTT protein up to 2 months postdose (last timepoint assessed).
- In the 120-mg RO7234292 group in the Phase I/IIa study, CSF mHTT protein levels were reduced by at least 35% in all 5 cases for which a Day 141 sample was collected (i.e., 8 weeks after the last dose), in line with the observed Q8W OLE data).
- Data from the ongoing Phase II OLE Study BN40697 (ISIS 443139-CS2) showed that 120-mg doses administered in Q4W and Q8W regimens achieved 66% and 47%

median reductions of CSF mHTT from baseline at trough, respectively, after 9 months. Both results exceed the 20%–40% target for CSF mHTT lowering at trough and steady state based upon efficacy data from nonclinical models, and exceed the result of approximately 40% median lowering observed in the completed Phase I/IIa study. The observed effects on CSF mHTT lowering in the OLE after administration of 3 or 4 doses of 120 mg were also approximately 40%, consistent with results from the Phase I/IIa study (ISIS 443139-CS1).

- Review of safety and tolerability data for RO7234292 from the ongoing Phase II OLE suggests that relative to the Q4W treatment regimen, the Q8W treatment regimen may be more suitable for chronic IT dosing. This is supported by observations of fewer overall AEs, decreased proportion of patients with moderate AEs, and fewer AEs considered possibly related to study drug in the Q8W regimen compared to the Q4W regimen (for details see the RO7234292 Investigator's Brochure).

The 120-mg dose has been chosen for the Q16W dosing group based on the following:

- The nonclinical PK/PD model and updated clinical PK/PD model predicted the observed Q8W 9-month reductions (for details see the RO7234292 Investigator's Brochure). From these models, a Q16W regimen is predicted to result in median CSF HTT trough lowering of 20%-25%, within the range of the 20%–40% target for CSF mHTT lowering at trough and steady state.
- Model predicted acute lowering for the 120 mg Q16W regimen is around 35%–40% CSF mHTT reduction, above observed threshold for efficacy based upon nonclinical models.
- Maintenance of trough lowering is not a necessary feature of this less frequent arm to test the primary hypothesis. The hypothesis of this 120 mg Q16W arm (acute lowering, followed by more full recovery of target protein) is supported by nonclinical evidence that transient ASO-mediated lowering of HTT protein is associated with sustained phenotypic benefit in the BACHD model (Kordasiewicz et al. 2012). Efficacy in this model is sustained for 6 months even after a complete recovery of target mRNA and protein.
- Testing the less frequent regimen is of high interest to mitigate potential unknown long-term complications associated with a more frequent IT dosing of 120 mg Q8W. This approach could also mitigate the theoretical risks of suppression of wild-type HTT and will provide a more patient-friendly long-term dosing regimen.

To date, RO7234292 has only been administered IT in clinical trials. Intrathecal bolus administration has been shown to overcome the challenges faced by ASOs, as they are unable to cross the blood-brain barrier and achieve adequate brain and spinal cord concentrations when administered systemically (Schoch and Miller 2017). Therefore, the IT drug delivery method will be used in this trial, as presently no alternatives exist.

In summary, a 120 mg Q8W dosing regimen and the less frequent dosing regimen of 120 mg Q16W have been selected for this OLE extension study to be consistent with

changes to the Phase III Study BN40423 in order to evaluate the long-term safety and tolerability of RO7234292 in patients with HD.

3.3.2 Rationale for Biomarker Assessments

3.3.2.1 Cerebrospinal Fluid Biomarkers

Measurement of protein levels in the CSF offers the potential to monitor molecular changes that take place in the CNS. A toxic gain-of-function mechanism of mHTT protein is widely considered to be the primary driver of disease pathophysiology in HD (Wild and Tabrizi 2017). Mutant HTT protein in human CSF is associated with disease stage and severity and with biomarkers of neuronal damage, including CSF (NfL) and CSF tau levels (Wild et al. 2015). Neurofilament light chain protein levels in CSF predict progressive MRI measures of brain atrophy, as well as progressive clinical decline in patients (Wild and Tabrizi 2017). Longitudinal analysis of mHTT, NfL, tau and other biomarkers related to HD, neurodegeneration, and inflammation in CSF may extend the current understanding of HD pathophysiology and progression and provide further data on how these putatively prognostic and potentially predictive biomarkers will respond to disease-modifying treatment.

3.3.2.2 Blood Biomarkers

Neurofilament light chain protein levels in blood correlate with NfL levels in CSF and could serve as prognostic blood biomarkers of disease onset and progression in HD (Byrne et al. 2017; Johnson et al. 2018). Longitudinal analysis of NfL and other biomarkers related to HD, neurodegeneration, and inflammation in blood may facilitate understanding of HD pathophysiology and progression.

3.3.2.3 Magnetic Resonance Imaging

Magnetic resonance imaging is a non-invasive method to assess structure and function of the human brain and can provide insights into pathophysiological mechanisms of neurologic and neuropsychiatric disease. Several MRI techniques have shown sensitivity to detect abnormal structure and function within brains of individuals suffering from HD.

All patients will undergo MRIs every 32 weeks to assess the effect of long-term treatment and LP on brain structure and function. All of the measures will be assessed in a consistent manner with the preceding study, including those designated to be optional. The acquisition parameters of each sequence, structure, and length of each MRI session and image processing algorithms will be outlined in a separate MRI manual.

Unscheduled MRIs in 3 patients who received monthly IT procedures in Study BN40697 reported enhancement in the cauda equina region; MRIs will be explored in this extension study to further assess the impact of frequent IT procedures.

For this purpose, in consenting patients from Study BN40697, optional MRI scans of brain and spine with contrast media will be collected upon study entry and every 32 weeks thereafter (for additional details refer to Study BN40955 Ixico Safety Read Manual). The contrast brain and spine MRI will be reviewed in-house or by ad-hoc independent external neuroimaging experts to look for the occurrence of abnormal MRI findings.

3.3.2.4 Safety Biomarkers

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

4. MATERIALS AND METHODS

4.1 PATIENTS

Up to approximately 1100 patients with HD will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed ICF

  If capacity to consent is in question, formal capacity assessment by an appropriately qualified professional should be obtained. In cases where capacity to consent is not fully present, but the participant is known previously to have favored participation in an open-label study and is able to assent, consent may be obtained by a legally authorized representative.
  (Note: Patients in Germany who are not fully capable of providing informed consent are not eligible for inclusion).

- 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 (refer to Appendix 11)

Ability and willingness to comply with the study protocol including the visit schedule and all assessments, in the investigator's judgment

- For women of childbearing potential: Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

Women must remain abstinent or use 2 methods of contraception, including at least 1 method with a failure rate of <1% per year, during the treatment period and for 5 months after the final dose of study drug.

A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. A vasectomized man must undergo a medical assessment that confirms the success of the surgery before he can be considered surgically sterile.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 5 months after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

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.

Patients must meet the following criteria for study entry during screening (some will be reassessed at the inclusion visit prior to randomization and study drug dosing):

- Signed ICF
- 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 (refer to Appendix 6)

- Independence Scale (IS) score ≥70
- Genetically confirmed disease by direct DNA testing with a CAG-Age product (CAP) score >400 (Zhang et al. 2011), calculated as follows:

  $$CAP = Age \times (CAG\ repeat\ length - 33.66)$$

- 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
  - Long-distance (e.g., >50 meters) use of wheelchairs for convenience or transfer is permitted.
- Body mass index 16–32 kg/m^2; total body weight >40 kg
- 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)
- Ability to tolerate blood draws and LPs
- 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
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- 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

  Platelet counts between 125,000 and 150,000 mm^3 are permissible as long as the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.

- 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

    Women of childbearing potential must have a negative urine pregnancy test at the inclusion visit (obtained as part of the preceding study assessments).

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.

Patients who meet any of the following criteria will be excluded from study entry:

- 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 judgment of the investigator. If suicidal ideation is present, a risk assessment should be completed 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 an appropriately qualified mental health professional.
- 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

  Abuse is defined as a maladaptive pattern of use that leads to failure to fulfill major work or social obligations or use in situations where it leads to physical danger or legal problems, and may be the focus of clinical attention.
- 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, arterio-venous malformation, meningiomas, hydrocephalus, subdural haematoma) as assessed by a centrally read MRI scan during the screening period

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

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. An independent interactive voice or web-based response system (IxRS) provider will assign patients to treatment and conduct randomization where required. If, during the course of the study, a single regimen is selected for the development program, all patients will then be assigned to the selected regimen.

All patients, study site personnel, Sponsor agents, and Sponsor personnel will be unblinded to the treatment assignment of this study; however, the treatment assignment from a blinded preceding study will remain blinded until the preceding study is unblinded.

An IxRS provider will hold the treatment assignment code to maintain the integrity of the blinding (active versus placebo) in the preceding study.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is RO7234292.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 RO7234292

RO7234292 will be supplied by the Sponsor as sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL of 6.0 mg/mL RO7234292 drug product for IT injection. For a 120-mg dose (20-mL dosing volume), 2 vials containing 10 mL of 6.0 mg/mL RO7234292 will be pooled by drawing them up into the same injection syringe containing 20 mL of study drug.

For information on the formulation, study drug preparation, storage, and handling of RO7234292, refer to the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated AEs, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience AEs are provided in Section 5.1.3.

4.3.2.1 RO7234292

Each dose of RO7234292 (120 mg) will be administered as a single IT bolus injection of 20 mL by a qualified physician experienced in performing LPs. In exceptional circumstances, study staff who are licensed physician assistants or nurse practitioners with extensive experience of performing LPs and administrating IMP for ASOs IT may be acceptable with Sponsor approval.

Guidelines for treatment interruption or discontinuation for patients who experience AEs are provided in Section 5.1.3.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO7234292) will be provided by the Sponsor where required by local health authority (HA) regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to RO7234292

The Sponsor will offer continued access to Roche IMP (RO7234292) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (RO7234292) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (RO7234292) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HD
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for HD
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant HD therapy should constitute the optimal supportive care for the individual according to the investigator's own best clinical judgment. Concomitant therapy consists

of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from the time of entry into Study BN40955 to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Throughout the study, investigators or treating physicians may prescribe concomitant medications or treatment deemed necessary to provide adequate supportive care or for treatment of AEs.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited:

- Experimental agents or marketed HD agents at experimental doses that are being tested for the treatment of HD, including, but not limited to, cholinesterase inhibitors, memantine, amantadine, and riluzole
- Antiplatelet or anticoagulant therapy, including, but not limited to, aspirin (unless ≤81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- Sedation for LP or IT bolus procedures in the study

  Depending on institutional guidelines, local anesthesia is permissible for the LP procedure.
- Anti-anxiety medication is strongly discouraged during scheduled MRI scans. If anti-anxiety medication is used, the scan must be performed at the end of the assessment day (before the LP) or preferably on a different day, to avoid impacting other assessments.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1a and Appendix 1b. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. *Effective 22 March 2021, dosing is paused, including enrollment. Patients already on the study will continue to be followed for safety and efficacy outcomes until study completion (see Appendix 1a, Appendix 1b, and Appendix 2b).*

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including any screening evaluations, if applicable). Informed Consent Forms for patients will be maintained at the study site, regardless of whether the patient is subsequently enrolled. If a patient's capacity to consent is in question, the investigator should consult an appropriately qualified colleague who will independently assess capacity. This additional assessment should also be documented. If the patient is judged to have questionable capacity, then assent of the patient in addition to signed consent by a legally authorized representative is required for study participation. (Note: Patients in Germany who are not fully capable of providing informed consent are not eligible for inclusion). If the patient's capacity is confirmed, the investigator may proceed with the patient's signing of the ICF.

All screening (if required) and inclusion visit evaluations must be completed and reviewed to confirm that patients meet eligibility criteria before enrollment.
The investigator will maintain a screening log to record details of all patients evaluated and to confirm eligibility or record reasons for inclusion failure, as applicable.

Patients who are required to undergo screening will be allowed a maximum of 1 re-screening within 8 weeks of the initial screening failure for patients who fail the initial screening (e.g., as a consequence of abnormal laboratory values or general medical status not meeting inclusion or exclusion criteria). The CAG repeat length testing from Q2 Solutions will be accepted for this study. If re-screening is required, the CAG repeat length testing from Q2 Solutions does not need to be repeated.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, and reproductive status will be recorded at screening (patients required to undergo screening only) and baseline (inclusion visit). In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from the time of entry into Study BN40955 to the study completion/discontinuation visit. At the time of each study drug administration, an interval medical history should be obtained and any changes in medications should be recorded.

Demographic data will include age, sex, self-reported race/ethnicity, and education level based on the International Standard Classification of Education scale will be recorded at screening (patients required to undergo screening only) and baseline (inclusion visit) for all patients except those undergoing screening. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed PK, PD, toxicity, and/or response to treatment.

The protocol number and patient number of the preceding study will be collected, as well as the patient's Huntington's disease identification number (HDID). For patients without an HDID, the number will be created via a web portal (see Section 8.4).

4.5.3 Physical and Neurologic Examinations

A complete physical examination, performed at specified visits (see Appendix 1a and Appendix 1b), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. The physical examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations, including weight at each visit. Height will be obtained from the preceding study. For patients required to undergo screening, height will be collected at screening only.

A neurologic examination, including fundoscopy, performed at screening (patients required to undergo screening only), inclusion and at every clinical visit, should include assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, gait, and coordination (see Appendix 12). The neurologic examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations. Neurologic examinations should be performed before and after treatment on each dosing day*, or before the lumbar puncture, if there is no study treatment administration.*

Any abnormality identified at screening (patients required to undergo screening only) and baseline (inclusion visit) should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation; normal age-related change; or HD-related clinical progression) should be recorded as AEs on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse, temperature, and systolic and diastolic blood pressure while the patient is in a seated position after resting for at least 5 minutes. All data should be recorded on the appropriate eCRF.

4.5.5 Collection of Cerebrospinal Fluid (Lumbar Puncture Procedure)

Within 72 hours prior to performing each scheduled LP, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed. The LP should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 p.m. or in the early afternoon between 12:00 p.m. and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. Cerebrospinal fluid (20 mL) is to be collected for analyses using a LP collection kit. If there are difficulties in collecting 20 mL of CSF, a minimum of 5 mL

should be collected over a maximum of 60 minutes, once CSF flow has been established. The operator must confirm CSF flow is present prior to injecting drug. A 24G atraumatic needle, as specified in the LP procedure and CSF collection guidelines, should be used to minimize risk of post–LP syndrome.

Depending on institutional guidelines, local anesthesia should be used for the procedure. Sedation may not be used. Spinal ultrasound may be used for the LP procedure if deemed necessary, but ultrasound is not required. Ultrasound guidance may be used if attempts at LP without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each LP. Fluoroscopy guidance can also be used, if local institutional guidelines dictate and local ECs/IRBs and HAs have approved the use of the technique, but it is not required. Where fluoroscopy is used, patients should also be informed and consent obtained.

For details on the LP and IT bolus dosing procedure, refer to the LP procedure and CSF collection guidelines and instructional video.

When applicable, study treatment administration will occur via a LP using a needle inserted into the L3/L4 space, although placement at a different level (either in the space above or the space below) is allowed if patient anatomy or clinical judgment dictates. The left lateral position is mandatory in the first instance for the procedure for consistency of procedure practice across sites and within patients, unless patient-specific factors require use of the upright, sitting position or the physician/operator has preexisting experience using LP/IT bolus dosing in the sitting position and prefers the use of the upright sitting position. Whichever position is used, once access is established to the IT space, the entire IT bolus procedure should be completed in the same position, to limit the risk of the needle losing position while the spinal needle is inserted. Subsequent LP administrations should preferably occur using the same position.

Patients will be discouraged from resting supine after the LP procedure and will be encouraged to mobilize immediately by walking around at a minimum and, if feasible, walking briskly for approximately 30 minutes. *If applicable*, the postdose neurological examination can occur *after walking*. Patients should not perform any activity that is associated with a change in the ambient air pressure for at least 24 hours *post LP procedure* (e.g., air travel, scuba diving, or hot air balloons).

In case of a failed IT bolus dosing procedure (e.g., due to an inadequate establishment of access to the IT space), a second dosing attempt may occur up to 7 days after the originally scheduled dosing attempt. For this additional visit, safety and tolerability evaluations on the day of LP administration will be performed as detailed in Appendix 1a and Appendix 1b, including neurological examination (predose and postdose), vital signs, and a review of AEs and concomitant medication. If the second dosing attempt occurs more than 72 hours after the last coagulation panel and platelet test, local laboratory

analysis of coagulation factors (INR and/or PT, aPTT) and platelets need to be conducted again and results reviewed prior to the LP attempt (see Appendix 1a and Appendix 1b).

Lumbar punctures will be performed as specified in the schedule of activities (see Appendix 1a, Appendix 1b, *and Appendix 2b*), with the last CSF sample obtained at the end-of-treatment visit for this study. No study drug will be administered at that visit.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Coagulation: INR and/or PT, aPTT, and platelet count
- Urine pregnancy test

  Urine pregnancy tests will be performed for women of childbearing potential at specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (analyzed at a central laboratory).
- Cerebrospinal fluid for safety: cell count (including RBCs and WBCs), glucose, and protein

Samples for the following laboratory tests will be sent to a central laboratory:

- Hematology: WBC count, RBC count, platelet count, hemoglobin, hematocrit, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Serum chemistry panel: bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, gamma-glutamyl transferase, and CPK
- Serum pregnancy test

  Serum pregnancy tests will be performed for women of childbearing potential to confirm a positive urine pregnancy test (if applicable).

  Serum pregnancy test will be performed for women of childbearing potential at screening (patients undergoing screening only). At subsequent visits it will be performed to confirm a positive urine pregnancy test (if applicable).
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination for all abnormal dipstick results (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Cerebrospinal fluid and blood (plasma) samples for PK analyses
- Blood (plasma) samples for immunogenicity analyses
- Cerebrospinal fluid samples for analysis of mHTT
- Plasma and CSF samples for exploratory research on biomarkers and biomarker assay development

Patients who are required to undergo screening will have the following additional laboratory tests sent to central laboratory:

- Thyroid panel: thyroid-stimulating hormone and free thyroxine (also known as T4) levels
- Viral serology: HBsAg and HCV antibody (or viral RNA if HCV antibody assay is positive)
- Blood sample for determination of CAG repeat length in HTT for patient eligibility. The CAG repeat length testing from Q2 Solutions will be accepted for this study.

Exploratory biomarkers research may include, but will not be limited to, total HTT or isoforms of HTT, NfL, tau, and other proteins related to HD, neurodegeneration, and inflammation.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and CSF samples collected for biomarker research and biomarker assay development will be destroyed no later than 10 years after the final Clinical Study Report has been completed
- Plasma and CSF samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; these samples will nevertheless be destroyed no later than 5 years after the final Clinical Study Report has been completed

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy in the study data publication.

4.5.7 Magnetic Resonance Imaging

Mandatory structural MRI will be used to assess brain volume, optional diffusion-weighted MRI/Neurite Orientation Dispersion and Density Imaging will be used

to examine structural brain connectivity, and optional resting-state functional MRI will be employed to identify functional connectivity. All of the measures will be assessed at the whole-brain and regional levels and will continue as in the preceding study. Patients will be required to undergo and tolerate the mandatory structural MRI. Patients who are required to undergo screening will undergo structural MRI at screening to confirm eligibility for the study. Patients will be encouraged to receive the diffusion-weighted MRI/Neurite Orientation Dispersion and Density Imaging and Resting-State functional MRI scans, but they will not be required.

The MRI should be performed using a 3-Tesla (3T) magnet. The acquisition parameters of each sequence, structure, and length of each MRI session, as well as image processing algorithms, will be outlined in a separate MRI manual. Magnetic resonance imaging scans will be managed by a central laboratory to monitor and ensure the integrity and quality of the acquired data. During central review, the Sponsor and/or site staff will be notified of any unexpected findings requiring clinical follow-up.

At specified timepoints, the MRI should be scheduled to occur before the LP (see Appendix 1a and Appendix 1b). The MRI scan should be performed 7−14 days prior to the LP to allow time for re-scanning if the quality of the initial MRI is inadequate. If the re-scan cannot be performed prior to the LP, then it can be conducted the day after the LP, as long as there are no post-LP contraindications and it occurs within 2 weeks of the original scan.

Anti-anxiety medication is strongly discouraged during scheduled scans, as described in Section 4.4.2.

4.5.8 Optional Magnetic Resonance Imaging of Brain and Spine with Contrast in Patients from Study BN40697

Optional MRI scans of brain and spine with contrast media will be collected in patients from Study BN40697, with MRI performed as described in Section 4.5.7. The optional MRIs will be obtained at specified timepoints, as outlined in Appendix 1a. The contrast brain and spine MRI will be reviewed in-house or by ad-hoc independent external neuroimaging experts to look for the occurrence of abnormal MRI findings.

4.5.9 Electrocardiograms

Single ECG recording will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1a and Appendix 1b), and may be obtained at unscheduled timepoints as clinically indicated.

The ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. Electrocardiogram recording must be performed after the patient has been resting in a supine position for at least 10 minutes. Electrocardiograms for each patient should be

obtained from the same machine whenever possible. All ECGs are to be obtained prior to other invasive procedures scheduled at that same time (e.g., blood draws) and should not be obtained within 30 minutes after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. All data should be recorded on the appropriate eCRF.

The ECG recordings may be electronically transferred to a central vendor. The investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.10 Patient-Reported, Clinician-Reported, and Performance Outcomes

Patient-reported outcome (PRO), clinician-reported outcome (ClinRO), and performance outcome (PerfO) data will be collected in the clinic to document the change from baseline over time. Additionally, PRO and PerfO data will be collected remotely in patients issued with devices. The instruments, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet HA requirements, instruments will be self-administered or administered by a trained rater (as appropriate). In-clinic data should be collected prior to the performance of the LP procedure.

Patients and clinicians will use an electronic device to capture ClinRO, PRO, and PerfO data during clinic visits, and scoring of ClinRO and PerfO measures will be supervised during acquisition and entry into a tablet to ensure instructions are given and appropriately followed. Patients who were issued with a smartphone and wrist-worn wearable in their preceding study will continue to use the smartphone and wrist-worn wearable to capture outcome data remotely and at specified visits (see Section 4.5.10.11).

In exceptional circumstances where a patient cannot attend clinic or investigator site has closed due to restrictions imposed as a result of the COVID-19 pandemic, ClinRO (refer to Appendix 8) can be collected remotely via telephone. For all other situations these all need to be completed in the clinic, otherwise it is a protocol deviation.

See Appendix 1a and Appendix 1b for the schedule of activities and Appendix 3 and Appendix 4 for a summary of timing and duration of each PRO, ClinRO, and PerfO assessment. Appendix 7 shows the order and approximate timing of assessments at each clinic visit. Appendix 5 shows the clinical assessments order and duration for patients required to undergo screening only. Appendix 8 shows the remote clinical assessments order and duration for patients who could not attend an in-clinic visit due to COVID-19 pandemic.

4.5.10.1 Composite Unified Huntington's Disease Rating Scale

The cUHDRS is a composite motor, cognitive, and global functional clinical outcome measure in patients with HD comprised of an equally weighted sum of Z scores of the TFC, the TMS, the SDMT, and the SWR scores from the UHDRS (Huntington Study Group 1996). It is a multidomain measure of clinical decline that tracks underlying progressive brain changes and is related to changes in daily functional ability (Schobel et al. 2017).

The formula for cUHDRS scoring was originally developed for use in HD Stages 1 and 2 (TFC 7–13) but has since been updated to encompass early HD Stage 3. This led to an update to the reference population (using ENROLL-HD data) from TFC=7–13 to TFC=5–13 (in both cases, a lower age cutoff of 20 years was used to limit the number of individuals included with juvenile-onset HD). The cUHDRS is scored using the following formula:

$$\text{cUHDRS} = \left(\frac{\text{TFC} - 8.8}{2.8}\right) - \left(\frac{\text{TMS} - 34.4}{17.4}\right) + \left(\frac{\text{SDMT} - 25.2}{12.4}\right) + \left(\frac{\text{SWRT} - 58}{21.2}\right) + 10.0$$

4.5.10.2 Total Functional Capacity Scale

The TFC is a validated measure of global patient function in HD. The TFC represents the investigator's assessment of the patient's capacity to perform a range of activities of basic daily living, including working, chores, managing finances, eating, dressing, and bathing. The 5-item assessment is based on a brief interview with the patient. The TFC score ranges from 0–13, with a higher score representing better functioning. A 1-point change in TFC score is a clinically meaningful change in patient function (e.g., a 1-point decline may indicate the loss of ability to work in a normal capacity) (Huntington Study Group 1996). The TFC takes approximately 10 minutes to administer and will be completed at specified clinic visits.

4.5.10.3 Total Motor Score

The TMS is a holistic measure of motor function in HD that is linked to both functional capacity based on the TFC score, independence, and driving status (Beglinger et al. 2012; Schobel et al. 2017).

The TMS score is the sum of the individual motor ratings obtained from administration of the 31-item motor assessment portion of the UHDRS by the investigator. The score ranges from 0–124, with a higher score representing more severe impairment. The TMS takes approximately 15 minutes to administer and will be completed at clinic specified visits.

4.5.10.4 Symbol Digit Modalities Test

The SDMT is used to assess attention, visuoperceptual processing, working memory, and psychomotor speed. It has been shown to have strong reliability and validity (Smith 1982). The patient pairs abstract symbols with specific numbers according to a

translation key. The test measures the number of items correctly paired (maximum of 110 correct pairs) in 90 seconds. The SDMT will be administered at specified clinic visits and can be completed in less than 5 minutes. It will also be administered at specified timepoints on the Roche HD mobile app (via electronic SDMT) in patients issued with devices.

4.5.10.5 Stroop Word Reading Test

The SWR Test is a measure of attention, processing, and psychomotor speed and depends upon quick verbal motor output. Patients are presented with a page of color names (i.e., ″BLUE,″ ″RED,″ or ″GREEN″) printed in black ink and are asked to read aloud as many words as possible within a given amount of time (in 45 seconds). The number of words read correctly is counted, with a higher score indicating better cognitive performance. It will also be administered at specified timepoints on the Roche HD mobile app (via electronic SWR) in patients issued with devices.

4.5.10.6 Independence Scale

A patient's IS score is a measure of disease progression in functional disability and will be completed to evaluate a patient's degree of independence at screening. It is a subscale of the UHDRS. The scale consists of 19 discrete levels ranging from 10–100 (by 5), in which a score of 100 indicates no special care is needed and a score of 10 indicates the patients is fed by tube and requires total bedcare. This scale will only be performed for patients who were screened and eligible for Study BN40423 but could not be randomized due to challenges relating to the COVID-19 pandemic.

4.5.10.7 Huntington's Disease Daily Activities Scale

The HD-DAS assesses patients' daily function. Following a semi-structured interview with the patient, the patient's ability level to perform daily tasks such as eating or using a telephone will be recorded. Each item is scored on a 4-point Likert-type scale, where 0 indicates no impact and 3 indicates severe impact. The HD-DAS can be completed in approximately 25 minutes.

4.5.10.8 Clinical Global Impression, Severity and Change Scales

The CGI-S is a single-item measure of current global severity and is completed by the clinician at specified clinic visits. The CGI-S is assessed using an 11-point numeric rating scale, where higher scores indicate greater severity. The CGI-S can be completed in approximately 2 minutes.

The CGI-C is a single-item measure of change in global status (since starting the study) and is completed by the clinician at specified post-baseline visits. The CGI-C has seven response options: ″very much worse,″ ″much worse,″ ″minimally worse,″ ″no change,″ ″minimally improved,″ ″much improved,″ and ″very much improved.″ The CGI-C can be completed in approximately 2 minutes. To assess the relevance of this change, a follow-up question with dichotomous response options (″yes″ or ″no″) asks if the change has had a meaningful impact on the patient’s well-being.

4.5.10.9 Montreal Cognitive Assessment

The MoCA is a patient-completed assessment used to detect cognitive impairment. It contains a series of basic assessments, including attention and visuospatial tasks. The total score ranges from 0–30, where lower scores indicate greater impairment. The MoCA will be used in this study to assess cognitive status at regular intervals throughout the study and takes approximately 10 minutes to administer.

4.5.10.10 Columbia-Suicide Severity Rating Scale

The C-SSRS is a structured tool to assess suicidal ideation and behavior. Four constructs are measured: severity of ideation, intensity of ideation, behavior, and lethality of actual suicide attempts. Binary (yes/no) data are collected for 10 categories, and composite endpoints based on the categories are followed over time to monitor patient safety (Posner et al. 2011). It maps to the Columbia-Classification Algorithm for Suicide Assessment and meets the criteria listed in the U.S. Food and Drug Administration (FDA) draft guidance for assessment of suicidality in clinical trials (FDA 2012). The C-SSRS will be used to assess eligibility for the study for patients required to undergo screening (full version at screening, requiring approximately 20 minutes to administer) and to monitor patients throughout the study at clinic visits (follow-up version, requiring approximately 5 minutes to administer, assuming absence of suicidal ideation and no change in clinical status from previous administration).

The patient should be referred for immediate psychiatric evaluation in any event of suspected active suicidal intent, significant suicidal behavior, or clinical finding suggesting that the patient is dangerous to himself or herself.

4.5.10.11 EuroQol 5-Dimension, 5-Level Questionnaire

The EQ-5D-5L is a validated self-report health status questionnaire used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status (Index score) from the 5-item scores (i.e., does not include the VAS). The EQ-5D-5L takes approximately 5 minutes to complete. The Index score will be used in this study for informing pharmacoeconomic evaluations. The VAS score will be used to assess health-related quality of life (HRQoL). The EQ-5D-5L will be completed by the patient at study drug administration visits on an electronic device. In addition, it will be completed remotely by the patient on the Roche HD mobile app.

4.5.10.12 Roche HD Mobile Application: Remote Testing (Smartphone and Wrist-Worn Wearable)

Smartphones and wrist-worn wearables have high-quality sensors that enable the remote, non-invasive, frequent, and precise measurement of motor and non-motor symptoms (Maetzler et al. 2013; Andrzejewski et al. 2016; Adams et al. 2017;

Lipsmeier et al. 2018). If a patient already has a preconfigured smartphone and wrist-worn wearable with installed software for the Roche HD mobile app assessments from the preceding study, they will continue to use those devices in this study. Although the majority of assessments on the Roche HD mobile app are consistent across the preceding studies, some of the PROs will differ. Patients will continue to complete the PROs from the preceding study, thus not all patients will complete all PROs (e.g., the WHODAS 2.0 will not be completed by patients previously in Study BN40423). Details of remote assessments are contained in Appendix 7. If patients did not have a preconfigured smartphone and wrist-worn wearable in the preceding study, they will not be provided devices in this study. Patients screened in Study BN40423 but not randomized due to logistical challenges resulting from COVID-19 will be provided with a smartphone and wrist-worn wearable. The devices and software will monitor motor symptoms, non-motor symptoms, and activities associated with routine daily living throughout the course of the study. Additional details are available in the Roche HD mobile app (smartphone) manual.

Patients will be asked to complete an ″active test″ every day at approximately the same time (ideally in the morning, after breakfast). The active test consists of a short, preconfigured schedule of tasks that assess motor symptoms (upper and lower body movements, upper limb dexterity, and voice) and non-motor symptoms (processing speed, voice). These tasks are described in Appendix 9. Testing will last approximately 5–10 minutes in total on a typical day of testing. Not all tests are daily. Additional information on the approach, tasks, and schedule are available in the Roche HD mobile app manual.

For ″passive monitoring,″ patients will be instructed to carry the smartphone in a manner convenient to them (e.g., in a pocket or in a Sponsor-provided pouch) and wear the wrist-worn wearable throughout the day as they go about their daily routines.

Patients will be encouraged to adhere to the daily schedule of tasks as much as possible; however, patients will not be excluded from the study for poor adherence nor will missing a daily test be considered a protocol deviation. Device sensor data will be recorded continuously, throughout the active tests and passive monitoring. Sound will only be recorded during selected active test tasks. Data will be encrypted and uploaded to secure servers when the smartphone is connected to Wifi. Patients will be asked to charge the devices overnight. If patients have a Wifi network at home, they will be encouraged to connect their smartphone to enable data transfer. If no Wifi network is available, the sensor data will be transferred during clinic visits or after the devices have been returned.

Devices may reach the end of their lifespan or be broken during this study. In those cases, they may be replaced upon discussion on a case-by-case basis.

During the course of this study (ca. 2022), the Roche HD mobile app may be available for download by study participants with compatible smartphones. All patients, will have the option to download the app on their personal smartphones and continue (or restart) with the Roche HD mobile app assessments and passive monitoring. If patients download the app on their personal smartphone, they should return the provisioned devices.

4.5.10.12.1 Roche HD Mobile Application: In-Clinic Assessments

Patients will be instructed to bring the smartphone and wearable to every clinic visit to check adherence and technical status of the devices. Every 16 weeks, when clinical ratings will occur, patients will be asked to conduct the In-Clinic Assessments (″Full active test″) under the supervision of trained site staff, with the exception of the EQ-5D-5L, which will be completed on the electronic device at the site. Patients should be instructed to not complete the Roche HD mobile app EQ-5D-5L on days that coincide with the study drug administration visit.

The smartphone and wearable must be returned to the clinic in cases where the patient does not meet eligibility criteria, at the end of the study, or upon early termination from the study.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for an end-of-treatment visit and safety follow-up visit (if applicable) after the final dose of study drug (see Appendix 1a and Appendix 1b for additional details).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent

- Study termination or site closure
- Loss of capacity to consent, if legal guardian consent is not possible

  Note: Withdrawal of patients who lose capacity to consent is a requirement in Germany.

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

RO7234292 is not approved and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with RO7234292 in completed and ongoing studies. Safety risks for the LP procedure and RO7234292 are outlined below in Sections 5.1.1 and 5.1.2, respectively. Please refer to the RO7234292 Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study, including the eligibility criteria. Patients will undergo safety monitoring during the study, including assessment of the incidence and severity of AEs. Guidelines for managing AEs, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Known Risks Associated with Lumbar Puncture

Post–lumbar puncture syndrome, spinal hematoma, and meningitis (see Sections 5.1.1.1–5.1.1.3) are potential risks associated with LP.

In the completed Phase I/IIa study, the most commonly reported AEs across all treatment groups (RO7234292, N=34; placebo, N=12) were procedural pain (54% of patients) and post–LP syndrome (37% of patients).

In the recently completed Phase II OLE Study BN40697, potential LP procedure-associated selected AEs were reported with similar incidence across the cohorts despite the difference in dosing frequency (16 patients [69.6%] in the Q4W cohort and 17 patients [73.9%] in the Q8W cohort). Overall, the most frequently reported event was procedural pain (41.3%). In the ongoing Phase III Study BN40423, patients enrolled under Protocol Versions 1–3 (receiving Q4W blinded treatment) were discontinued following discontinuation of the Q4W dosing. These patients' treatment assignments are now unblinded and hereby referred to as original design cohort (ODC). In the ODC, potential LP procedure associated selected AEs were reported with similar incidence across the three cohorts (17 patients [47.2%] in the placebo cohort, 14 patients [40%] in the Q4W cohorts, and 17 patients [47.2%] in the Q8W cohort). Overall, the events reported with highest incidence were procedural pain and post-lumbar puncture syndrome (14% each).

As of 07 August 2020, in the ongoing Study BN40955, potential LP procedure associated selected AEs were reported in 30 patients [22.9%] in the Q8W cohort and 11 patients [15.1%] in the Q16W cohort. Overall the most frequently reported event was procedural pain (9.2% in the Q8W cohort and 4.1% in the Q16W cohort). Many of the complications associated with LP can be avoided by the mandatory use of a 24G atraumatic needle with a stylet, adherence to procedural guidelines (see LP manual and instructional video), and careful assessment of the patient, including neurologic examination with fundoscopy both prior to and post–LP procedure. Lumbar puncture should be avoided when a contraindication is present.

Cerebrospinal fluid leakage is more likely with larger bore needles. To minimize this risk, a 24G atraumatic needle will be used. Training for use of the 24G atraumatic needle in this study will be provided prior to initiation of LP, as will a review of extension tubing use and the need to gently aspirate CSF for timely collection. If headache with characteristics of low-pressure syndrome is present after the procedure and persists despite standard of care treatment, a blood patch should be considered. Formation of a subarachnoid epidermal cyst (i.e., when a skin plug is introduced into the arachnoid

space) can be avoided by use of a needle with stylet, which is mandatory. Rarely, brain herniation can occur in the setting of LP and increased intracranial pressure.

There are specific contraindications to performing LP. These include unstable cardiorespiratory status, where positioning patient for LP may not be tolerated, signs of cerebral herniation or incipient cerebral herniation, signs of increased intracranial pressure, or focal neurological findings on examination. In those patients, LP (and IT treatment administration) should not be performed and appropriate diagnostic work-up should be initiated. On a case-by-case basis and following discussion with the Medical Monitor, such patients may be able to resume treatment.

In the setting of HD, for the purposes of LP and IT bolus injection of RO7234292, moderate to severe truncal chorea may also be prohibitive.

5.1.1.1 Post–Lumbar Puncture Syndrome

RO7234292 is delivered directly to the CNS by IT LP injection. Post–LP syndrome (e.g., headaches, nausea, vomiting, infection, hemorrhage, nerve irritation pain) can occur with IT administration. Experience to date with post–LP syndrome, as reported in the completed Phase I/IIa study, includes headache, which occurred after 10% of procedures and was transient and mild in the vast majority of patients.

In the recently completed Phase II OLE Study BN40697, post-LP syndrome events (such as post-LP syndrome, headache, migraine, nausea, vomiting or procedural headache) occurring within 5 days of LP were reported in 9 patients (39.1%) in the Q4W cohort and 13 patients (56.5%) in the Q8W cohort.

In the Study BN40423 ODC, post-LP syndrome events (post-LP syndrome, headache, migraine, nausea, vomiting or procedural headache) occurring within 5 days of LP were reported in 14 patients (38.9%) in the placebo cohort, 8 patients (22.9%) in the Q4W cohort and 14 patients (38.9%) in the Q8W cohort.

As 07 August 2020, in the ongoing Study BN40955, post-LP syndrome events (such as post-LP syndrome, headache, migraine, nausea, vomiting or procedural headache) occurring within 5 days of LP were reported in 7 patients (5.3%) in the Q8W cohort and 2 patients (2.7%) in the Q16W cohort.

The majority of these events were mild or moderate and non-serious. No events led to treatment interruption or discontinuation.

Patients should walk post–LP, (see Section 4.3.2.1). However, if a patient develops a headache after the LP with characteristic features, which makes walking intolerable, the patient should be encouraged to first sit down and if the headache persists then the patient should lie in a comfortable position, which is most likely in the supine position owing to the postural nature of the symptoms. Supportive treatment may include

rehydration, consumption of caffeinated drinks, simple analgesics, opioids, and antiemetics. If these conservative measures fail, more specific measures may be indicated.

5.1.1.2 Spinal Hematoma

Post–lumbar puncture spinal hematoma is a very rare but important potential risk that can present as persistent back pain, radicular pain, new sensory or motor symptoms, sphincter disturbance, or meningism. Prompt MRI scanning should be performed if suspicion of spinal hematoma arises. Patients with susceptibility to bleeding, patients with coagulopathy, and patients receiving anticoagulant therapy are at an increased risk of spinal hematoma and will be excluded from the study (see Section 4.1.2). Management of spinal hematomas should include consultation with neurosurgical colleagues.

5.1.1.3 Meningitis

Meningitis is a rare potential risk of LP. Patients may present with headache, meningism, photophobia, neck stiffness, and pyrexia. Guidelines for management of patients with suspected meningitis are provided in Table 2.

5.1.2 Potential Risks Associated with RO7234292

The potential risks identified below have been considered in relation to clinical data available as of *07 August 2020*, including the completed Phase I/IIa study and its Phase II OLE Study (BN40697)*, Study BN40423 (ODC), and the ongoing Study BN40955*.

5.1.2.1 Neurologic Changes

In cynomolgus monkeys, acute, transient deficits in lower spinal reflexes (patellar reflex in particular) were typically observed 2–8 hours following dosing, in the 13-week and the chronic toxicity studies. The transient changes in patellar reflex were observed in all treatment groups, including controls, with a slightly higher incidence in the high-dose groups. These findings were fully reversible within 24 hours following dosing. No other treatment-related changes in general sensory and motor function parameters nor changes in the cerebral reflexes were observed.

In the Phase I/IIa multiple ascending dose (MAD) study (ISIS 443139-CS1), no adverse trends in neurological examinations were detected and only a few drug-related neurological AEs were observed in ≥2 patients. See the RO7234292 Investigator's Brochure for more information.

In the *other completed and* ongoing *studies, among events associated with peripheral nervous system,* 2 cases of asymptomatic lumbar radiculopathy that were characterized by loss of ankle reflexes without changes in motor or sensory function *and one serious adverse event (SAE) of radiculopathy and hyporeflexia (Suspected Unexpected Serious Adverse Reaction [SUSAR] case) have been observed in the Phase II OLE Study*

BN40697 at the Q4W 120 mg cohort. In Study BN40423 ODC, one case of lumbar radiculopathy (post traumatic, considered not related to study drug by the investigator) was reported in the Q8W cohort. In Study BN40955, no treatment-emergent radiculopathy cases have been reported.

Among reflex change events in Study BN40697, areflexia and reflexes abnormal were reported in 1 patient each in the Q4W cohort and hyporeflexia was reported in 1 patient each in the Q4W and Q8W cohorts, respectively. In Study BN40955, treatment-emergent areflexia was reported in 1 patient in the Q8W cohort, and none were reported in the Q16W cohort. No reflex change AEs have been reported in Study BN40423 ODC. For details, see the RO7234292 Investigator's Brochure.

Among events associated with the central nervous system in Study BN40697, dysarthria was reported in 2 patients in the Q4W cohort; coordination abnormal was reported in 1 patient in the Q4W cohort; pleocytosis was reported in 1 patient in the Q4W arm; and ataxia was reported in 1 patient each in the Q4W and Q8W cohorts, respectively. An SAE of cerebrovascular accident was reported in 1 patient in the Q4W cohort, which was considered not related to study drug by the investigator. SAEs of hemiparesis, myelitis, and neuritis (SUSAR cases) were reported in another patient in the Q4W cohort. In Study BN40423 ODC, ataxia (SUSAR case) and dysarthria were reported in 1 patient each in the Q4W cohort. In Study BN40955, treatment-emergent event of ataxia was reported in 1 patient each in the Q8W and Q16W cohorts, respectively, pleocytosis was reported in 1 patient in the Q8W cohort, and two neurological SUSAR cases were reported in 2 patients in the Q8W cohort (1 patient each for arachnoiditis and aseptic meningitis). For details see the RO7234292 Investigator's Brochure. Following LP administration and post-LP mobilization, neurologic examinations should be conducted. In addition, patients should be observed in-clinic for any complications or complaints post-LP and IT bolus injection of RO7234292.

5.1.2.2 Elevations in CSF WBCs and Protein

The CSF WBC elevations were also observed in the chronic non-human primate study with slight increases over time. Increases were mild, and there was no apparent dose dependency.

CSF protein and WBC increases have been observed in the RO7234292 program.

In Study BN40697, one patient was diagnosed with chemical meningitis (SUSAR case) in the Q4W cohort. As of 04 October 2020, in the ongoing Study BN40955, one patient experienced aseptic meningitis (clinically not infectious) and one patient experienced arachnoiditis, in the Q8W cohort.

For details on CSF proteins and WBC laboratory values and non-serious AEs of CSF WBC and protein increases, please refer to the RO7234292 Investigator's Brochure.

5.1.2.3 Thrombocytopenia

Reductions in platelet count have been observed after systemic administration of some 2′-MOE chimeric ASOs to clinical trial subjects. However, no clinically significant reductions in platelet counts have been observed in clinical studies for RO7234292 to date. In one 13-week and one 9-month IT toxicity studies of RO7234292 in the cynomolgus monkey, there were no effects on hematology or coagulation parameters.

No clinically significant reduction in platelet counts *has been observed in the completed and ongoing studies in the RO7234292 program* to date.

Platelet counts will be monitored at each study visit prior to LP. See Table 2 for patient stopping and treatment discontinuation rules.

5.1.2.4 Kidney Effects

Reductions in renal function have been observed after administration of some 2′-MOE containing chimeric ASOs to clinical trial subjects. In the 13-week and 9-month toxicity studies of RO7234292 in cynomolgus monkeys, there were no test article–related histologic findings in the visceral organs or effects on clinical chemistries.

No clinically significant reduction in kidney function was observed in the completed RO7234292 Phase I/IIa study. *Among the other completed and ongoing studies, in the recently completed Phase II OLE study BN40697, one case of moderate and non-serious proteinuria was reported in the Q4W cohort, which resolved without any intervention, was considered by the investigator to be related to the study treatment, and the patient continued study drug administration.* No other clinically significant kidney abnormality has been observed.

Kidney function will be monitored at each study visit. Guidelines for management of patients who develop decreased renal function are provided in Table 2.

5.1.2.5 Liver Effects

Elevations in liver enzymes have been observed after administration of some 2′-MOE chimeric ASOs to clinical trial subjects. However, no clinically significant elevation in liver enzymes have been observed in the clinical studies for RO7234292 to date.

In the 13-week and 9-month toxicity studies of RO7234292 in cynomolgus monkeys, there were no drug–related histologic findings in the visceral organs, including the liver, or effects on clinical chemistry test levels. No clinically significant elevations in liver enzymes were observed in the completed RO7234292 Phase I/IIa study. *Among the other completed and ongoing studies, in the recently completed Phase II OLE study BN40697, one mild AE of hepatic enzyme increase was reported in 1 patient in the Q4W cohort, which resolved without any intervention and was considered by the investigator not related to RO7234292.* No drug-related clinically significant hepatic abnormality has been observed to date.

Liver enzymes will be monitored at each study visit. Guidelines for management of patients who develop decreased liver function are provided in Table 2.

5.1.2.6 Hydrocephalus

Hydrocephalus is included as a warning in the labeling of one marketed IT-administered 2′-MOE chimeric ASO.

Ventricular volume expansion has been described in the RO7234292 Investigator's Brochure and is being monitored in all RO7234292 studies.

An SAE of hydrocephalus following chemical meningitis was reported in a patient who has undergone shunting in the Q4W cohort of the recently completed Phase II OLE Study BN40697. In ongoing blinded Study BN40423, 1 patient with symptomatic communicating hydrocephalus has been shunted (SUSAR case) and 1 patient with a medical history of hydrocephalus had an event of hydrocephalus (verbatim: worsening hydrocephalus) that was considered by the investigator not to be related to the study treatment.

For details, *and description of non-serious AEs, refer to* the RO7234292 Investigators Brochure; for management guidelines, see Section 5.1.3.3.

5.1.2.7 Neuropsychiatric Changes

RO7234292 is directly administered to the CNS, with limited clinical experience. Nonclinical studies in animals did not show any adverse effects on the CNS. Though a single case of completed suicide has occurred in the ongoing Phase II OLE study (Study BN40697), when weighing all available details of the case, the investigator has concluded that this event was not related to RO7234292. Patients should be closely monitored for signs and symptoms of neuropsychiatric changes in addition to routine monitoring with the C-SSRS and the MoCA battery.

5.1.2.8 Potential Risk due to Reduction of Target Protein HTT

By specifically targeting mRNA from both *HTT* alleles, RO7234292 lowers levels of both mHTT protein and normal wild-type huntingtin (wtHTT) protein in all patients, regardless of genetic variations. The ASO modality provides partial, transient, reversible, and titratable HTT lowering. Partial HTT lowering is safe and well tolerated in normal rodents and non-human primates, as shown in multiple studies using ASOs and non-reversible approaches. Furthermore, no safety signals of concern emerged during the completed Phase I/IIa study of RO7234292 in adults with HD
(see RO7234292 Investigator's Brochure), in which partial lowering was achieved.

Transgenic mice expressing human mHTT develop progressive HD-like phenotypes that recapitulate many aspects of HD in humans. Antisense oligonucleotide-mediated mHTT lowering provides therapeutic benefits and often restores normal functioning in transgenic and fully humanized animal models of HD, with generally similar results

regardless of whether wtHTT is also lowered. Moreover, no detrimental effects of partial wtHTT lowering in animal models have been reported in multiple studies using ASOs and non-reversible approaches.

Still, the current understanding of the diverse cellular functions of HTT suggests potential theoretical risks associated with reducing total HTT levels in people with HD. More than two decades of research findings implicate HTT in a wide array of cellular functions, including microtubule-based transport, F−actin-based trafficking, Rab-based trafficking, brain-derived neurotrophic factor transport, ciliogenesis, transcription, chromatin modification, post-transcriptional gene-expression regulation, neurogenesis, synaptogenesis, synaptic plasticity, signaling pathways, cell stress responses, cell survival, selective macro-autophagy and DNA damage repair, as detailed in a recent review article (Liu and Zeitlin 2017).

Although functional HTT (mutant or wild-type) is essential for embryogenesis, near-complete genetic ablation of HTT has little or no reported neurological effect in normal adult animals. However, complete ablation of wtHTT protein expression throughout life results in a worsening motor phenotype and, in male transgenic mice, age-dependent emergence of brain atrophy and decreased testicular size (Van Raamsdonk et al. 2005). In contrast, decreases in mHTT protein expression ameliorate disease, and increases in mHTT protein exacerbate disease in animal models of HD, regardless of concomitant changes in wtHTT protein levels.

No clinically significant new neurologic events were observed in the completed Phase I/IIa study. As a precaution, a full neurologic examination will be conducted at each study visit (on dosing days before and after dosing), and additional monitoring of cognition will be conducted throughout the study using the MoCA.

5.1.3 Management of Patients who Experience Adverse Events

5.1.3.1 Dose Modifications

No dose modifications are permitted in this study, whether by varying the amount of study drug volume injected or the frequency of procedure per protocol (i.e., all participants will receive 20 mL of study drug at every study drug administration either on a Q8W or Q16W basis as assigned by IxRS).

5.1.3.2 Treatment Interruption

Study drug may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If study drug has been withheld for >60 days from the date of the first missed dose, because of signs of persistent drug-induced toxicity or if the scheduled dose has been missed, the investigator should consult the Medical Monitor to determine if discontinuation from study drug is warranted. Study drug may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.3.3 Management Guidelines

Guidelines for management of specific AEs are outlined in Table 2. Additional guidelines are provided in the subsections below.

Initial clinical laboratory tests with results meeting criteria for withholding study drug must be repeated on new specimens as soon as possible, and results must be available prior to administering the next dose of study drug. In general, patients who do not reach the stopping rule may continue dosing; however, the investigator and Sponsor should confer as to whether additional close monitoring of the patient is indicated.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken
Elevations in CSF WBC count or proteins or suspected meningitis, radiculitis, arachnoiditis, hydrocephalus, or other acute neurologic symptoms	• Withhold study drug if diagnosis of meningitis, radiculitis, arachnoiditis, hydrocephalus, or acute neurologic symptoms is suspected and initiate appropriate diagnostic work-up as indicated. • Clinical signs and symptoms of hydrocephalus (e.g., new onset of persistent or worsening gait disturbance, change in level of consciousness/cognition, changes in continence, or a combination of all 3 signs) are required for diagnosis of suspected hydrocephalus. • Clinical signs and symptoms of meningitis (e.g., headache, stiff neck, fever) plus confirmatory WBC count are required for diagnosis of suspected meningitis; and clinical signs and symptoms are required for diagnosis of radiculitis, arachnoiditis, or acute neurologic symptoms. Isolated low-level (e.g., 5–50 μL WBC count) elevations in CSF WBC count without clinical symptoms does not meet criteria for diagnosis of suspected meningitis. • The Medical Monitor should be consulted in all cases where CSF WBC count elevations above 10/μL are present, or a change from baseline in CSF proteins greater than 2× baseline or where there is uncertainty to discuss next steps of patient management in the study. • If diagnosis of suspected meningitis, radiculitis, arachnoiditis, hydrocephalus, or other acute neurologic symptoms is refuted, the study drug may be resumed after consultation with the Medical Monitor. • In the event meningitis, radiculitis, arachnoiditis, hydrocephalus, or acute neurologic symptom diagnosis is confirmed, standard of care therapies should be instituted as indicated.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Thrombocytopenia	• If platelet count is ≤100,000/mm^3: – Monitor platelet count weekly. • If platelet count is ≤75,000/mm^3 and >50,000/mm^3 in the absence of major bleeding or clinically relevant non-major bleeding: – Withhold study drug until the platelet count has recovered to >100,000/mm^3. – The suitability of the patient for continued dosing and frequency of monitoring should be discussed with the Medical Monitor. • If platelet count is ≤50,000/mm^3: – Permanently discontinue study drug. – Monitor platelet counts daily until two successive values show improvement. Then monitor every 2–3 days until platelet count is stable, and at least weekly until platelet count returns to normal. • Treatment per standard of care should be considered for patients whose platelet count is <25,000/mm^3.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Decreased renal function	• Withhold study drug in the event of a persistent (>2 weeks) decrease in eGFR or CrCl or increase in creatinine, as defined below: – eGFR or CrCl (using Cockcroft-Gault) <60 mL/min. – Creatinine level increase of 2.0× above baseline. – Study drug may be resumed when follow-up test results show that the patient no longer meets the dose interruption criteria.
Elevated liver enzymes	• ALT or AST is >3×ULN: – Monitor weekly until ALT and AST return to ≤1.2×ULN. – Further investigation into the liver enzyme elevations may include hepatitis serologies and other diagnostic tests at the discretion of the investigator in consultation with the Medical Monitor. • Withhold study drug in the event of liver enzymes that meet the following criteria without an alternative explanation (as discussed with the Medical Monitor): – ALT or AST >5×ULN. – ALT or AST >3×ULN, combined with total bilirubin >2× ULN or INR >1.5. – ALT or AST >3× ULN coinciding with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia. – Discontinue study drug permanently if levels do not return to baseline after 30 days.

CrCl=creatinine clearance; CSF=cerebrospinal fluid; eGFR=estimated glomerular filtration rate; ULN=upper limit of normal.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including serious adverse events (SAEs) and adverse events of special interest (AESIs), performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms ″severe″ and ″serious″ are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as LP) should be reported (see Section 5.4.2 for instructions for reporting SAEs).

After initiation of study drug, all adverse events will be reported until 5 months after the final dose of study drug.

Instructions for reporting AEs that occur after the AE reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

″How have you felt since your last clinic visit?″

″Have you had any new or changed health problems since you were last here?″

5.3.3 Assessment of Severity of Adverse Events

The Adverse Event Severity Grading Scale indicated in Table 3 provides guidance for assessing AE severity. Laboratory values determined as an AE should be graded as per Appendix 10, which is based on the NCI CTCAE (v5.0).

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating ″yes″ or ″no″ accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only 1 AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of IT bolus-related reaction or anaphylactic reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For AEs other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from ″non-serious″ to ″serious,″ providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., ″elevated potassium,″ as opposed to ″abnormal potassium″). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as ″hyperkalemia.″

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent AEs).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3×ULN) in combination with either an elevated total bilirubin (>2×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST >3×ULN in combination with total bilirubin >2×ULN
- Treatment-emergent ALT or AST >3×ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event); either as a SAE or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of HD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of HD, "Huntington's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the AE reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the inclusion visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the

preexisting condition has changed by including applicable descriptors (e.g., ″more frequent headaches″).

5.3.5.10 Lack of Efficacy or Worsening of Huntington's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or a SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an AE.

An event that leads to hospitalization under the following circumstances is not considered to be a SAE, but should be reported as an AE instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

5.3.5.12 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as ″special situations″), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves AEs, but may result in AEs.
Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should

be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For RO7234292, AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the AE term. Check the ″Accidental overdose″ and ″Medication error″ boxes.
- Medication error that does not qualify as an overdose: Enter the AE term. Check the ″Medication error″ box.
- Medication error that qualifies as an overdose: Enter the AE term. Check the ″Accidental overdose″ and ″Medication error″ boxes.

In addition, all special situations associated with RO7234292, regardless of whether they result in an AE, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and ″accidental overdose″ as the event term. Check the ″Accidental overdose″ and ″Medication error″ boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the ″Medication error″ box.
- Medication error that qualifies as an overdose: Enter the drug name and ″Accidental overdose″ as the event term. Check the ″Accidental overdose″ and ″Medication error″ boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and ″Intercepted medication error″ as the event term. Check the ″Medication error″ box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The ″Accidental overdose″ and ″Medication error″ boxes would need to be checked on both eCRF pages.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived by the Sponsor from PRO or digital wearable device (HD mobile app) data, and safety analyses will not be performed using PRO or digital wearable device data. Sites are not expected to review the PRO or digital wearable device data for AEs.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local HA and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, SAEs and AESIs will be reported until 5 months after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting SAEs that occur >5 months after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 5 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In

addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For SAEs, AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any SAE that occurs after the end of the AE reporting period (defined as 5 months after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable HAs based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference document:

- RO7234292 Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 ANALYSIS POPULATIONS

The intent-to-treat (ITT) population will consist of all patients who received any study treatment. Randomized patients who received incorrect therapy from that intended will be summarized in the group according to their planned randomized treatment.

The ITT population will be the primary population for all analyses of efficacy and biomarker variables.

The safety population will consist of all patients who received any study treatment. The safety population will be the primary population for all safety analyses. For the purpose of all safety analyses, it will be assessed whether patients received a treatment different from the one they were randomized to at any time during the course of the study. In case the number and duration of such ″treatment switches″ warrants it, the safety population may be redefined by reallocating individual patients to the treatment actually received, as opposed to which treatment they were randomized to.

6.2 DETERMINATION OF SAMPLE SIZE

The sample size for this study is determined by the number of patients from preceding studies who may be eligible for enrollment in this study and is estimated to be up to approximately 1100 patients.

6.3 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll in the study, discontinue from the study, and complete the study will be summarized overall and by treatment arm. Reasons for premature study withdrawal will be listed and summarized.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. The Adverse Event Severity Grading Scale (see Section 5.3.3) will be used for assessing AE severity. Laboratory values determined as an AE should be graded as per Appendix 10, which is based on the NCI CTCAE (v5.0).

All safety data, including AEs, laboratory tests, neurologic examination, C-SSRS, MoCA, ECG, and vital signs, will be reported in individual listings and summarized by treatment for each assessment time using descriptive statistics. For continuous variables, both the original value as well as the change from baseline will be reported.

The incidence of AEs will be summarized on the basis of body systems and dictionary preferred terms. The incidence of AEs by severity and relationship to study drug or study procedure and incidence of marked abnormal laboratory test results will be provided.

6.6 EXPLORATORY EFFICACY ANALYSES

The efficacy endpoints will be summarized by treatment arm for each assessment time using summary tables, in terms of both absolute values and change from baseline.

Additional statistical modeling may be considered and will eventually be specified in the Statistical Analysis Plan (SAP).

6.7 EXPLORATORY PHARMACOKINETIC ANALYSES

The PK population will include all patients who received at least 1 dose of RO7234292 and had sufficient sampling to permit PK evaluation.

For patients in the PK population, CSF and plasma concentrations of RO7234292 will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation. Nonlinear mixed-effects modeling will be used to analyze the concentration–time data for RO7234292 in CSF and plasma following IT administration. A covariate analysis will be conducted to evaluate the effect of covariates such as body weight, age, and sex on RO7234292 exposure. Population and individual estimates of primary PK parameters (e.g., clearance, distribution volume) and secondary PK parameters (e.g., average trough plasma concentration) will be computed and used to explore the exposure-response relationship on selected endpoints, as well as safety measures. The data from this study may be pooled with data from other studies conducted with RO7234292 to support the population PK/PD modeling.

Details of this mixed-effects modeling and exploration of exposure-response analysis and results will be described and reported in a document separate from the Clinical Study Report.

6.8 EXPLORATORY IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received. The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) will be summarized by treatment group. For those who are ADA-positive, titers will be estimated, as well as antibody subtype. In addition, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized.

When determining post-baseline incidence, patients are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of one or more post-baseline samples is at least is at least 4-fold greater than the titer of the baseline sample (treatment-enhanced ADA

response). Patients are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

6.9 EXPLORATORY BIOMARKER ANALYSES

The biomarker endpoints will be summarized by treatment arm for each assessment time using summary tables, in terms of both absolute values and change from baseline.

Additional statistical modeling may be considered and will eventually be specified in the SAP.

6.10 HEALTH STATUS UTILITY ANALYSIS

The health status utility endpoints will be summarized using tables, listings, and graphs, as appropriate. Additional statistical modeling may be considered.

6.11 OPTIONAL INTERIM ANALYSES

The Sponsor may choose to conduct one or more interim analyses including safety, PK, PD biomarkers and clinical endpoints as relevant. Details of each interim analysis will be described in a dedicated SAP, which will be finalized before the conduct of the interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, electronic data from clinic visits (see Section 7.3) and electronic data obtained from the Roche HD mobile app (see Section 7.4) will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

Electronic Case Report Forms and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Patient-reported outcome, ClinRO, and PerfO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. Electronic Case Report Forms will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff.
Electronic Case Report Forms should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED, CLINICIAN-REPORTED, AND PERFORMANCE OUTCOME DATA

An electronic device will be used to capture in-clinic PRO, ClinRO, and PerfO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure vendor web portal. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 ELECTRONIC DATA OBTAINED BY THE ROCHE HD DIGITAL MOBILE APPLICATION

During ″active tests″ and ″passive monitoring,″ the smartphone and wrist-worn wearable records movement and location data. Data on the technical status and connectivity of the devices is also recorded. Patients can choose to pause location data recording. No patient identifiable information is stored on the devices. For selected ″active test″ tasks, touch and sound is also recorded. Video is not recorded.

Roche HD mobile app (smartphone and wrist-worn wearable) sensor data are encrypted and uploaded to secure servers whenever the smartphone is connected to Wifi.
All sensor data will be managed by the Sponsor who will monitor and ensure the integrity and quality of the acquired data. This includes, but is not limited, to the analysis of sensor data together with protocol-specified assessments and activities associated with routine daily living. The data will not be analyzed for efficacy until study end, unless they are chosen to be a part of a pre-specified interim analysis along with other clinical and/or biomarker endpoints.

7.5 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.7.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable HAs.

7.6 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with HA requirements pertaining to computerized systems used in clinical research.
An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit

trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.7 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO, PerfO, and ClinRO data (if applicable), ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local HAs, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor.
Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local HAs, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the U.S. or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the ″Consent Forms″) before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for HA submission purposes according to local requirements.

If applicable, the ICF will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods,

and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. If the legally authorized representative signs the Consent Form with the patient, the patient will still need to provide assent in the case he/she is no longer capable of providing consent. Assent implies willingness or, minimally, lack of objection to taking part and will need to be documented by the site. (Note: Patients in Germany who are not fully capable of providing informed consent are not eligible for participation).

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for HA submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study. If the legally authorized representative signs the Consent Form for the patient, the patient will still need to provide assent in the case that he/she is no longer fully capable of providing consent. (Note: Patients in Germany who are not fully capable of providing informed consent are not eligible for participation).

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the U.S., each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local HA and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with HA requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy in the study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local HAs, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and

used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. Linking of data will be facilitated by the HDID number (see Section 4.5.2). The HDID is a unique coded identifier for persons participating in studies in HD. This HDID will stay the same for a person throughout all trials. The use of the unique identifier will assure that people are only enrolled once in large observational studies like ENROLL-HD, REGISTRY, COHORT, PREDICT-HD, and TRACK-HD and will also allow approved comparison and combination of data between studies. The HDID is a 9-digit number created by a secure one-way algorithm, based on unchanging information (date of birth, birth name, place of birth, and mother's maiden name). The identifying data are used for the split second needed by the algorithm needed to generate the HDID and are never stored electronically on the web portal or in the study database. It is expected that patients from preceding studies have a pre-existing HDID number. For patients without a pre-existing HDID number in the source notes, the investigator should store the original data and the newly generated HDID in the patient's source documents and in the investigator file. The HDID can be generated within the web portals of the observational studies or in the specially defined portal for the HDID generation under:

https://hdid.enroll-hd.org.

In addition, redacted Clinical Study Reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate HAs. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess

whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to HAs. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., AE rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local HAs; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 100 sites globally will participate to enroll up to approximately 1100 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details) and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a Marketing Authorization Application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a Marketing Authorization Application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening

	Inclusion Visit [a]	Treatment Period [b]	EoT [c]	SFU [d]
Week	Last applicable visit of preceding study [a]	Treatment and Assessment Frequency	+4 weeks	+20 weeks
Day (Window)		±1 week [e]	±1 week	±1 week
Signed informed consent [f]	x			
Review of inclusion and exclusion criteria	x			
Demographic data	x			
Medical history and baseline conditions [g]	x			
Vital signs [h]	x [i]	At each clinic visit	x	x
Complete physical examination [j]	x [i]	Q32W	x	x
Neurologic examination [l]	x [i]	At each clinic visit (see Appendix 12)	x	x
ECG [m]	x [i]	Q32W	x	x
Hematology [n]	x [i]	At each clinic visit	x	x
Chemistry [o]	x [i]		x	x
Pregnancy test [p]	x [i]		x	x
Urinalysis [q]	x [i]		x	x
Local PT and/or INR, aPTT, platelet count [s]	x [i]	At each study drug administration visit	x	x

Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening (cont.)

	Inclusion Visit [a]	Treatment Period [b]	EoT [c]	SFU [d]
Week	Last applicable visit of preceding study [a]	Treatment and Assessment Frequency	+4 weeks	+20 weeks
Day (Window)		±1 week [e]	±1 week	±1 week
Plasma sampling for PK [r]	x [i]	Q16W for 48 weeks and then Q32W thereafter		
Plasma sampling for immunogenicity testing [r]	x [i]		x	x
Plasma samples for biomarkers	x [i]		x	x
CSF sample for PK/safety/biomarkers [s]	x [i]	At each study drug administration	x	
MoCA	x [i]	Q16W	x	
C-SSRS [t]	x [i]	At each study drug administration	x	
Mandatory Structural MRI [u]	x [i]	Q32W [k]	x	
Optional resting-state functional MRI and diffusion-weighted MRI / NODDI [u]	x [i]	Q32W [k]	x	
Optional MRI brain and spine with contrast media for patients from Study BN40697 [v]	x	Q32W	x	

Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening (cont.)

	Inclusion Visit [a]	Treatment Period [b]	EoT [c]	SFU [d]
Week	Last applicable visit of preceding study [a]	Treatment and Assessment Frequency	+4 weeks	+20 weeks
Day (Window)		±1 week [e]	±1 week	±1 week
HD-DAS	x [i]	Q16W	x	
TFC [w]	x [i]		x	
TMS [w]	x [i]		x	
CGI-S	x [i]		x	
CGI-C			x	
SDMT [w]	x [i]		x	
SWR [w]	x [i]		x	
Roche HD mobile app	x [i]	Continuous remote data collection, as well as Q16W in-clinic [x]	x	
EQ-5D-5L	x	At each study drug administration [y]	x	
Q8W study drug administration [s, cc]	x	Q8W		
Q16W study drug administration [s, cc]	x	Q16W		
Telephone Safety follow-up [z]		Q8W: Q8W (alternating with in-clinic visits) for 1 year Q16W arm: Q8W (alternating with in-clinic visits) for 1 year; then Q16W		
Concomitant medications [aa]	x	Each clinic visit and telephone safety follow-up call	x	x
Adverse events [bb]	x	Each clinic visit and telephone safety follow-up call	x	x

Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening (cont.)

CGI-C=Clinical Global Impression, Change; CGI-S=Clinical Global Impression, Severity; C–SSRS=Columbia-Suicide Severity Rating Scale; CSF=cerebrospinal fluid; cUHDRS=composite Unified Huntington's Disease Rating Scale; eCRF=electronic Case Report Form; EoT=end-of-treatment; EQ-5D-5L=EuroQol 5-Dimension, 5 Level Questionnaire; HD=Huntington's disease; HD-DAS=HD Daily Activities Scale; LP=lumbar puncture; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; NODDI=Neurite Orientation Dispersion and Density Imaging; PK=pharmacokinetic; SDMT=Symbol Digit Modalities Test; SFU=safety follow-up; SWR=Stroop Word Reading; TFC=Total Functional Capacity Scale; TMS=Total Motor Score; Q8W=every 8; Q16W=every 16 weeks; Q32W=every 32 weeks.

Notes: All assessments should be performed at the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Inclusion visit should be the last applicable visit of the preceding study as defined in Section 3.1.1. For patients entering from Study BN40423 prior to implementation of Protocol Version 4, the inclusion visit should occur at the end-of-treatment visit for Study BN40423. For patients entering from Study BN40697, in the event of any delay in start-up activities where it is not possible to conduct the inclusion visit at the time of the last applicable visit in Study BN40697, a separate inclusion visit should be scheduled 4 weeks or 8 weeks (±1 week) for a patient previously treated Q4W or 8 weeks (±1 week) later for a patient previously treated Q8W.

[b] If dosing at the inclusion visit is not possible, the Medical Monitor should be consulted and a short treatment interruption may be permitted.

[c] Patients who complete treatment (e.g., will continue treatment on commercially available drug) or who discontinue study drug prematurely will return to the clinic for a treatment completion visit 4 weeks (±7 days) after the decision to discontinue. For patients continuing treatment with RO7234292 outside of the study, the end of study visit should occur before the patient's next dose of RO7234292.

[d] Safety follow-up visit occurs +20 weeks after EoT.

[e] Excluding MRIs, which have a visit window of −14 to − 7 days.

[f] Informed consent must be documented before any Study BN40955–specific procedure is performed and may be obtained up to 12 weeks before initiation of Study BN40955 study treatment.

[g] Medical history, including clinically significant diseases, surgeries, and reproductive status, will be recorded at baseline (inclusion visit).

[h] Vital signs include respiratory rate, pulse, temperature, and systolic and diastolic blood pressure while the patient is in a seated position after resting for at least 5 minutes. Record abnormalities observed at the inclusion visit on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening (cont.)

[i] Assessments do not need to be repeated if completed as part of the last visit in the preceding study and the inclusion visit occurs at the last visit in the preceding study. If the inclusion visit is delayed (see footnote "[a]"), then the following assessments should be repeated: vital signs; complete physical examination; neurologic examination; ECG; hematology; chemistry; pregnancy test; local PT and/or INR, aPTT, platelet count; urinalysis; plasma sample for PK/immunogenicity/biomarkers; CSF sample for PK/safety/biomarkers; C-SSRS; and any clinical outcome assessments (i.e., HD-DAS, TFC, TMS, CGI-S, SDMT, SWR) that were not completed at the last visit in the preceding study.

[j] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. The physical examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations, including weight. Any abnormality identified at baseline (inclusion visit) should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related change) should be recorded as adverse events on the Adverse Event eCRF. Height will be obtained from preceding study.

[k] For patients who are already enrolled in this study who previously had an MRI before they transitioned to the new dosing regimen, the scheduled post-inclusion visit MRI should be calculated from the date of the inclusion visit. As the 32-week time point for MRI collection have been reached for patients from Study BN40697 prior to approval of Study BN40955 Protocol v4.0, these patients will have their Week 48 MRI collected then follow the 32-weekly schedule thereafter. For example: MRI will be collected at Week 49, followed by Week 65 and Week 97. Patients from Study BN40423 (enrolled prior to Study BN40423 protocol Versions 4) who have reached or have passed the 32-week visit schedule prior to Study BN40955 Protocol v4.0 approval at site will have unscheduled MRI at the next clinic visit once the site is active on Protocol v4.0 then continue with the 32-weekly schedule thereafter. For example: unscheduled MRI (next clinic visit following protocol being active at site), then followed by Week 65 and Week 97. Patients from Study BP40410 who have completed inclusion visit prior to Study BN40955 Protocol v4.0 or to Study BP40410 v4.0 approval at site will have unscheduled MRI at the next clinic visit once the site is active on Study BN40955 Protocol v4.0 then continue with the 32-weekly schedule thereafter. For example: unscheduled MRI (next clinic visit following protocol being active at site), then followed by Week 33, Week 65, and Week 97.

Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening (cont.)

[l] A neurologic examination(including fundoscopy), performed at every clinical visit, should include assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, gait, and coordination. The neurologic examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations. Neurologic examinations should be performed before and after treatment on each dosing day*, or before the lumbar puncture, if there is no study treatment administration*. Weight should also be measured at each visit. Any abnormality identified at baseline (inclusion visit) should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation, normal age-related change or HD-related clinical progression) should be recorded as adverse events on the Adverse Event eCRF.

[m] Inclusion visit ECG is in accordance with the preceding study requirements. Subsequent ECGs should be a single ECG performed after the patient has been resting in a supine position for at least 10 minutes. Lead placement should be as consistent as possible. ECGs for each patient should be obtained from the same machine whenever possible. All ECGs are to be obtained prior to other invasive procedures scheduled at that same time (e.g., blood draws) and should not be obtained within 30 minutes after any meal.

[n] Hematology includes WBC count, RBC count, platelet count, hemoglobin, hematocrit, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[o] Serum chemistry panel includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, gamma-glutamyl transferase, and CPK.

[p] Baseline pregnancy test is in accordance with preceding study requirements. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination if clinically indicated (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[r] Pharmacokinetics and immunogenicity samples will be collected prior to dosing. *PK plasma samples are not required to be collected after the study treatment is paused. Immunogenicity plasma samples will continue to be collected.*

Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening (cont.)

[s] *While study dosing is paused, the CSF sample for safety/biomarkers and local PT and/or INR, aPTT and Platelet count will be collected every 16 weeks for all patients. Details about the lumbar puncture schedule are addressed in Appendix 2b. CSF sample for PK analysis is not required after the treatment is paused.* Within 72 hours prior to performing each scheduled LP, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed. Collection for these local laboratory tests may occur at any time in the 72 hours prior to the LP. The LP should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 p.m. or in the early afternoon between 12:00 p.m. and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. Cerebrospinal fluid (20 mL) is to be collected for analyses using a LP collection kit. If there are difficulties in collecting 20 mL of CSF, a minimum of 5 mL should be collected over a maximum of 60 minutes, once CSF flow has been established. If only 5 mL is collected after 60 minutes, the operator must confirm CSF flow is present prior to injecting drug at 60 minutes. A 24G atraumatic needle, as specified in the LP procedure and CSF collection guidelines, should be used. Depending on institutional guidelines, local anesthesia should be used for the procedure. Sedation may not be used. Spinal ultrasound may be used for the LP procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at LP without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each LP. Fluoroscopy guidance can also be used, if local institutional guidelines dictate and local IRB/ECs and health authorities have approved the use of the technique, but it is not required. Where fluoroscopy is used, patients should also be informed and consent obtained. Patients will be discouraged from resting supine after the LP procedure and will be encouraged to mobilize immediately by walking around at a minimum and, if feasible, walking briskly for approximately 30 minutes. Patients should not perform any activity that is associated with a change in the ambient air pressure for at least 24 hours *post LP procedure* (e.g., air travel, scuba diving, or hot air balloons). In case of a failed IT bolus dosing procedure (e.g., due to an inadequate establishment of access to the IT space), a second dosing attempt may occur up to 7 days after the originally scheduled dosing attempt. For this additional visit, safety and tolerability evaluations on the day of LP administration will be performed as detailed in Appendix 1a, including neurological examination (predose and postdose), vital signs, and a review of adverse events and concomitant medication. If the second dosing attempt occurs more than 72 hours after the last coagulation panel and platelets test, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets need to be conducted again and results reviewed prior to the LP attempt. For patients entering from Study BN40697, the drug administered at the inclusion visit will be the last dose of Study BN40697 unless the visit is delayed as described in footnote "[a]," in which case it will be the first dose in Study BN40955. For patients entering from Study ML41885, the drug administered at the inclusion visit will be the first dose in Study BN40955. For all other patients, the first dose in Study BN40955 will take place at the inclusion visit.

[t] The C-SSRS will be used to monitor the patients throughout the study at clinic visits (follow-up version, requiring approximately 5 minutes to administer, assuming absence of suicidal ideation and no change in clinical status from previous administration). *C-SSRS will continue to be performed as per the original schedule even if the study drug administration is paused.*

Appendix 1a
Schedule of Activities for All Patients Except Those Undergoing Screening (cont.)

[u] Magnetic resonance imaging must be scheduled to occur before the LP. The MRI scan should be performed 7–14 days prior to the LP to allow time for re-scanning if the quality of the initial MRI is inadequate. If the re-scan cannot be performed prior to the LP, then it can be conducted the day after the LP, as long as there are no post-LP contraindications and it occurs within 2 weeks of the original scan.

[v] Optional MRI of brain and spine with contrast media will be completed upon study entry or upon transition to the new regimen and then every 32 weeks thereafter. This only applies to patients enrolling from Study BN40697.

[w] The cUHDRS is a composite motor, cognitive, and global functional clinical outcome measure in patients with HD comprised of the TFC, the TMS, the SDMT, and the SWR scores.

[x] The electronic devices for remote data collection will be the same devices from the preceding study where possible. Devices must be returned to the clinic at the end of the study or upon early termination from the study. If patients did not have a preconfigured smartphone and wrist-worn wearable in the preceding study, they will not be provided devices in this study.

[y] The EQ-5D-5L will only be completed in-clinic at each study drug administration visit and in cases where the Roche HD mobile device has reached the end of its lifespan or been lost. If the EQ-5D-5L collection was duplicated in error (i.e., collected in Roche HD mobile app and site electronic device) during the study drug administration visit, the EQ-5D-5L data collected in the site electronic device will take precedence. *The EQ-5D-5L will continue to be performed as per the original schedule even if the study drug administration is paused.*

[z] Telephone safety follow-up will be conducted Q8W (alternating with in-clinic visits) for 1 year for all patients, and then Q16W in between study administration visits for Q16W arm to check for any change in patient status (e.g., adverse events and concomitant medications) since their last visit and depending on patient's health status. An unscheduled clinic visit may be arranged, if needed. If a patient is due for a telephone safety call and they are in-clinic then this telephone safety follow-up call can be completed in-clinic at the site's discretion. As a result of the COVID-19 pandemic, only where sites are impacted, these telephone safety calls can be conducted instead of an in-clinic visit.

[aa] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from the time of entry into Study BN40955 to the study completion/discontinuation visit.

[bb] After initiation of study drug at baseline (inclusion visit), all adverse events will be reported until 5 months after the final dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment.

[cc] *Effective 22 March 2021, Q8W and Q16W study drug administration is paused.*

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic

	Screening [a]	Inclusion visit		Treatment Period	EoT [b]	SFU [bb]
Week	–4 to –1	1		Treatment Assessment and Frequency	±4 weeks	±20 weeks
Day (Window)	–28 to –2	–1	1	±1 week [v]	±1 week [v]	±1 week
Signed informed consent [c]	x					
Review of inclusion and exclusion criteria	x	x				
Demographic data	x					
Medical history and baseline conditions [d]	x	x [e]				
Blood sample for CAG repeat length [a]	x					
Viral serology [f]	x					
Thyroid panel [g]	x					
Vital signs [h]	x	x [e]		At each clinic visit	x	x
Complete physical examination [i]	x	x [e]		Q32W	x	x
Neurologic examination [j]	x	x [e]		At each clinic visit (see Appendix 9)	x	x
ECG [k]	x	x [e]		Q32W	x	x

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic (cont.)

	Screening [a]	Inclusion visit		Treatment Period	EoT [b]	SFU [bb]
Week	−4 to −1	1		Treatment Assessment and Frequency	±4 weeks	±20 weeks
Day (Window)	−28 to −2	−1	1	±1 week [v]	±1 week [v]	±1 week
Hematology [l]	x	x		At each clinic visit	x	x
Chemistry [m]	x	x			x	x
Pregnancy test [n]	x	x [e]			x	x
Urinalysis [o]	x	x			x	x
Local PT and/or INR, aPTT, Platelet count [x, u]		x		At each study drug administration visit	x	x
Plasma sample for PK [p]			x	Q16W for 48 weeks and then Q32W thereafter		
Plasma sample for immunogenicity testing [p]			x		x	x
Plasma sample for biomarkers			x		x	x
CSF sample for PK/safety/biomarkers [u]			x	At each study drug administration	X	
Mandatory Structural MRI [q]	x			Q32W	x	
Optional resting-state functional MRI and Diffusion-weighted MRI/NODDI [r]	X			Q32W	x	
Independence Scale	x					
MoCA	x		x	Q16W	x	
C-SSRS [r]	x	x [e]		At each study drug administration	x	

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic (cont.)

	Screening [a]	Inclusion visit		Treatment Period	EoT [b]	SFU [bb]
Week	−4 to −1	1		Treatment Assessment and Frequency	±4 weeks	±20 weeks
Day (Window)	−28 to −2	−1	1	±1 week [v]	±1 week [v]	±1 week
HD-DAS			X	Q16W	x	
TFC [s]			x		x	
TMS [s]	x		x		x	
CGI-S			x		x	
CGI-C					x	
SDMT [s]			x		x	
SWR [s]			x		x	
EQ-5D-5L [w]			x	At each study drug administration	x	
Roche HD mobile app	x		x	Continuous remote data collection, as well as Q16W in-clinic [t]		
Q8W Study drug administration [u, cc]			x	Q8W		
Q16W Study drug administration [u, cc]			x	Q16W		

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic (cont.)

	Screening [a]	Inclusion visit		Treatment Period	EoT [b]	SFU [bb]
Week	−4 to −1	1		Treatment Assessment and Frequency	±4 weeks	±20 weeks
Day (Window)	−28 to −2	−1	1	±1 week [v]	±1 week [v]	±1 week
Telephone Safety follow-up [x]				Q8W arm: Q8W (alternating with in-clinic visits) for 1 year Q16W arm: Q8W(alternating with in-clinic visits) for 1 year, then Q16W		
Concomitant medications [y]	x	x	x	Each clinic visit and telephone safety follow-up call	x	x
Adverse events [z]	x	x	x	Each clinic visit and telephone safety follow-up call	x	x

CAG=cytosine, adenine, and guanine; CGI-C=Clinical Global Impression, Change; CGI-S=Clinical Global Impression, Severity; CSF=cerebrospinal fluid; C−SSRS=Columbia-Suicide Severity Rating Scale; cUHDRS=composite Unified Huntington's Disease Rating Scale; DCL=diagnostic confidence level; eCRF=electronic Case Report Form; EoT=end-of-treatment; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; HA=health authority; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HD=Huntington disease; HD-DAS=HD Daily Activities Scale; IRB/EC=Institutional Review Board/Ethics Committee; LP=lumbar puncture; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; NODDI=Neurite Orientation Dispersion and Density Imaging; PK=pharmacokinetic; Q8W=every 8 weeks; Q16W=every 16 weeks; Q32W=every 32 weeks; SDMT=Symbol Digit Modalities Test; SFU=safety follow-up; SWR=Stroop Word Reading; TFC=Total Functional Capacity Scale; TMS=Total Motor Score.

Notes: All assessments should be performed at the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic (cont.)

[a] A maximum of 1 re-screening will be allowed within 8 weeks of the initial screening failure for patients who fail the initial screening (e.g., as a consequence of abnormal laboratory values or general medical status not meeting inclusion or exclusion criteria). The CAG repeat length testing from Q2 Solutions will be accepted for this study. If re-screening is required, the CAG repeat length testing from Q2 Solutions does not need to be repeated. The screening MRI and viral serology from the initial screening may be acceptable as part of the re-screening assessments, if performed within 12 weeks of the inclusion visit.

[b] Patients who complete treatment (e.g., will continue treatment on commercially available drug) or who discontinue study drug prematurely will return to the clinic for a treatment completion visit 4 weeks (±7 days) after the decision to discontinue. For patients continuing treatment with RO7234292 outside of the study, the end of study visit should occur before the patient's next dose of RO7234292.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[d] Medical history, including clinically significant diseases, surgeries, reproductive status, will be recorded at screening and at baseline (inclusion visit).

[e] Assessments may take place on Day −1 or Day 1.

[f] Viral serology: HBsAg and HCV antibody (or viral RNA if HCV antibody assay is positive).

[g] Thyroid panel: thyroid-stimulating hormone and free thyroxine (also known as T4) levels.

[h] Vital signs include respiratory rate, pulse, temperature, and systolic and diastolic blood pressure while the patient is in a seated position after resting for approximately 5 minutes. Record abnormalities observed at screening and at the inclusion visit on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. The physical examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations, including weight. Any abnormality identified screening and at baseline (inclusion visit) should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related change) should be recorded as adverse events on the Adverse Event eCRF. Height will be obtained from screening and inclusion visit only.

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic (cont.)

[j] A neurologic examination (including fundoscopy), performed at every clinical visit, should include assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, gait, and coordination. The neurologic examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations. Neurologic examinations should be performed before and after treatment on each dosing day, *or before the lumbar puncture, if there is no study treatment administration*. Weight should also be measured at each visit. Any abnormality identified at screening and baseline (inclusion visit) should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation, normal age-related change or HD-related clinical progression) should be recorded as adverse events on the Adverse Event eCRF.

[k] Electrocardiograms should be triplicate at screening and subsequent ECGs should be a single ECG performed after the patient has been resting in a supine position for at least 10 minutes. Lead placement should be as consistent as possible. Electrocardiograms for each patient should be obtained from the same machine whenever possible. All ECGs are to be obtained prior to other invasive procedures scheduled at that same time (e.g., blood draws) and should not be obtained within 30 minutes after any meal.

[l] Hematology includes WBC count, RBC count, platelet count, hemoglobin, hematocrit, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[m] Serum chemistry panel: includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, gamma-glutamyl transferase, and CPK.

[n] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination for all abnormal dipstick results (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[p] Pharmacokinetics and immunogenicity samples will be collected prior to dosing. *PK plasma samples are not required to be collected after the study treatment is paused. Immunogenicity plasma samples will continue to be collected*.

[q] Magnetic resonance imaging should take place as early as possible within the screening window but may take place at any time during screening. The MRI safety and efficacy screening scan will need to pass the central laboratory image quality control check and the results must be available before the patient can be enrolled in the study. Magnetic resonance imaging must be scheduled to occur before the LP. The follow-up MRI scan should be performed 7–14 days prior to the LP to allow time for re-scanning if the quality of the initial MRI is inadequate. If the re-scan cannot be performed prior to the LP, then it can be conducted the day after the LP, as long as there are no post-LP contraindications and it occurs within 2 weeks of the original scan.

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic (cont.)

[r] The C-SSRS will be used to assess eligibility for the study (full version at screening, requiring approximately 20 minutes to administer) and to monitor the patients throughout the study at clinic visits (follow-up version, requiring approximately 5 minutes to administer, assuming absence of suicidal ideation and no change in clinical status from previous administration). *C-SSRS will continue to be performed as per the original schedule even if the study drug administration is paused.*

[s] The cUHDRS is a composite motor, cognitive, and global functional clinical outcome measure in patients with HD comprised of the TFC, the TMS, the SDMT, and the SWR scores.

[t] The electronic devices for remote data collection will be supplied to patients at screening and must be returned to the clinic in cases where the patient does not meet eligibility criteria, at the end of the study, or upon early termination from the study.

[u] *While study dosing is paused, the CSF sample for safety/biomarkers and local PT and/or INR, aPTT and Platelet count will be collected every 16 weeks for all patients. Details about the lumbar puncture schedule are addressed in Appendix 2b. CSF sample for PK analysis is not required after the treatment is paused.* Within 72 hours prior to performing each scheduled LP, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed. Collection for these local laboratory tests may occur at any time in the 72 hours prior to the LP. The LP should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 p.m. or in the early afternoon between 12:00 p.m. and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. Cerebrospinal fluid (20 mL) is to be collected for analyses using a LP collection kit. If there are difficulties in collecting 20 mL of CSF, a minimum of 5 mL should be collected over a maximum of 60 minutes, once CSF flow has been established. If only 5 mL is collected after 60 minutes, the operator must confirm CSF flow is present prior to injecting drug at 60 minutes. A 24G atraumatic needle, as specified in the LP procedure and CSF collection guidelines, should be used. Depending on institutional guidelines, local aesthesia should be used for the procedure. Sedation may not be used. Spinal ultrasound may be used for the LP procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at LP without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each LP. Fluoroscopy guidance can also be used, if local institutional guidelines dictate and local IRB/ECs and HAs have approved the use of the technique, but it is not required. Where fluoroscopy is used, patients should also be informed and consent obtained. Patients will be discouraged from resting supine after the LP procedure and will be encouraged to mobilize immediately by walking around at a minimum and, if feasible, walking briskly for approximately 30 minutes. Patients should not perform any activity that is associated with a change in the ambient air pressure for at least 24 hours *post LP procedure* (e.g., air travel, scuba diving, or hot air balloons). In case of a failed IT bolus dosing procedure (e.g., due to an inadequate establishment of access to the IT space), a second dosing attempt may occur up to 7 days after the originally scheduled dosing attempt. For this additional visit, safety and tolerability evaluations on the day of LP administration will be performed as detailed in Appendix 1b, including neurological examination (predose and postdose), vital signs, and a review of adverse events and concomitant medication. If the second dosing attempt occurs more than 72 hours after the last coagulation panel and platelets test, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets need to be conducted again and results reviewed prior to the LP attempt.

Appendix 1b
Schedule of Activities for Patients who were Eligible for the GENERATION-HD1 Study but not Randomized due to Logistical Challenges Resulting from the COVID-19 Pandemic (cont.)

[v] Excluding MRIs, which have a visit window of −14 to −7 days.

[w] The EQ-5D-5L will only be completed in-clinic at each study drug administration visit. *The EQ-5D-5L will continue to be performed as per the original schedule even if the study drug administration is paused.*

[x] Telephone safety follow-up will be conducted Q8W (alternating with in-clinic visits) for 1 year for all patients, and then Q16W in between study administration visits for Q16W arm to check for any change in patient status (e.g., adverse events and concomitant medications) since their last visit and depending on patient's health status. An unscheduled clinic visit may be arranged, if needed. If a patient is due for a telephone safety call and they are in-clinic then this telephone safety follow-up call can be completed in-clinic at the site's discretion. As a result of the COVID-19 pandemic, only where sites are impacted, these telephone safety calls can be conducted instead of an in-clinic visit.

[y] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from the time of entry into Study BN40955 to the study completion/discontinuation visit.

[z] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug at baseline (inclusion visit), all adverse events will be reported until 5 months after the final dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment.

[aa] Safety follow-up visit occurs +20 weeks after EoT.

[bb] The DCL will be assessed at screening only (i.e., without the full TMS assessment). The TMS scale will be assessed (excluding the DCL) at all other timepoints.

[cc] *Effective 22 March 2021, Q8W and Q16W study drug administration is immediately paused.*

Appendix 2a Visit Schedule for the First 2 Years of Treatment

Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Week	1	5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97
Q8W study drug administration [a]	x	P	x	P	x	P	x	P	x	P	x	P	x		x		x		x		x		x		x [b]
Q16W study drug administration [a]	x	P	CV	P	x	P	CV	P	x	P	CV	P	x		P		x		P		x		P		x [c]
Efficacy assessments	x				x				x				x				x				x				x [d]

CV=non-treatment clinic visit; P=phone call; Q8W=every 8 weeks; Q16W=every 16 weeks.

Notes: The non-treatment clinic visit includes collection of the following assessments during the first year of assignment to Q16W regimen: vital signs, neurologic examination, hematology, chemistry, pregnancy test, urinalysis, concomitant medications, and adverse events.

[a] *Q8W and Q16W study drug administration should be immediately paused until further assessments can be conducted following the release of the USM- DIL on March 22, 2021*

[b] Patients will continue Q8W dosing until end-of-treatment.

[c] Patients will continue alternating telephone safety follow-up and treatment visits until end-of-treatment.

[d] Patients will continue efficacy assessments Q16W throughout treatment period.

Appendix 2b Visit Schedule for the First 2 Years of Study Participation While on Treatment Pause

Month	***0***	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***	***12***	***13***	***14***	***15***	***16***	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***
Week	***1***	***5***	***9***	***13***	***17***	***21***	***25***	***29***	***33***	***37***	***41***	***45***	***49***	***53***	***57***	***61***	***65***	***69***	***73***	***77***	***81***	***85***	***89***	***93***	***97[a]***
Q8W [b, c]	***LP***	*P*	*NLP[d]*	*P*	***LP***	*P*	*NLP[d]*	*P*	***LP***	*P*	*NLP[d]*	*P*	***LP***		*NLP[d]*		***LP***		*NLP[d]*		***LP***		*NLP[d]*		***LP***
Q16W [e]	***LP***	*P*	*CV*	*P*	***LP***	*P*	*CV*	*P*	***LP***	*P*	*CV*	*P*	***LP***		*P*		***LP***		*P*		***LP***		*P*		***LP***

CV=non-treatment clinic visit; P=phone call; Q8W=every 8 weeks; Q16W=every 16 weeks; LP=clinic visit with lumbar puncture; NLP= clinic visit without lumbar puncture

Notes: The non-treatment clinic visit includes collection of the following assessments during the first year of assignment to Q16W regimen: vital signs, neurologic examination, hematology, chemistry, pregnancy test, urinalysis, concomitant medications, and adverse events.

[a] *All patients should continue performing the corresponding visits as described in Appendix 2b beyond the first 2 years.*

[b] *Q8W=patients randomized to Q8W and paused from receiving RO7234292 study drug following the USM-DIL (dated 22 March 2021).*

[c] *Patients who were randomized to Q8W study drug administration and paused from receiving RO7234292 study drug will continue to undergo clinic visits performing LP and alternate non LP (NLP) visits. At the LP visits, CSF sample for safety/biomarkers will be performed. Local PT and/or INR, aPTT, Platelet count and neurological examinations will be performed prior to LP only. CSF sample for PK and plasma for PK will not be required after study treatment was paused. Immunogenicity samples will continue to be collected.*

[d] *Non-LP visits will continue as described in Appendix 1a and Appendix 1b. CSF samples for PK/safety/biomarkers and local PT/and/or INR, aPTT and platelet count are not required at these visits. Neurological examinations should be performed at Non-LP visits.*

[e] *Q16W=patients randomized to Q16W and paused from receiving RO7234292 study drug following the USM-DIL (dated 22 March 2021)..*

Appendix 3 Clinician-Reported Outcomes

Assessment	Name	Items	Concepts	Approx. Duration	Timing
IS	Independence Scale	1	Functional Disability	3	Screening (for patients required to undergo screening only)
TFC	Total Functional Capacity Scale	5	Overall function	10 min	Inclusion visit, every 16 weeks, and EoT visit
TMS	Total Motor Score	31	Motor function	15 min	DCL only: screening (only for patients required to undergo screening) TMS without DCL: inclusion visit, every 16 weeks, and EoT visit
C-SSRS [a]	Columbia-Suicide Severity Scale	5	Suicidal ideation and behavior	20 min full version; 5 min follow-up version	Full version at screening in-clinic (only for patients required to undergo screening); Follow-up version at each study drug administration visit
CGI-S	Clinical Global Impression, Severity	1	Overall severity of patient status	2 min	Inclusion visit, every 16 weeks, and EoT visit
CGI-C	Clinical Global Impression, Change	1	Overall change in patient status	2 min	Every 16 weeks and EoT visit
HD-DAS	Huntington's Disease Daily Activities Scale	25	Daily function	25 min	Inclusion visit, every 16 weeks, and EoT visit

DCL=diagnostic confidence level; EoT=end-of-treatment; IS=Independence Scale.

[a] *C-SSRS will continue to be performed as per the original schedule even if the study drug administration is paused.*

Appendix 4 Patient-Reported Outcomes, Performance Outcomes, and Roche HD Mobile Application

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, PerfO, Behavior	Timing	Location
Roche HD mobile app	Roche HD mobile app with daily Active Test and Passive Monitoring	NA	Tasks (″active test″) that assess motor symptoms (upper and lower body movements, upper limb dexterity, voice) and non-motor symptoms (processing speed/voice); continuous passive monitoring	10	Sensor data, PRO, PerfO	Remote: up to daily Clinic visits: Inclusion visit, every 16 weeks, and EoT visit	Roche HD mobile app
EQ-5D-5L [a]	EuroQol 5-Dimension, 5-Level Questionnaire	6	Health utilities	5	PRO	Remote: up to weekly	Roche HD mobile app
						In-clinic: at each study drug administration visit	In-clinic
HD-SDI	Huntington's Disease, Speaking Difficulty Item	1	Speech	1	PRO	Remote: up to weekly	Roche HD mobile app [b]
MoCA	Montreal Cognitive Assessment	11	Overall cognitive status	10	PerfO	Screening (only for patients required to undergo screening), Inclusion visit, every 16 weeks, and EoT visit	In-clinic

Appendix 4 Patient-Reported Outcomes, Performance Outcomes, and Roche HD Mobile Application (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, PerfO, Behavior	Timing	Location
SDMT/ eSDMT	Symbol Digit Modalities Test	Max number in 90 seconds	Cognitive	5	PerfO	Inclusion visit, every 16 weeks, and EoT visit	In-clinic
						Remote: Up to weekly	Roche HD mobile app (eSDMT)
SWR/eSWR	Stroop Word Reading Test	Max numbers in 45 seconds	Cognitive	5	PerfO	Inclusion visit, every 16 weeks, and EoT visit	In-clinic
						Remote: Up to weekly	Roche HD mobile app (eSWR)
WHODAS 2.0	World Health Organisation Disability Assessment Schedule 2.0	15	Health-related quality of life	10	PRO	Remote: Monthly	Roche HD mobile app [b]
WPAI	Work Productivity and Activity Impairment	6	Work productivity	5	PRO	Remote: Monthly	Roche HD mobile app [b]

app=application; EoT=end-of-treatment; HD=Huntington disease; NA=not applicable; PerfO=performance outcome; PRO=patient-reported outcome.

[a] Complete during in-clinic visit at each study drug administration and in cases where Roche HD mobile has reached the end of its life span or has been lost. *EQ-5D-5L will continue to be performed as per the original schedule even if the study drug administration is paused.*

[b] Only applicable if previous study also used this remote assessment.

Appendix 5 Clinical Assessments Order and Duration for Patients Required to Undergo Screening Only

Table 1 Screening Visit Clinical Assessments

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Diagnostic Confidence Level [a] Independence Scale MoCA C-SSRS	~60	Qualified study physician

C-SSRS=Columbia-Suicide Severity Rating Scale; DCL=Diagnostic Confidence Level; MoCA=Montreal Cognitive Assessment; TMS=Total Motor Score.

[a] The DCL will be assessed at screening only (i.e., without the full TMS assessment). The TMS scale will be assessed (excluding the DCL) at all other timepoints.

Appendix 6 Diagnostic Confidence Level for Patients Required to Undergo Screening Only

The Diagnostic Confidence Level is calculated as shown below (from Unified Huntington's Disease Rating Scale [UHDRS] Total Motor Score [TMS] Scale, Item 17):

DIAGNOSIS CONFIDENCE LEVEL

To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a subject at risk for HD?

0=normal (no abnormalities)

1=non-specific motor abnormalities (less than 50% confidence)

2=motor abnormalities that may be signs of HD (50%–89% confidence)

3=motor abnormalities that are likely signs of HD (90%–98% confidence)

4=motor abnormalities that are unequivocal signs of HD (> 99% confidence)

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136–42.

Appendix 7 Clinical Assessments Order and Duration

Table 1 Clinical Assessments

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Huntington's Disease Daily Activities Scale TFC TMS C-SSRS [a] CGI-S CGI-C (not required at inclusion visit)	~60	Qualified study physician
Break (if needed)		~20–30	
2	MoCA SDMT SWR EQ-5D-5L	~20	Qualified study personnel
Break (if needed)		~20–30	
3	Roche HD mobile application	~20	Qualified study personnel

CGI-C=Clinical Global Impression, Change; CGI-S=Clinical Global Impression, Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; EQ-5D-5L=EuroQol 5-Dimension, 5 Level Questionnaire; MoCA=Montreal Cognitive Assessment; SDMT=Symbol Digit Modalities Test; SWR=Stroop Word Reading; TFC=Total Functional Capacity Scale; TMS=Total Motor Score.

[a] Collected at Screening (for patients required to undergo screening) then repeated at every study drug administration clinical visit. *C-SSRS will continue to be performed as per the original schedule even if the study drug administration is paused.*

Appendix 8 Remote Clinical Assessments Order and Duration (COVID-19 Impacted Sites where a Patient Cannot Attend the Clinic or the Investigator Site Has Closed due to Restrictions Imposed as a Result of COVID-19)

Table 1 Revised Assessment Schedule for Remote Data Collection (During COVID-19 Pandemic Only) Every Dosing Visit (for C-SSRS), 16 Weeks and EoT Visit

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Huntington's Disease Daily Activities Scale Total Functional Capacity Scale Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change	~60	Qualified study physician

Huntington's Disease Daily Activities Scale (HD-DAS) and Total Functional Capacity (Phone call)

- A phone call to the patient should be conducted by the study physician.
- The study physician should enter data for the scales directly onto the tablet, and for sites that use more than 1 tablet, must ensure that the appropriate tablet that has the patient data is used.

Columbia-Suicide Severity Rating Scale (via a phone interview with the patient)

- The study physician should also complete the Columbia-Suicide Severity Rating Scale (C-SSRS) on the tablet via a phone interview with the patient.
- This is a critical safety endpoint, and of particular importance in this population.

Clinical Global Impression scales

- The study physician should complete the Clinical Global Impression scales (using the tablet) following the phone calls for the other Block 1 assessments.

Symbol Digit Modalities Test, Stroop Word Reading, and Montreal Cognition Assessment

- For the Performance Outcomes in Block 2 (Symbol Digit Modalities Test [SDMT], Stroop Word Reading [SWR], and Montreal Cognition Assessment [MoCA]), currently these assessments should not be collected remotely.

Appendix 9 Roche HD Mobile Application: Active Test

The following tasks are part of the ″active tests″ conducted on the Roche Huntington's disease (HD) mobile application by the patient. This constitutes a comprehensive list; all patient-reported outcomes (PROs) (i.e., EuroQol 5-Dimension, 5-Level Questionnaire [EQ-5D-5L], Work Productivity and Activity Impairment [WPAI], HD Speaking Difficulty Item [HD-SDI], WHO Disability Assessment Schedule [WHODAS 2.0]) are not on all devices.

If a patient already has a preconfigured smartphone and wrist-worn wearable with installed software for the Roche HD mobile app assessments from the preceding study, they will continue to use these in this study. If patients did not have a preconfigured smartphone and wrist-worn wearable in the preceding study, they will not be provided devices.

Tasks take 5–10 minutes per day. If the patient does not complete the active test on a certain day, scheduled tasks that occur less frequently than every second day (i.e., EQ-5D-5L, WPAI, HD-SDI, 2-Minute Walk Test) are rolled over to the next time the active test is completed.

Daily Questions

Two daily single-item questions on mood and physical energy will be assessed, asking patients about their mood and physical health at the time they are performing the ″active tests.″ The assessments aim to capture daily mood fluctuations and will be used as a control for the other motor and cognitive assessments.

Cognitive Test (electronic Symbol Digit Modalities Test)

The Cognitive Test asks participants to match symbols with numbers according to a key as quickly and accurately as possible. The key, symbols, and numbers are all displayed on a smartphone screen. The test assesses visuomotor integration and measures visual attention and motor speed. It is modeled on the pen and paper Symbol Digit Modalities Test (SDMT; Smith 1968). The SDMT has been shown to be sensitive to symptom changes in patients with early HD (Tabrizi 2012) and is part of the Unified Huntington's Disease Rating Scale (UHDRS) assessment (Huntington’s Study Group, 1996).

Word Reading Test (eSWR)

The Word Reading Test asks participants to read aloud color words written in black font on a smartphone screen. Their voice will be recorded. The test assesses cognitive processing speed, and is modeled on the Stroop Word Reading (SWR) (Stroop 1935). The ″Word Reading″ part of the SWR Test has been shown to be sensitive to symptom changes in patients with early HD (Tabrizi 2012) and is part of the UHDRS assessment (Huntington’s Study Group 1996).

Speeded Tapping Test

The Speeded Tapping Test asks participants to tap the smartphone screen as fast and regularly as possible, using the index finger of both the left and right hands. The test assesses bradykinesia. Performance will also be impacted by chorea and dystonia. It is modeled on tapping tests shown to be sensitive to symptom changes in early HD (Bechtel et al. 2010; Tabrizi et al. 2012). A similar finger tapping task is also included as part of the UHDRS assessment (Huntington's Study Group 1996).

Draw a Shape Test

The Draw a Shape Test asks participants to trace a series of increasingly complex shapes on the smartphone screen. The shapes include lines, a square, a circle, an eight, and a spiral. This test is designed to assess visuomotor coordination and fine motor impairment in patients with early HD. It is modeled on circle tracing tasks that have been shown to be sensitive to symptom changes in early HD (Say et al. 2011; Tabrizi et al. 2013).

Chorea Test

The Chorea Test asks participants to hold the smartphone still in their hand with their arm outstretched, and wear the wrist-worn wearable. As a dual task, participants will also need to count backwards aloud. To ensure correct execution, voice will be recorded. The test is designed to assess chorea. It draws on other sensor-based approaches to measure chorea (Reilmann et al. 2010, 2011; Kegelmeyer et al. 2017). A chorea assessment is also part of the UHDRS (Huntington's Study Group 1996).

Balance Test

The Balance Test asks participants to stand still while wearing the smartphone and wrist-worn wearable. It is an assessment for patients' static balance function. Sensor-based approaches for measuring static balance have been shown to be sensitive to differences in symptoms in early HD (Dalton et al. 2013). The test is also part of established scales like the Berg Balance Scale (Berg et al. 1992), which are used in HD (Busse et al. 2009; Rao et al. 2009). The test is anchored to the UHDRS assessments for maximal dystonia, maximal chorea, and tandem walking (Huntington Study Group 1996).

U-Turn Test

The U-Turn Test asks participants to walk and turn safely between 2 points that are at least four steps apart, while wearing the smartphone and wrist-worn wearable. They need to make at least 5 turns. The test is designed to assess gait and lower-body bradykinesia, which are also assessed by the UHDRS. It is modeled on the Timed Up and Go Test, which has been clinically validated for the HD population (Busse et al. 2009; Rao et al. 2009). The test is anchored to the UHDRS gait, bradykinesia body, and tandem walking items (Huntington Study Group 1996).

Walk Test

The Walk Test asks participants walk as fast as is safely possible for 200 meters or 2 minutes every day. Ideally, the test is conducted on a straight path with no obstacles (e.g., in a park). Sensor-based approaches for measuring gait have been shown to be sensitive to differences in symptoms in early HD (Dalton et al. 2013). The test is anchored to the UHDRS gait, bradykinesia body, and tandem walking items (Huntington Study Group 1996).

EuroQoL 5-Dimension, 5-Level Questionnaire

The EQ-5D-5L is a validated self-report health status questionnaire used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a Visual Analog Scale (VAS) that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status (Index score) from the 5-item scores (i.e., does not include the VAS). The EQ-5D-5L takes approximately 5 minutes to complete. The Index score will be used in this study for informing pharmacoeconomic evaluations. The VAS score will be used to assess health-related quality of life (HRQoL). The EQ-5D-5L will be completed remotely at specified timepoints by the patient on the Roche HD mobile app.

Work Productivity and Activity Impairment

The WPAI contains 6 items assessing the impact of disease on employment status (yes/no), hours missed due to disease, hours missed due to other reasons, hours worked, and impact on productivity and on daily activities (both using an 11-point numeric rating scale, where higher scores indicate greater impact). The WPAI takes approximately 5 minutes to complete. The WPAI will be completed by the patient (about him/herself). It will be completed at specified timepoints remotely by the patient on the Roche HD mobile app.

HD Speaking Difficulty Item

The HD-SDI includes a single question assessing difficulty speaking over the past 7 days. It is assessed using a 5-point Likert scale, where higher scores indicate a greater frequency of difficulty. The HD-SDI can be completed in less than 1 minute and will be completed at specified timepoints remotely by the patient on the Roche HD mobile app.

WHO Disability Assessment Schedule 2.0

The WHODAS 2.0 (12-item version) assesses disability and aspects of HRQoL. It is intended for use in any disease population, and it is linked to the concepts in the International Classification of Functioning, Disability, and Health. The 12-item version contains 15 items, 12 of which produce a total score, with 3 additional questions administered to assess overall difficulty and activity impairment. All items are scored on a 0–4 Likert-type scale. The total raw score is converted

onto a 0–100 point scale, where higher scores indicate greater difficulty. The WHODAS 2.0 will take approximately 10 minutes to complete.

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Appendix 10 Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to laboratory test abnormalities are based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage
Eosinophils increased[1]	650 – 1,500 cell/mm^3	1,501 - 5,000 cell/mm^3	>5,000 cell/mm^3
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 x LLN or ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 x ULN
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 x ULN
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Appendix 10: Grading Scale for Adverse Events Relating to Laboratory Abnormalities (cont.)

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 x ULN
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 mg/dL; >13.9 mmol/L; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 mmol/L; hospitalization indicated
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 mg/dL; <3.0 mmol/L	<40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions[‡]
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	-	<130 mmol/L
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 mg/dL; <0.6 mmol/L
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 x ULN

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein <1.0 g/24 hrs -	2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

LLN=lower limit of normal; ULN=upper limit of normal.

Appendix 11 List of Preceding Clinical Trials

Patients from the following Roche-sponsored or Genentech-sponsored clinical trials are eligible for consideration for enrollment in Study BN40955.

Table 1 Preceding Clinical Trials

Protocol Number	Protocol Title
BP40410	AN OPEN-LABEL, ADAPTIVE MULTI-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
BN40422	A MULTI-SITE, PROSPECTIVE, LONGITUDINAL, COHORT STUDY MEASURING CEREBROSPINAL FLUID-MUTANT HUNTINGTIN PROTEIN IN PATIENTS WITH HUNTINGTON'S DISEASE
BN40423	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
BN40697	AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RO7234292 (ISIS 443139) IN HUNTINGTON'S DISEASE PATIENTS WHO PARTICIPATED IN PRIOR INVESTIGATIONAL STUDIES OF RO7234292 (ISIS 443139)
ML41885	A PHASE II, MULTI-CENTER, OPEN-LABEL STUDY TO EVALUATE SAFETY/TOLERABILITY OF INTRATHECALLY ADMINISTERED TOMINERSEN IN PATIENTS WITH LATE-ONSET MANIFEST HUNTINGTON'S DISEASE

Appendix 12 Guidance for Neurological Examination

Perform the neurological examination in the same way every time at screening and at every clinic visit. At dosing visits, perform examination predose and postdose after the participant has walked for 30 minutes post–drug injection.

Neurological Examination

- Mental status (appearance, level of consciousness, behavior, speech)
- Cranial Nerves II (including Visual Acuity and Fundoscopy)–XII
- Motor examination (bulk, tone, and strength)
- Coordination
- Abnormal movements
- Gait
- Reflexes
- Sensation (vibration, light touch, pin prick/temperature)

Note: The neurological examination should be followed at the non-dosing clinic visits, end-of-treatment visit, and safety follow-up visit. *At visits when a lumbar puncture is performed without study treatment administration, the neurological examination should be performed prior to the lumbar puncture.*