Official Title: 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

NCT Number: NCT03761849

Document Dates: Protocol Version 6: 02-April-2021

Protocol Version 4: 16-April-2019

PROTOCOL

TITLE:	**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**
PROTOCOL NUMBER:	BN40423
VERSION NUMBER:	6
EUDRACT NUMBER:	2018-002987-14
IND NUMBER:	137873
NCT NUMBER	NCT03761849
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 18:14:05	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Region-Specific Protocols		
Version	**Date Final**	**Region**	**Version**	**Date Final**
6	See electronic date stamp on title page	—	—	—
5	5 November 2019	—	—	—
4	16 April 2019	—	—	—
1	18 September 2018	VHP	3	24 January 2019
		European Union	2	13 December 2018

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol 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 every 8 weeks [Q8W] and every 16 weeks [Q16W] and placebo) in Study BN40423 be 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 as per protocol, without study drug administration. Study BN40955 (open-label extension [OLE]) is exploring similar 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 that no further study treatment will be administered in this study as of 22 March 2021. Patients on the study will continue to be followed for safety and efficacy outcomes until study completion (Sections 1.3, 3.1.1, 4.5, and 4.6, and Figure 2, and Appendices 1a and 1b).
- It has been clarified that neurologic examinations should be performed prior to lumbar puncture (LP), if there is no study treatment administration (Sections 3.1.1 and 4.5.3, and Appendices 1a, 1b, and 9).
- Language has been added to clarify that patients will no longer be able to enter the OLE study (BN40955) after completion of this study (Section 3.1.1).
- It has been clarified that all patients in the treatment period will discontinue study treatment and enter the early treatment termination (ETT) schedule. The previous version of the protocol already described the ETT schedule for following of individuals, for safety and efficacy outcomes, who have discontinued the study drug but not withdrawn consent for continued study participation (Sections 3.1.1, 4.2, and 4.6, and Figure 1 and 2). Additional clarification on visits and assessments required on the ETT schedule has been provided (Section 3.1.1.1, and Figure 3, and Appendices 1a and 1b).
- The ETT visit window has been extended from 28 ($\pm$ 7 days) from last dose to within 56 days of the decision to discontinue study treatment (i.e., from 22 March 2021). This extension has been made to facilitate scheduling of the ETT visit using the existing planned visit schedule (Section 3.1.1.1, and Appendices 1a and 1b).

- It has been clarified that following the iDMC recommendation to discontinue study treatment dosing in this study, the Sponsor will be unblinded to treatment assignment, to allow for data analyses to occur, in order to enhance the understanding of RO7234292 effects and to inform RO7234292 program next steps (Sections 3.1.2, 4.2, and 4.5.9.22).
- End of study and length of study have been adjusted, as a result of all patients moving to the ETT schedule (Section 3.2).
- 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, Appendices 1a and 1b).
- As per protocol, individuals will have an LP at the ETT visit. Additional safety assessments including lumbar puncture and laboratory tests have been added to the end of treatment (EoT) assessment for ETT to ensure complete and adequate collection of follow-up safety outcomes (Section 4.5.5, Appendices 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.
- Adverse event reporting period has been clarified, as a result of all patients moving to ETT schedule and discontinuing study treatment (Sections 5.3.1 and 5.4.2.2).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**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**
PROTOCOL NUMBER:	BN40423
VERSION NUMBER:	6
EUDRACT NUMBER:	2018-002987-14
IND NUMBER:	137873
NCT NUMBER	NCT03761849
TEST PRODUCT:	RO7234292
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:	**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**
PROTOCOL NUMBER:	BN40423
VERSION NUMBER:	6
EUDRACT NUMBER:	2018-002987-14
IND NUMBER:	137873
NCT NUMBER	NCT03761849
TEST PRODUCT:	RO7234292
PHASE:	Phase III
INDICATION:	Huntington's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of RO7234292 compared with placebo in patients with manifest Huntington's disease (HD). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score at Week 101

  Note: The primary efficacy endpoint for the U.S. Food and Drug Administration (FDA) will be change from baseline in the Total Functional Capacity (TFC) score at Week 101

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in scores for the following individual scales at Week 101:
  - TFC
  - Total Motor Score (TMS)
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading Test (SWR)

  Note: For the U.S. FDA, the first secondary endpoint will be change from baseline in the cUHDRS score at Week 101 instead of TFC, as TFC will be the primary endpoint.

- Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S) score at Week 101
- Proportion of patients with a decrease from baseline of ≥ 1 point on the TFC at Week 101
- Proportion of patients with a decline from baseline of ≥ 1.2 points on the cUHDRS at Week 101
- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline at Week 101

Exploratory Efficacy Objective

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

- Change from baseline in the Apathy Evaluation Scale (AES) score at Week 101
- Change from baseline in the Symptoms of Major Depressive Disorder Scale (SMDDS) score at Week 101
- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score at Week 93
- Change from baseline in the Patient Global Impression, Severity Scale (PGI-S) score at Week 101
- Change from baseline in the Quality of Life in Neurological Disorders (Neuro-Qol) Cognition Function Short Form at Week 101
- Change from baseline in the Huntington's Disease Speaking Difficulty Item Scale (HD-SDI) score at Week 101
- Change from baseline in the Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale (HD-CIAOS) score at Week 101
- Change from baseline in the in-clinic patient-reported EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-score and visual analogue scale (VAS) at Week 101
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) at Week 101

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of RO7234292 compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale
- Change from baseline in Montreal Cognitive Assessment (MoCA)
- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory results
- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct

Pharmacokinetic Objectives

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

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

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

Immunogenicity Objectives

The immunogenicity objective for this study is 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
- Titer and antibody subtype, determined if ADAs are identified

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Biomarker Objectives

Primary Biomarker Objective

The primary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in CSF mHTT protein level at Week 101

Secondary Biomarker Objective

The secondary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in whole and regional brain volumes (caudate, whole brain, and ventricular), as determined by structural magnetic resonance imaging (MRI), at Week 101
- Change from baseline in CSF neurofilament light chain (NfL) protein level at Week 101

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to RO7234292 (i.e., predictive biomarkers), 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 adverse events or can lead to improved adverse event 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 in blood, plasma, and CSF and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers (e.g., putamen, cortical grey matter, cortical white matter volumes, resting state functional MRI signal) 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- and companion-reported EQ-5D-5L Index and VAS scores at specified timepoints

- Change from baseline in companion self-reported and proxy-reported Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) scores at specified timepoints
- Change from baseline in patient- and companion-reported Work Productivity and Activity Impairment (WPAI) scores at specified timepoints

Study Design

Description of Study

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

Effective 22 March 2021, no further study treatment will be administered in this study. Patients on the study will continue to be followed for safety and efficacy outcomes until study completion.

Prospective patients will undergo screening assessments during a 4-week screening period. A maximum of one re-screening will be allowed within 8 weeks of the initial screening failure for patients who fail the initial screening. If re-screening is required, the CAG repeat length testing from the initial screening does not need to be repeated (historical values prior to screening will not be accepted). The screening MRI and viral serology from the initial screening, including from other Roche RO7234292 studies, may be acceptable as part of the re-screening assessments if performed within 12 weeks of the baseline visit.

Upon completion of the screening period, eligible patients will be randomly allocated in a 1:1:1 ratio to receive RO7234292 every 8 weeks (Q8W; RO7234292 Q8W arm), RO7234292 every 16 weeks (Q16W; RO7234292 Q16W arm), or placebo Q8W (placebo arm) by IT injection. To maintain the study blind and integrity, patients in the RO7234292 Q16W arm will also receive placebo (i.e., alternating doses of active drug and placebo).

During scheduled clinic visits, patients will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, MoCA, C-SSRS, neuroimaging assessments (neurologic safety sequences), and a review of any adverse events including related concomitant medications, as detailed in the schedule of activities. Patients in Japan must be monitored in the hospital setting for at least 24 hours after Day 1 study drug administration. Discharge will be determined at the discretion of the principal investigator.

In the case of a failed IT bolus dosing procedure *or a failed CSF collection procedure* (e.g., due to an inadequate establishment of access to the IT space), a second attempt may occur up to 7 days after the originally scheduled attempt. For this additional visit, safety and tolerability evaluations on the day of LP administration will be performed as detailed in the protocol, including neurological examination (predose and postdose*, or pre-procedure if no study treatment is being administered*), vital signs, and a review of adverse events and concomitant medication. If the second attempt occurs more than 3 days after the first attempt, 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.

During the treatment period, a telephone safety follow-up call will be conducted for the months in which no clinic visits are scheduled to check for any change in patient status (i.e., adverse events, concomitant medications) since the patient's last visit. Where deemed appropriate, an unscheduled clinic visit should be arranged for safety follow-up; no dosing will occur at these unscheduled visits. A safety follow-up telephone call will also be conducted approximately 2 months after the *last in-clinic visit at* Week 101.

Effective 22 March 2021, all patients will discontinue study treatment and will no longer be able to enter the OLE study (BN40955) after completing this study.

For patients enrolled in Study BN40423 who discontinue study treatment prematurely, but do not withdraw consent for continued participation in the study, *an ETT schedule will apply*.

An independent Data Monitoring Committee (iDMC) and independent Data Coordinating Center (iDCC) will be employed to monitor and evaluate patient safety throughout the study as well as to evaluate evidence of early efficacy.

Clarification of Existing Study Design for Early Treatment Termination (Applicable to all Patients from 22 March 2021)

Following the iDMC recommendation and Sponsor's decision to discontinue study treatment in this study, as of 22 March 2021, all patients will transition to the existing ETT schedule.

All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study, will return to the clinic for the following visits as part of the ETT schedule:

- *ETT visit to be performed within a maximum of 56 days of the decision to discontinue study treatment.*
- *Follow-up study visits at Weeks 53 and 69 (if not already completed) for collection of clinical outcome data for the primary and secondary endpoints. If the ETT visit falls within ± 30 days of either scheduled visits at Week 53 or Week 69, then only the ETT visit should be performed.*
- *End-of-treatment (EoT) visit at Week 101 (EoT for ETT).*

Therefore, after discontinuation of study treatment, patients will attend a minimum of two and up to four in-clinic visits depending on which visits have already been completed at the time of study drug discontinuation.

After discontinuation of study treatment, telephone safety follow-up calls will be conducted every 8 weeks between the clinic visits to check for any change in patient status (i.e., adverse events, concomitant medications) since the patient's last visit. Where deemed appropriate, an unscheduled clinic visit should be arranged for safety follow-up.

For patients consented to version 6 of the protocol, who received their last dose of study treatment less than 5 months before the scheduled Week 101 EoT for ETT visit, an additional safety telephone call should be performed 5 months after the last dose.

Study Design Overview for Patients Enrolled prior to Implementation of Protocol Version 4

All patients enrolled in Study BN40423 prior to implementation of the Version 4 protocol amendment will be prematurely discontinued by the Sponsor from this study and will be offered treatment in the OLE Study BN40955, once approval has been granted by the relevant competent authority and ECs/IRBs.

Patients who choose to enroll in the OLE will complete an end-of-treatment visit in Study BN40423, which can also serve as the inclusion visit for Study BN40955. All patients who are prematurely discontinued by the Sponsor who choose not to consent to Study BN40955 will additionally undergo safety follow-up telephone call approximately 2 months after the last dose and a 5-month postdose safety follow-up visit.

Number of Patients

Approximately 801 patients with HD will be enrolled in this global study from the implementation of Protocol Version 4 and onwards. This is in addition to patients who enrolled prior to Version 4, who will be discontinued from this study and offered participation in OLE Study BN40955.

Target Population

Inclusion Criteria

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

- Signed Informed Consent Form
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form and at the time of first dose administration
- Manifest HD diagnosis, defined as a diagnostic confidence level (DCL) score of 4
- Independence Scale (IS) score ≥ 70
- Genetically confirmed disease by direct DNA testing with a CAP score > 400 (Zhang et al. 2011), calculated as follows:

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

- 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 lumbar punctures
- Creatinine clearance (CrCl) ≥ 60 mL/min (Cockcroft-Gault formula)
- Ability and willingness, in the investigator's judgment, to comply with all aspects of the protocol including completion of interviews and questionnaires for the duration of the study
- Ability and willingness, in the investigator's judgment, to carry a smartphone, wear a digital monitoring device, and complete smartphone-based tasks
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment
- Signed study companion consent for participation who fulfills all of the following criteria:
  - Age ≥18 years
  - Reliable and competent, in the investigator's judgment
  - Sufficiently knowledgeable of the patient's condition to complete study companion assessments of the patient, and likely to remain sufficiently knowledgeable throughout the study, in the investigator's judgment
  - Able to comment on study participant's symptoms and functioning experience
  - Able and willing to attend in person all clinical visits for completion of companion assessments and for input into the clinician-rated TFC scale

    Note: Companions must have no cognitive, behavioral or motor change, in the opinion of the investigator, that would question the validity of the acquired observer-reported data.

    All effort should be made to retain the study companion; however, should this not be possible, a study companion should be replaced and new consent obtained.

    A study companion is required for all patients who enroll after implementation of Version 5 of the protocol. The companion is optional but highly recommended for patients who enrolled under Protocol Versions 1–4.
- 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 two 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 (≥ 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.

Exclusion Criteria

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 done by an appropriately qualified mental health professional to assess whether it is safe for the patient to participate in the study. Mild passive suicidal ideation (i.e., occasional thoughts that life is not worth living or is hard) without history of attempts or hospitalization over the past 12 months is generally acceptable for study participation, but final decision on participation should be made carefully and in consultation with 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
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study drug

  Women of childbearing potential must have a negative serum pregnancy test result at screening and a confirmatory urine pregnancy test prior to initiation of study drug.

- Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Positive for hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) at screening
- Known HIV infection
- Current or previous use of an antisense oligonucleotide (including small interfering RNA)
- Current or previous use of anti-psychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks from initiation of study treatment
- Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) and/or tetrabenazine, valbenazine, or deutetrabenazine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
- Current use of supplements (e.g., coenzyme Q10, vitamins, creatine) at a dose that has not been stable for at least 6 weeks prior to screening or is anticipated to change during the study

- Current use of an antidepressant or benzodiazepine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
- Treatment with investigational therapy within 4 weeks or 5 drug-elimination half-lives prior to screening, whichever is longer
- Antiplatelet or anticoagulant therapy within 14 days prior to screening or anticipated use during the study, including, but not limited to, aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- History of bleeding diathesis or coagulopathy
- Platelet count less than the lower limit of normal

  Platelet counts between 125,000 and 150,000 mm3 are permissible as long as the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.
- History of gene therapy, cell transplantation, or any experimental brain surgery
- Concurrent or planned concurrent participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions (e.g., lumbar puncture)

  Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
- Drug (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) 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 approximately *101* weeks (*25* months) after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4.5 years, *however following the decision to stop study treatment, the total length of the study, from screening of the first patient to the end of the study, is now expected to be approximately 4 years.*

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are RO7234292 and RO7234292 placebo.

Test Product (Investigational Drug)

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), two 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, preparation, and handling of RO7234292, refer to the pharmacy manual.

Placebo

RO7234292 placebo will be supplied by the Sponsor as a sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL RO7234292 placebo drug product for IT injection. The liquid is no different in color than the active drug.

For a 20 mL dosing volume, two vials containing 10 mL of RO7234292 placebo will have to be pooled by drawing them up into the same injection syringe containing 20 mL of placebo drug product.

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

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change from baseline in cUHDRS score at Week 101. This is defined as the attribute "variable" of the primary estimand.

Note: The primary efficacy endpoint for the U.S. FDA will be change from baseline in the TFC score at Week 101. TFC will be analyzed the same way as the cUHDRS.

The primary efficacy analysis for this study will compare each active treatment arm, RO7234292 Q8W and RO7234292 Q16W, against the placebo arm. To account for the multiple comparison, an appropriate procedure will be used to maintain the overall two-sided type I error at 5% (details will be given in the SAP).

The analysis of the primary endpoint will be performed by means of analysis of covariance (ANCOVA). The model will include the corresponding endpoint baseline score, CAG repeat length, baseline CAP score, and treatment as covariates; the final list of covariates will be defined in the SAP. On the basis of this analysis, least squares mean for the treatment differences at Week 101 and corresponding 95% CIs will be derived.

The robustness of the primary method of estimation described above may be explored by alternative sensitivity estimators based on varying assumptions underlying the multiple imputation strategy. These sensitivity analyses will be described in the SAP.

Determination of Sample Size

The planned sample size is adequate to capture meaningful clinical decline on both the TFC and cUHDRS and was estimated on the basis of data available from non-interventional studies (TRACK-HD, COHORT, ENROLL-HD) and a randomized placebo-controlled study (2CARE). Based on these data, using the anticipated trial population, a meta-analysis for the change from baseline at 24 months in TFC score suggested a natural decline of 1.36 points and a corresponding pooled standard deviation of 1.78. A conservative treatment discontinuation rate at Week 101 for patients receiving placebo or active is assumed to be 20% and 15%, respectively. Using these assumptions, the simulation described in the protocol was performed to estimate the sample size.

It was estimated that 267 patients per arm will provide approximately 80% power, at a two-sided $\alpha = 0.025$ level, to detect a 40% slowing of clinical decline for RO7234292 as compared with placebo at 101 weeks. This treatment effect translates into an expected average decline of ~0.82 points at 101 weeks for the RO7234292 arms. The minimal detectable difference with these assumptions is ~0.38 points.

Optional Interim Analyses

The Sponsor may choose to conduct one or more interim analyses for efficacy. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct an interim analysis, along with the rationale, specification of the endpoint (e.g., clinical and/or biomarker endpoint), number of patients, and statistical details for each analysis, will be introduced via a future protocol amendment, which will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of an interim analysis, and the iDMC Charter will be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of an interim analysis of efficacy data, the type I error rate will be controlled to ensure statistical validity is maintained. Additional criteria for recommending that the study be stopped for positive efficacy will be added to a future protocol amendment.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ANCOVA	analysis of covariance
AES	Apathy Evaluation Scale
app	application
ASO	antisense oligonucleotide
CAP	CAG–Age Product
CGI-C	Clinical Global Impression–Change
CGI-S	Clinical Global Impression–Severity
ClinRO	clinician-reported outcome
CrCl	creatinine clearance
CrGI-C	Companion-Reported Global Impression–Change
CrGI-S	Companion-Reported Global Impression–Severity
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
cUHDRS	composite Unified Huntington's Disease Rating Scale
DCL	diagnostic confidence level
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
EMA	European Medicines Agency
FDA	Food and Drug Administration
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HD	Huntington's disease
HD-CIAOS	Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale
HD-DAS	Huntington's Disease Daily Activities Scale
HDID	Huntington's Disease Identification Number
HD-SDI	Huntington's Disease Speaking Difficulty Item
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HRQoL	health-related quality of life
HTT	huntingtin (gene)
HTT	huntingtin (protein)
HUI	Health Utilities Index
HUI2	HUI Mark 2
HUI3	HUI Mark 3
ICE	intercurrent event
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IS	Independence Scale
IT	intrathecal
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LP	*lumbar puncture*
mHTT	mutant huntingtin (protein)
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Neuro-Qol	Quality of Life in Neurological Disorders
NfL	neurofilament light chain (protein)
NRS	numeric rating scale
NSDR	non–study drug–related (reasons)
ObsRO	observer-reported outcome
OLE	open-label extension
PD	pharmacodynamic
PerfO	performance outcome
PGI-C	Patient Global Impression–Change
PGI-S	Patient Global Impression–Severity
PK	pharmacokinetic
PRO	patient-reported outcome
Q4W	every 4 weeks

Abbreviation	Definition
Q8W	every 8 weeks
Q16W	every 16 weeks
QTc	corrected QT interval
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities Test
SDR	study drug–related (reasons)
SMDDS	Symptoms of Major Depressive Disorder Scale
SWR	Stroop Word Reading
TFC	Total Functional Capacity Scale
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
VAS	visual analogue scale
WES	whole exome sequencing
WGS	whole genome sequencing
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 CAG repeats in exon 1 of the Huntingtin *HTT* gene on chromosome 4, which encodes for a mutant huntingtin (mHTT) protein. Based upon nonclinical and clinical evidence, mHTT is considered the primary driver of HD pathophysiology (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 to 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). Motor onset is typically confirmed through use of the 15-item motor examination of the Unified Huntington's Disease Rating Scale (UHDRS). After completion of the examination, a certified motor rater assigns a diagnostic confidence level (DCL) score. Scores range from 0 to 4, with 0 representing no impairment and 4 representing unequivocal motor signs of HD ($\geq$99% confidence). Among the considerable clinical phenotypic heterogeneity of the disease, motor onset is one of the more robust and consistently-agreed-upon disease features. Behavioral features, including emotional disorders and personality changes, do not have a uniform presentation, are episodic in nature, and do not usually progress steadily over time (Ross et al. 2014).

Individuals with HD can be categorized as having either premanifest disease (diagnosed prior to motor onset) or manifest disease (diagnosed on the basis of motor onset). The premanifest disease period can be subdivided into presymptomatic and prodromal periods. During the presymptomatic period, from birth to young adulthood, individuals are not clinically distinguishable from controls. During the prodromal period, which can last many years before threshold clinical motor diagnosis, subtle motor changes and variable cognitive and behavioral changes appear but are not sufficient to make the clinical diagnosis of HD.

The manifest disease period can be subdivided into five 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 five clinical stages are defined by the score on the 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 et al. 1979).

Currently approved treatments aim to reduce the burden of symptoms, maximize function, and improve the patient's quality of life (Nance et al. 2011). Tetrabenazine and deutetrabenazine target abnormal involuntary movements (i.e., chorea) associated with HD, and these symptomatic therapies have a challenging benefit–risk profile. These drugs have been linked to many significant adverse events, including parkinsonism, akathisia, sedation, 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).

To date, there are no approved treatments able to slow or stop the clinical progression of HD.

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 ISIS443139 and IONIS-HTTRx. 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 (Crooke and Bennett 1996; Cerritelli and Crouch 2009), including cells of interest in the CNS (e.g., neurons and neuroglia). Reduction of the *HTT* gene mRNA, which in turn limits translation of the wild-type and mutant huntingtin protein, could potentially inhibit all downstream toxic effects 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 and non-human primates, 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 (Kordasiewicz et al. 2012; Stanek et al. 2013).

Nonclinical proof-of-concept studies with ASOs targeting mutant *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, bacterial artificial chromosome (BAC)HD 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 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 and 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) four 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 intrathecally 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 support 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 an analysis conducted when all individuals in Study BN40697 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

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 manifest HD. Building on the completed Phase I/IIa study and the ongoing Phase II OLE study, this Phase III, double-blind, placebo-controlled study (BN40423) will collect longer-term clinical efficacy and safety data to definitively evaluate the benefit and potential risks of RO7234292 when administered by IT bolus injection Q8W or every 16 weeks (Q16W; every 4 months) over a 25-month (2-year) period to patients with manifest HD.

Review of safety and tolerability 9-month data for RO7234292 from the Phase II OLE suggests 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 adverse events, decreased proportion of patients with moderate adverse events, and fewer adverse events considered possibly related to study drug in the Q8W regimen compared to the Q4W regimen (for details see the RO7234292 Investigator’s Brochure).

There have been no acute safety concerns meriting a change to the ongoing Phase II OLE study protocol (BN40697). However, given the 9-month CSF mHTT results, which suggest 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 justify a change in Study BN40423 to explore less frequent dosing regimens by continuing the Q8W RO7234292 and placebo arms, 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 ~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 ~25% are predicted to be maintained in a 120-mg Q16W paradigm.

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 recommended that all dosing (120 mg Q8W and Q16W and placebo) in Study BN40423 be 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 as per protocol, without study drug administration.

As a result of iDMC's recommendation and Sponsor's decision, effective 22 March 2021, no further study treatment will be administered in this study. Patients on the study will continue to be followed for safety and efficacy outcomes until study completion (see Section 3.1.1.1, Appendix 1a, and Appendix 1b).

The known potential risks related to lumbar punctures are elaborated, along with mitigation measures, in Section 5.1.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of RO7234292 compared with placebo in patients with manifest HD. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score at Week 101

  Note: The primary efficacy endpoint for the U.S. Food and Drug Administration (FDA) will be change from baseline in the TFC score at Week 101.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in scores for the following individual scales at Week 101:
  - TFC
  - Total Motor Score (TMS)
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading (SWR) Test

Note: For the U.S. FDA, the first secondary endpoint will be change from baseline in the cUHDRS score at Week 101 instead of TFC, as TFC will be the primary endpoint.

- Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S) score at Week 101
- Proportion of patients with a decrease from baseline of ≥ 1 point on the TFC at Week 101
- Proportion of patients with a decline from baseline of ≥ 1.2 points on the cUHDRS at Week 101
- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline at Week 101

2.1.3 Exploratory Efficacy Objective

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

- Change from baseline in the Apathy Evaluation Scale (AES) score at Week 101
- Change from baseline in the Symptoms of Major Depressive Disorder Scale (SMDDS) score at Week 101
- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score at Week 93
- Change from baseline in the Patient Global Impression, Severity Scale (PGI-S) score at Week 101
- Change from baseline in the Quality of Life in Neurological Disorders (Neuro-Qol) Cognition Function Short Form at Week 101
- Change from baseline in the Huntington's Disease Speaking Difficulty Item Scale (HD-SDI) score at Week 101
- Change from baseline in the Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale (HD-CIAOS) score at Week 101
- Change from baseline in the in-clinic patient-reported EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-score and visual analogue scale (VAS) at Week 101
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) at Week 101

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of RO7234292 compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale (see Table 4)
- Change from baseline in Montreal Cognitive Assessment (MoCA)

- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory results
- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct

2.3 PHARMACOKINETIC OBJECTIVES

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

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

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

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is 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
- Titer and antibody subtype, determined if ADAs are identified

The exploratory immunogenicity objective for this study is 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 BIOMARKER OBJECTIVES

2.5.1 Primary Biomarker Objective

The primary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in CSF mHTT protein level at Week 101

2.5.2 Secondary Biomarker Objective

The secondary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in whole and regional brain volumes (caudate, whole brain, and ventricular), as determined by structural magnetic resonance imaging (MRI), at Week 101
- Change from baseline in CSF neurofilament light chain (NfL) protein level at Week 101

2.5.3 Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to RO7234292 (i.e., predictive biomarkers), 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 adverse events or can lead to improved adverse event 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 in blood, plasma, and CSF (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers (e.g., putamen, cortical grey matter, cortical white matter volumes, resting state functional MRI signal) (see Section 4.5.7) 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- and companion-reported EQ-5D-5L Index and VAS scores at specified timepoints
- Change from baseline in companion self-reported and proxy-reported Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) scores at specified timepoints
- Change from baseline in patient- and companion-reported Work Productivity and Activity Impairment (WPAI) scores at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

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

Effective 22 March 2021, no further study treatment will be administered in this study. Patients on the study will continue to be followed for safety and efficacy outcomes until study completion (see Section 3.1.1.1, Appendix 1a, and Appendix 1b).

Prospective patients will undergo screening assessments during a 4-week screening period. A maximum of one re-screening will be allowed within 8 weeks of the initial screening failure for patients who fail the initial screening (see Section 4.5.1). If re-screening is required, the CAG repeat length testing from the initial screening does not need to be repeated (historical values prior to screening will not be accepted). The screening MRI and viral serology from the initial screening, including from other Roche RO7234292 studies, may be acceptable as part of the re-screening assessments if performed within 12 weeks of the baseline visit.

Upon completion of the screening period, eligible patients will be randomly allocated in a 1:1:1 ratio to receive RO7234292 Q8W (RO7234292 Q8W arm), RO7234292 Q16W (RO7234292 Q16W arm), or placebo Q8W (placebo arm) by IT injection, as described in Table 1. To maintain the study blind and integrity, patients in the RO7234292 Q16W arm will also receive placebo (i.e., alternating doses of active drug and placebo).

Table 1 Treatment Regimens after Implementation of Protocol Version 4

Arm	Treatment Regimen
RO7234292 Q8W arm	RO7234292 loading dose: 120 mg at Days 1 and 29 (2 doses) RO7234292: 120 mg Q8W from Week 13 to Week 93 (11 doses)
RO7234292 Q16W arm	RO7234292 loading dose: 120 mg at Days 1 and 29 (2 doses) RO7234292: 120 mg Q16W from Week 21 to Week 85 (5 doses) Placebo: Q16W from Week 13 to Week 93 (6 doses)
Placebo arm	Placebo: at Days 1 and 29 (2 doses) and Q8W from Week 13 to Week 93 (11 doses)

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

Note: Effective 22 March 2021, no further study treatment will be administered in this study.

During scheduled clinic visits, patients will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, MoCA,

C-SSRS, neuroimaging assessments (neurologic safety sequences), and a review of any adverse events including related concomitant medications, as detailed in Appendix 1a. Patients in Japan must be monitored in the hospital setting for at least 24 hours after Day 1 study drug administration. Discharge will be determined at the discretion of the principal investigator.

In the case of a failed IT bolus dosing procedure *or a failed CSF collection procedure* (e.g., due to an inadequate establishment of access to the IT space), a second attempt may occur up to 7 days after the originally scheduled 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*, or pre-procedure if no study treatment is being administered*), vital signs, and a review of adverse events and concomitant medication. If the second attempt occurs more than 3 days after the first attempt, 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).

During the treatment period, a telephone safety follow-up call will be conducted for the months in which no clinic visits are scheduled to check for any change in patient status (i.e., adverse events, concomitant medications) since the patient's last visit (see Appendix 1a). Where deemed appropriate, an unscheduled clinic visit should be arranged for safety follow-up; no dosing will occur at these unscheduled visits. A safety follow-up telephone call will also be conducted approximately 2 months after the *last in-clinic visit at* Week 101.

Effective 22 March 2021, all patients will discontinue study treatment and will no longer be able to enter the OLE study (BN40955) after completing this study.

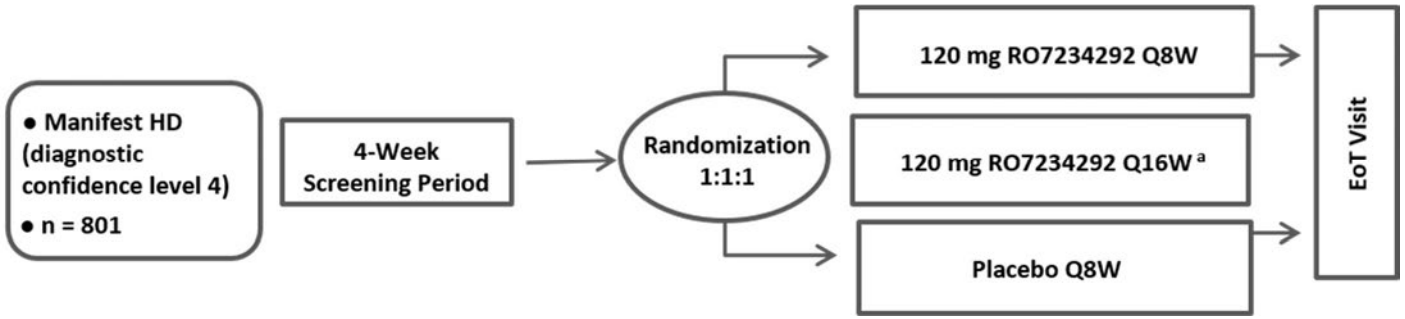
For patients enrolled in Study BN40423 who discontinue study treatment prematurely, but do not withdraw consent for continued participation in the study, *an ETT schedule will apply (Section 3.1.1.1)*.

An iDMC and independent Data Coordinating Center (iDCC) will be employed to monitor and evaluate patient safety throughout the study as well as to evaluate evidence of early efficacy (see Section 3.1.2).

The Sponsor may choose to conduct one or more interim analyses during the study (further details are given in Section 6.12).

Figure 1 and Figure 2 present the study schema and overview of the dosing schedule respectively, for patients enrolled in Study BN40423 after implementation of Protocol Version 4. A schedule of activities is provided in Appendix 1a.

Figure 1 Study Schema for Patients Enrolled after Implementation of Protocol Version 4

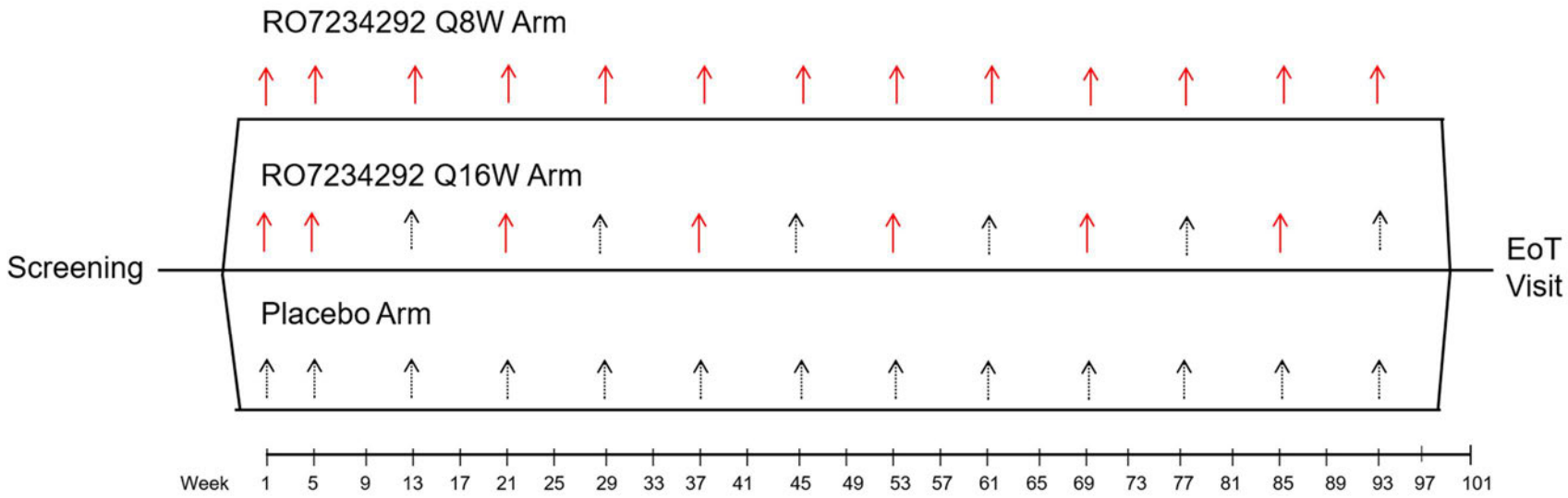


EoT = end of treatment; *ETT = early treatment termination;* HD = Huntington disease; Q8W = every 8 weeks; Q16W = every 16 weeks.

[a] Patients in the RO7234292 Q16W arm will receive placebo at alternating visits to keep the double blind, as shown in Figure 2 and Appendix 1a

NOTE: *Effective 22 March 2021, all patients will be discontinued from study treatment and follow the ETT schedule (see Section 3.1.1.1).*

Figure 2 Dosing Schema for Patients Enrolled after Implementation of Protocol Version 4



EoT = end of treatment; Q8W = every 8 weeks; Q16W = every 16 weeks.

Notes: Red, solid arrows indicate study drug administration, while black, dotted arrows indicate placebo administration. Patients in the RO7234292 Q8W arm will receive a loading dose of RO7234292 on Days 1 and 29 (loading period), followed by active study drug Q8W. Patients in the RO7234292 Q16W arm will receive a loading dose of RO7234292 on Days 1 and 29 (loading period), followed by alternating Q8W doses of placebo and active study drug.

NOTE: *Effective March 22, 2021, no further study treatment will be administered in this study. Effective 22 March 2021, all patients will be discontinued from study treatment and follow the ETT schedule (see Section 3.1.1.1).*

3.1.1.1 Clarification of Existing Study Design for Early Treatment Termination (Applicable to all Patients from 22 March 2021)

Following the iDMC recommendation and Sponsor's decision to discontinue study treatment in this study, as of 22 March 2021, all patients will transition to the existing ETT schedule, outlined below and in Appendix 1b.

All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study, will return to the clinic for the following visits as part of the ETT schedule:

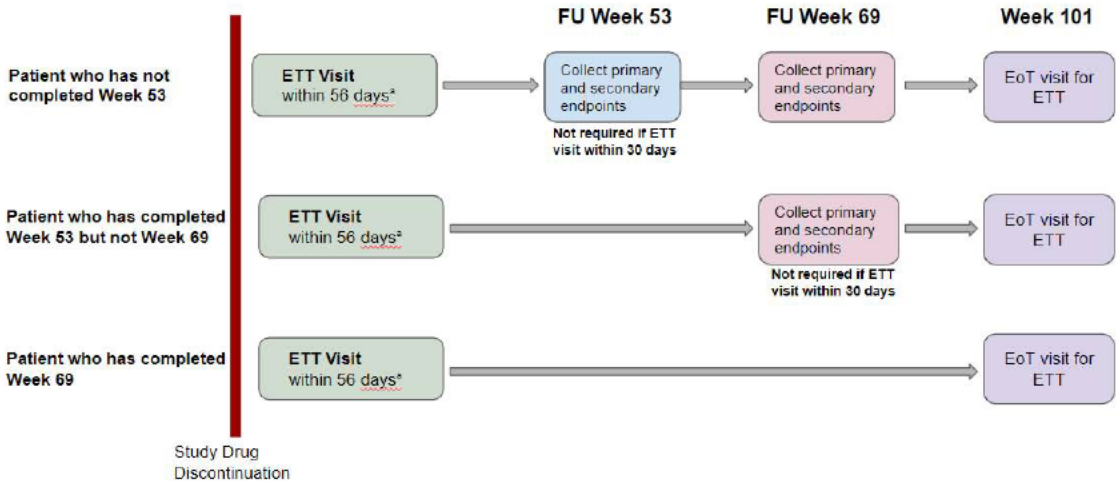
- *ETT visit to be performed within a maximum of 56 days of the decision to discontinue study treatment.*
- *Follow-up study visits at Weeks 53 and 69 (if not already completed) for collection of clinical outcome data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, 2.2, and Appendix 1b). If the ETT visit falls within ± 30 days of either scheduled visits at Week 53 or Week 69, then only the ETT visit should be performed.*
- *End-of-treatment (EoT) visit at Week 101 (EoT for ETT).*

Therefore, after discontinuation of study treatment, patients will attend a minimum of two and up to four in-clinic visits depending on which visits have already been completed at the time of study drug discontinuation as shown in Figure 3.

After discontinuation of study treatment, telephone safety follow-up calls will be conducted every 8 weeks between the clinic visits to check for any change in patient status (i.e., adverse events, concomitant medications) since the patient's last visit (see Appendix 1b). Where deemed appropriate, an unscheduled clinic visit should be arranged for safety follow-up.

For patients consented to version 6 of the protocol, who received their last dose of study treatment less than 5 months before the scheduled Week 101 EoT for ETT visit, an additional safety telephone call should be performed 5 months after the last dose.

Figure 3 Visit Schedule Scenarios for Early Treatment Termination (Applicable to all Patients from 22 March 2021)



EoT =end of treatment; ETT =early treatment termination; FU =follow-up.

[a] *The ETT visit should be performed within 56 days of the decision to discontinue study treatment. A telephone safety follow-up call will be conducted every 8 weeks between the clinic visits, to check for any change in patient status since the patient's last visit.*

3.1.1.2 Study Design Overview for Patients Enrolled prior to Implementation of Protocol Version 4

All patients enrolled in Study BN40423 prior to implementation of the Version 4 protocol amendment will be prematurely discontinued by the Sponsor from this study and will be offered treatment in the OLE Study BN40955, once approval has been granted by the relevant competent authority and ECs/IRBs.

Patients who choose to enroll in the OLE will complete an end-of-treatment visit in Study BN40423, which can also serve as the inclusion visit for Study BN40955. All patients who are prematurely discontinued by the Sponsor who choose not to consent to Study BN40955 will additionally undergo a safety follow-up telephone call approximately 2 months after the last dose and a 5-month postdose safety follow-up visit.

Table 2 presents the treatment regimen for all patients before implementation of the Version 4 protocol.

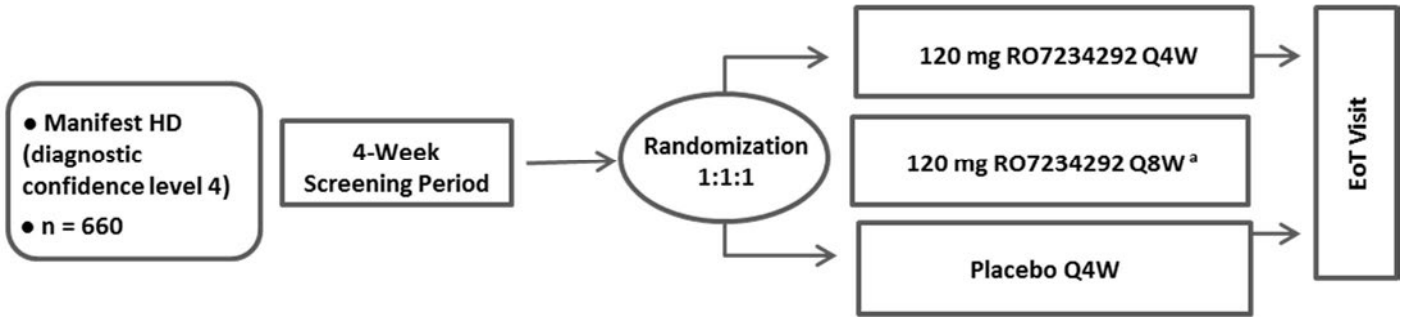
Table 2 Treatment Regimens prior to Implementation of Protocol Version 4

Arm	Treatment Regimen
RO7234292 Q4W arm	– RO7234292: 120 mg Q4W from Week 1 to Week 97 (25 doses)
RO7234292 Q8W arm	– RO7234292 loading dose: 120 mg at Days 1 and 29 (2 doses) – Placebo: Q8W from Week 9 to Week 97 (12 doses) – RO7234292: 120 mg Q8W from Week 13 to Week 93 (11 doses)
Placebo arm	– Placebo: Q4W from Week 1 to Week 97 (25 doses)

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

Figure 4 and Figure 5 present study schema and overviews of the dosing schedule, respectively. A schedule of activities is provided in Appendix 10, with additional assessments described in Appendix 11, Appendix 12, Appendix 13, and Appendix 14.

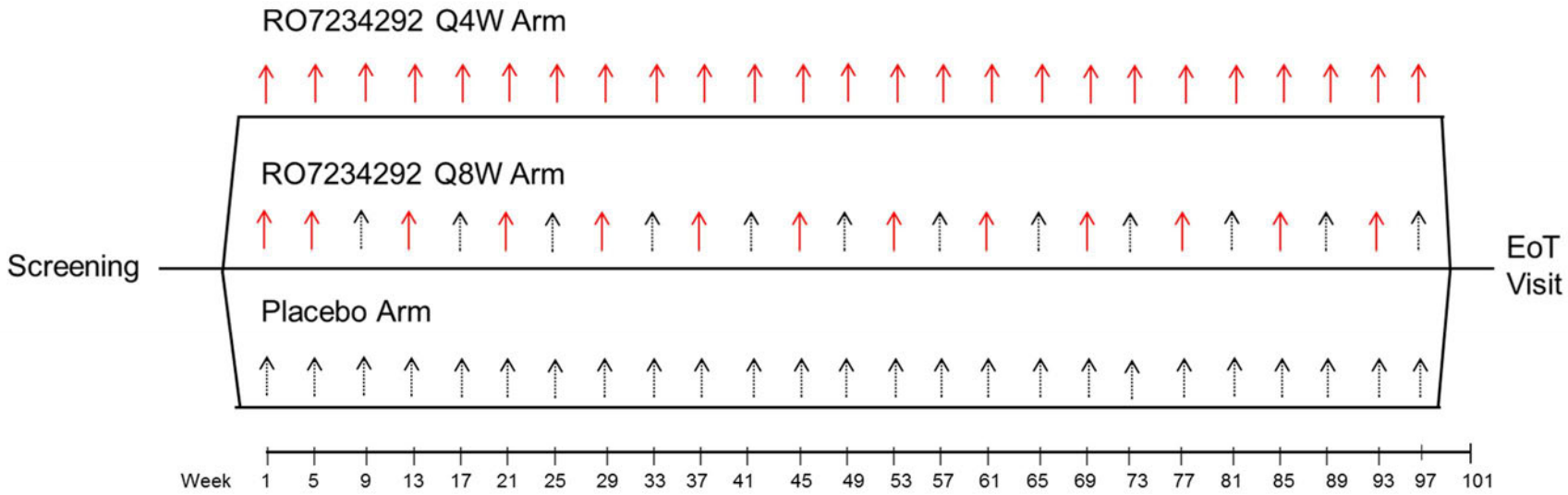
Figure 4 Study Schema for Patients Enrolled prior to Implementation of Protocol Version 4



EoT = end of treatment; HD = Huntington disease; Q4W = every 4 weeks; Q8W = every 8 weeks.

Notes: All patients who enroll prior to implementation of Protocol Version 4 will be prematurely discontinued from treatment by the Sponsor and offered treatment in the open-label extension study (BN40955). These patients will complete an EoT visit in Study BN40423, which can also serve as the screening visit for Study BN40955. All patients who are prematurely discontinued by the Sponsor who choose not to consent to Study BN40955 will additionally undergo a safety follow-up telephone call approximately 2 months after the last dose and a 5-month postdose safety follow-up visit. Patients in the Q8W arm will remain in the Q8W arm of the OLE study (BN40955). Patients in the placebo arm or Q4W arms will be randomly allocated to the Q8W or Q16W arms in Study BN40955.

Figure 5 Dosing Schema for Patients Enrolled prior to Implementation of Protocol Version 4



EoT = end of treatment; Q4W = every 4 weeks; Q8W = every 8 weeks.

Notes: Red, solid arrows indicate study drug administration, while black, dotted arrows indicate placebo administration. Patients in the RO7234292 Q8W arm will receive a loading dose of RO7234292 on Days 1 and 29 (loading period), followed by alternating doses of placebo and active study drug.

3.1.2 Independent Data Monitoring Committee

The incidence and nature of adverse events, serious adverse events, adverse events of special interest, and abnormalities from neuroimaging assessments; vital signs; ECG assessments; laboratory parameters; and any other relevant safety information will be reviewed on a regular basis by an iDMC in an unblinded fashion. This information may also include MRI data and exploratory CSF biomarkers, for example NfL and Tau. These reviews will occur approximately every 6 months or at the discretion of the iDMC.

The iDMC will also undertake evaluation of any interim analysis. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities, will be detailed in an iDMC Charter.

As a result of the iDMC's recommendation and the Sponsor's decision to permanently stop study treatment, the Sponsor will be unblinded to treatment assignment. Following the unblinding, the Sponsor will also monitor and evaluate patient safety outcomes.

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 approximately *101* weeks (*25* months) after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4.5 years*, however following the decision to stop study treatment, the total length of the study, from screening of the first patient to the end of the study, is now expected to be approximately 4 years*.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for RO7234292 Dose and Schedule

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, two active dosing regimens and a placebo arm will be used in this study: RO7234292 Q8W (RO7234292 Q8W arm), RO7234292 Q16W (RO7234292 Q16W arm), and placebo Q8W (placebo arm) by IT injection. To maintain

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

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 preclinical 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 intrathecally Q4W for four 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 five 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 three or four 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 Phase II OLE suggest 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 adverse events, decreased proportion of patients with moderate adverse events, and fewer adverse events 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. 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 intrathecally in clinical trials. IT 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.

A 25-month (2-year) study treatment length has been chosen because the signal-to-noise characteristics of the primary endpoint cUHDRS (TFC for U.S. FDA)—as investigated in prospective observational cohort studies and in placebo groups of prior clinical trials—suggest that this length is optimal for trial efficacy. A treatment duration of 25 months will also enable demonstration of sustained, durable benefit on slowing clinical progression as presumed to be achievable with RO7234292 (which is proposed to be administered as a chronic treatment to slow clinical progression). Studies with a shorter treatment duration, such as 18 months, would require a dramatically larger sample size (i.e., 50%) under the 30% slowing of clinical progression assumption. This would result in a potential risk of signal dilution due to inherent variability of a larger number of sites and clinical raters, resulting in a potential increased risk of type II error.

In summary, a 120-mg Q8W dosing regimen and the less frequent dosing regimen of 120 mg Q16W have been selected for this Phase III study to maximize CSF mHTT protein lowering acutely and to test the hypothesis of clinical efficacy, as a function of more versus less frequent dosing, while mitigating theoretical risks of long-term IT dosing of 120 mg and of non-allele specific lowering of HTT. The 25-month duration is

also considered appropriate for providing evidence of the benefit–risk profile of RO7234292 and longer-term tolerability of IT administration.

3.3.2 Rationale for Patient Population

Patients with manifest HD (DCL score of 4 [i.e., motor abnormalities ≥99% likely to be due to HD]) who are ambulatory without assistance, verbal, and possess a CAG–Age Product (CAP) score of >400 (Zhang et al. 2011; see Section 4.1.1) and an Independence Scale (IS) score of ≥70 will be included in this study. This patient population represents manifest disease where disability might be more plausibly reversed or slowed in response to a therapeutic intervention compared with patients with more advanced disease (Penney et al. 1990). This definition also corresponds to the patients most commonly recruited at present for clinical trials aiming to slow clinical progression. Such cohorts are known to have a longitudinal decline in clinical measures (Paulsen et al. 2014) over a timeframe appropriate for clinical trials.

3.3.3 Rationale for Control Group

Patients will be randomly allocated to receive active treatment (RO7234292 Q8W or Q16W) or placebo in this double-blind study because there are no disease-modifying standard-of-care treatments for patients with HD. The placebo arm will be compared with the RO7234292 treatment arms to enable a robust assessment of the primary endpoint and the benefit-risk profile. As each patient completes the study or is prematurely discontinued by the Sponsor as a consequence of the changes to the study through Protocol Version 4, they will be given the option of receiving RO7234292 in an OLE study (BN40955), provided they meet eligibility criteria and the data from the ongoing RO7234292 program support continued development. Approval of Study BN40955 must also be granted by the relevant competent authority and EC/IRB.

3.3.4 Rationale for Biomarker Assessments

3.3.4.1 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). mHTT 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). NfL 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.

3.3.4.2 Blood Biomarkers

NfL levels in blood correlate with NfL levels in CSF and could serve as prognostic blood biomarkers of disease onset and progression in HD (Wild and Tabrizi 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.

3.3.4.3 Genetic Testing to Determine CAG Repeat Length

HD is caused by mutation in exon 1 of the *HTT* gene located on chromosome 4, resulting in a polyglutamine (CAG) expansion in the huntingtin protein. Above 35 CAG repeats, the age of HD onset is inversely correlated with the length of the expansion (Duyao et al. 1993). CAG repeat length will be determined by direct DNA testing performed centrally.

3.3.4.4 Clinical Genotyping

Although CAG repeat length is inversely correlated to age of onset in HD, it only accounts for approximately 50% of the variance. Identification of other genetic modifiers of disease severity and disease progression in HD could provide important insights, as has been recently shown in the Genetic Modifiers of Huntington's Disease Consortium (2015), where relatively common single nucleotide polymorphisms in the HD population were found to be associated with either an accelerated or delayed age of motor onset. A blood sample will be collected to detect individual single nucleotide polymorphisms, including SNP analysis of the huntingtin gene, to explore, for example, their influence on progression rates, age of onset, disease severity, or response to treatment.

3.3.4.5 Magnetic Resonance Imaging

MRI 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. Structural MRI will be used to assess brain volume, diffusion-weighted MRI will be used to examine structural brain connectivity, and 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. 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.

Structural Magnetic Resonance Imaging

Numerous structural MRI studies have demonstrated wide-spread brain atrophy, including whole-brain, caudate, and ventricular changes in patients with premanifest and manifest HD (Douaud et al. 2006; Harrington et al. 2016). Brain volume correlates with cognitive function (Peinemann et al. 2005). Further, whole-brain, caudate, and ventricular volumes can predict and track progressive clinical decline in patients with HD

and can also be associated with molecular biomarkers of neurodegeneration, such as NfL (Tabrizi et al. 2012).

Diffusion Magnetic Resonance Imaging

Widespread changes in basal ganglia–cortical structural connectivity have also been observed in patients with HD (Novak et al. 2015), including associations between striatum-sensorimotor cortex connections and UHDRS motor scale and TMS (Bohanna et al. 2011), suggesting that the clinical phenotype in manifest HD may be a result of altered structural connectivity.

Resting-State Functional Magnetic Resonance Imaging

Resting-state functional MRI studies have generated evidence for functional connectivity alterations and their correlation to several clinical and cognitive measures in patients with HD (Werner et al. 2014; Dogan et al. 2015; Liu et al. 2016; Espinoza et al. 2018), implying that disrupted functional integrity of distinct brain networks may underlie clinical progression in HD.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 801 patients with HD will be enrolled in this global study from the implementation of Protocol Version 4 and onwards. This is in addition to patients who enrolled prior to Version 4, who will be discontinued from this study and offered participation in OLE Study BN40955.

4.1.1 Inclusion Criteria

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

- Signed Informed Consent Form
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form and at the time of first dose administration
- Manifest HD diagnosis, defined as a DCL score of 4 (see Appendix 8)
- Independence Scale (IS) score ≥ 70
- Genetically confirmed disease by direct DNA testing with a CAP score > 400 (Zhang et al. 2011), calculated as follows:

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

- 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 lumbar punctures
- Creatinine clearance (CrCl) ≥ 60 mL/min (Cockcroft-Gault formula)
- Ability and willingness, in the investigator's judgment, to comply with all aspects of the protocol including completion of interviews and questionnaires for the duration of the study
- Ability and willingness, in the investigator's judgment, to carry a smartphone, wear a digital monitoring device, and complete smartphone-based tasks
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment
- Signed study companion consent for participation who fulfills all of the following criteria:
  - Age ≥ 18 years
  - Reliable and competent, in the investigator's judgment
  - Sufficiently knowledgeable of the patient's condition to complete study companion assessments of the patient, and likely to remain sufficiently knowledgeable throughout the study, in the investigator's judgment
  - Able to comment on study participant's symptoms and functioning experience, as required per Appendix 1
  - Able and willing to attend in person all clinical visits for completion of companion assessments and for input into the clinician-rated TFC scale

    Note: Companions must have no cognitive, behavioral or motor change, in the opinion of the investigator, that would question the validity of the acquired observer-reported data.

    All effort should be made to retain the study companion; however, should this not be possible, a study companion should be replaced and new consent obtained.

    A study companion is required for all patients who enroll after implementation of Version 5 of the protocol. The companion is optional but highly recommended for patients who enrolled under Protocol Versions 1–4.

- 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 two 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 (≥ 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.

4.1.2 Exclusion Criteria

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 done by an appropriately qualified mental health professional to assess whether it is

safe for the patient to participate in the study. Mild passive suicidal ideation (i.e., occasional thoughts that life is not worth living or is hard) without history of attempts or hospitalization over the past 12 months is generally acceptable for study participation, but final decision on participation should be made carefully and in consultation with 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
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study drug

  Women of childbearing potential must have a negative serum pregnancy test result at screening and a confirmatory urine pregnancy test prior to initiation of study drug.
- Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Positive for hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg) at screening
- Known HIV infection
- Current or previous use of an antisense oligonucleotide (including small interfering RNA)
- Current or previous use of anti-psychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks from initiation of study treatment
- Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) and/or tetrabenazine, valbenazine, or deutetrabenazine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
- Current use of supplements (e.g., coenzyme Q10, vitamins, creatine) at a dose that has not been stable for at least 6 weeks prior to screening or is anticipated to change during the study
- Current use of an antidepressant or benzodiazepine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation

- Treatment with investigational therapy within 4 weeks or 5 drug-elimination half-lives prior to screening, whichever is longer
- Antiplatelet or anticoagulant therapy within 14 days prior to screening or anticipated use during the study, including, but not limited to, aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- History of bleeding diathesis or coagulopathy
- Platelet count less than the lower limit of normal

  Platelet counts between 125,000 and 150,000 mm^3 are permissible as long as the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.
- History of gene therapy, cell transplantation, or any experimental brain surgery
- Concurrent or planned participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions

  Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
- 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) as assessed by a centrally read MRI scan during the screening period

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

All patients who were enrolled prior to implementation of Protocol Version 4 and have not already discontinued for another reason will be prematurely discontinued and offered treatment in OLE Study BN40955. The treatment assignments of these patients will remain blinded until at least after the entire cohort has been discontinued from

Study BN40423. Patients will receive either the Q8W regimen or Q16W regimen in Study BN40955. These patients will not be included in the primary analysis for Study BN40423.

Patients enrolled after implementation of Protocol Version 4 will be randomly allocated to receive 120 mg of RO7234292 Q8W, 120 mg of RO7234292 Q16W, or placebo Q8W. An independent interactive voice or web-based response system (IxRS) provider will conduct randomization and hold the treatment assignment code.

Effective 22 March 2021, all patients will be discontinued from study treatment and will follow the ETT schedule of assessments, outlined in Appendix 1b. Patients who do not consent to version 6 of the protocol should be discontinued from the study.

Study site personnel and patients will *remain* blinded to treatment assignment during the study. *Following the Sponsor's decision to permanently discontinue study treatment, the Sponsor will become unblinded to treatment assignment. Other* individuals who require access to patient treatment assignments to fulfill their job roles during the clinical trial include the unblinding group, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, iDMC members, and iDCC members.

While PK and ADA samples must be collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignment in order to identify appropriate samples for analysis. PK samples from patients assigned to the placebo arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples will be analyzed for all patients. Post-baseline ADA samples from patients assigned to the placebo arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment. The investigator *and* patient will remain blinded to treatment assignment. *Following the Sponsor's decision to permanently discontinue study treatment, the Sponsor will become unblinded to treatment assignment including the Sponsor's* Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are RO7234292 and RO7234292 placebo.

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), two 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, preparation, and handling of RO7234292, refer to the pharmacy manual.

4.3.1.2 Placebo

RO7234292 placebo will be supplied by the Sponsor as a sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL RO7234292 placebo drug product for IT injection. The liquid is no different in color than the active drug.

For a 20 mL dosing volume, two vials containing 10 mL of RO7234292 placebo will have to be pooled by drawing them up into the same injection syringe containing 20 mL of placebo drug product.

For information on the formulation, preparation, and handling of RO7234292 placebo, 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 adverse events, should be reported as described in Section 5.3.5.12

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

4.3.2.1 RO7234292 and Placebo

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

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

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO7234292 or placebo) will be provided by the Sponsor. 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 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 web site:

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 screening to the end-of-treatment visit for patients who enter OLE Study BN40955 or the safety follow-up visit for patients who do not enroll in the OLE study. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Contraceptive agents
- Supplements (e.g., coenzyme Q10, vitamins, creatine) if the dose has been stable for at least 6 weeks prior to screening and the dose is not anticipated to change during the study
- Antipsychotics only if prescribed for motor symptoms or for mood stabilization (i.e., irritability or aggressiveness) and/or tetrabenazine/deutetrabenazine/valbenazine if the dose has been stable for at least 12 weeks prior to screening and the dose is not anticipated to change between screening and the start of study treatment

  If clinically indicated, dose changes or medication stopping or starting can occur as per investigator judgment during the course of the study.
- Antidepressant or benzodiazepine if the dose has been stable for at least 12 weeks prior to screening and the dose is not anticipated to change between screening and the start of study treatment

If clinically indicated, dose changes or medication stopping or starting can occur as per investigator judgment during the course of the study.

- Anti-epileptics if given for mood stabilization, pain, restless legs, or insomnia
- Aspirin at doses ≤ 81 mg/day
- Local anesthesia for the lumbar puncture procedure, depending on institutional guidelines

  Sedation may not be used for lumbar puncture.

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 lumbar puncture or IT bolus procedures in the study

  Depending on institutional guidelines, local anesthesia is permissible for the lumbar puncture procedure
- Use of anti-anxiety medication is discouraged during scheduled MRI scans in the study. Anti-anxiety medication used to prevent movement disorder to allow successful MRI scan is not permitted in this study, as movement disorder too severe to scan under drug-free conditions is an overall study exclusionary criterion.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study and guidance on the order these assessments can be performed are provided in Appendix 1a *and Appendix 1b*, and Appendix 5, respectively. 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, patients will be discontinued from study treatment but will continue to be followed for safety and efficacy outcomes as outlined in Section 3.1.1.1, Appendix 1a and Appendix 1b.*

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 screening evaluations). Informed Consent Forms for patients and study companions 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's capacity is confirmed, the investigator may proceed with signing of the Informed Consent Form.

All screening 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 screened and to confirm eligibility or record reasons for screening failure, as applicable.

A maximum of one 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). If re-screening is required, CAG repeat length testing from the initial screening does not need to be repeated (historical values will not be accepted). The screening MRI and viral serology from the initial screening, including from other Roche RO7234292 studies, may be acceptable as part of the re-screening assessments if performed within 12 weeks of the baseline visit.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, HD history (including past hospitalizations [i.e., number, duration, and reason]) over the last 2 years, reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline. Alcohol and/or drug 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. Daily use of any drug (i.e., cannabinoid, opioid, stimulant, hallucinogen, designer) or daily alcohol use that meets criteria for either abuse or psychological or physiological dependence is not permitted and is exclusionary. Occasional use that does not meet the criteria for abuse is permissible in this study.

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from screening to the end-of-treatment visit for patients who enter OLE Study BN40955 or the safety follow-up visit for patients who do not enroll in the OLE study will be recorded. At the time of each study drug administration and telephone safety follow-up calls, an interval medical history should be obtained and any changes in medications and any physician visits for HD or general medical care 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. Demographic data and social status data (e.g., relationship to patient and employment status) will also

be collected for the study companion. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment.

A unique HD identification number (HDID) will be collected from patients who already have an 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 screening and other specified visits (see Appendix 1), 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. Height will be measured at screening and baseline only.

A neurologic examination, including fundoscopy, performed at screening 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 9). The neurologic examination 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 (Week 1) 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.

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 approximately 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 lumbar puncture, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal

variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, 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–lumbar puncture syndrome.

Sedation may not be used. Depending on institutional guidelines, local anesthesia should be used for the procedure. Spinal ultrasound may be used for the lumbar puncture procedure if deemed necessary, but ultrasound is not required. Ultrasound may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. Fluoroscopy guidance can also be used, if local institutional guidelines dictate and local 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.

For details on the lumbar puncture and IT bolus dosing procedure, please refer to the LP procedure and CSF collection guidelines and instructional video. *Effective 22 March 2021, no further study treatment will be administered.*

When applicable, study treatment administration will occur via a lumbar puncture 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 pre-existing experience using LP/intrathecal bolus dosing in the sitting position and prefers the use of the upright sitting position, as guided by the patient, his or her judgment. 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 occur using the same position.

Patients will be discouraged from resting supine after the lumbar puncture procedure and will be encouraged to mobilize immediately by walking around at a minimum and, if feasible, walking briskly for approximately 30 minutes, after which the postdose neurological examination can occur *(if study treatment was administered)*. 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).

Lumbar punctures will be performed as specified in the schedule of activities (see Appendix 1), with the last CSF sample obtained at the Week 101 end-of-treatment

visit. *After discontinuation of study treatment, LPs will be performed at the ETT and EoT for ETT visits (see Appendix 1a and Appendix 1b).* No study drug will be administered at *these visits*.

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).

- CSF for safety: cell count (RBCs and WBCs), glucose, and protein

The following samples 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
- 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)
- Serum pregnancy test

  Serum pregnancy tests will be performed for women of childbearing potential at screening. 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)
- CSF and blood (plasma) samples for PK analyses and metabolite identification
- Blood (plasma) samples for immunogenicity analyses
- Blood sample for determination of CAG repeat length in *HTT* for patient eligibility
- Blood sample for clinical genotyping to look at factors influencing HTT function and severity of the disease
- CSF samples for analysis of mHTT, NfL, and tau levels to evaluate the effects of RO7234292 compared with placebo (primary and secondary biomarker endpoints)
- Blood, plasma, and CSF samples for exploratory research on biomarkers and biomarker assay development

Exploratory biomarker research may include, but will not be limited to, total HTT protein, and other proteins related to HD, neurodegeneration, and inflammation. Research may involve extraction of DNA and analysis of mutations, single nucleotide polymorphisms, and other genetic variations. Research will not be aimed at distinguishing germline mutations from somatic mutations.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Blood, 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.
- Blood, 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; therefore, these samples will 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, including data on mutations, 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 on study data publication.

4.5.7 Magnetic Resonance Imaging

Structural MRI will be used to assess brain volume, diffusion-weighted MRI will be used to examine structural brain connectivity, and 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. All scans are mandatory unless a site does not have the capability to perform a resting-state functional MRI or diffusion-weighted MRI. For these cases, the Medical Monitor should be consulted; approval to continue without these scans would 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. MRI scans will be managed by a central laboratory to monitor and ensure the integrity and quality of the acquired data. The screening MRI will be evaluated by the central laboratory to determine patient eligibility. Local neuroradiologists will still be responsible for assessing MRI-related ongoing safety monitoring. During central review, the Sponsor and/or site staff will be notified of any unexpected findings requiring clinical follow-up.

MRI 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 QC and the results must be available before the patient can be enrolled in the study.

After patient enrollment at specified timepoints, the MRI must be scheduled to occur before the lumbar puncture (see Appendix 1). The MRI scan should be performed 7–14 days prior to the lumbar puncture 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 lumbar puncture, then it can be conducted the day after the lumbar puncture, as long as there are no post-lumbar puncture contraindications and it occurs within 2 weeks of the original scan.

4.5.8 Electrocardiograms

Triplicate ECG recording will be obtained at specified timepoints, within approximately 5 minutes of each other, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as clinically indicated. For patients in Japan, additional triplicate ECG monitoring will be performed at 2 (± 30 minutes), 4 (± 30 minutes), and 6 (± 30 minutes) hours following the first administration of study drug (Day 1).

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. ECG recording must be performed after the patient has been resting in a supine position for at least 10 minutes. 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.

4.5.9 Patient-Reported, Clinician-Reported, Study Observer-Reported, and Performance Outcomes

Patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) data will be collected in the clinic to document the change from baseline over time. To enable valid acquisition of all study companion–related assessments, including the study companion input to the TFC scale, study companions are required to attend in person all study visits when the TFC rating occurs. Additionally, PRO, ObsRO, and PerfO data will be collected remotely. 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 health authority 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 lumbar puncture procedure.

Patients, clinicians, and study companions will use an electronic device to capture outcome 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. Paper must not be used to capture clinical outcome data, unless it is for performance outcome measures (e.g., SWR, SDMT, and MoCA). Performance measure outcomes must be completed in ink and not pencil.

Patients will use a smartphone and wrist-worn wearable to capture outcome data remotely and at specified visits (see Section 4.5.9.22). Study companions will use an electronic device to capture data remotely and at specified visits. The electronic devices and/or instructions for completing the questionnaires electronically will be provided to patients and study companions by site staff. Study companion device data will be transmitted to a centralized database maintained by the electronic device vendor. The patient device data will be transmitted to a centralized database maintained by the

Sponsor. The data will be available for access by appropriate study personnel. If the device is lost, a replacement will be sent. All devices are encrypted and password protected. See Appendix 1 for the schedule of activities, and Appendix 2 and Appendix 3 for a summary of timing and duration of each PRO, ClinRO, ObsRO, and PerfO assessment. Appendix 4 shows the order and approximate timing of assessments at each clinic visit, while Appendix 5 provides guidelines for the order of assessments. Appendix 10 through Appendix 14 show relevant information for patients who enrolled in Study BN40423 before implementation of Protocol Version 4.

4.5.9.1 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:

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

4.5.9.2 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 and the study companion. The TFC score ranges from 0 to 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 clinic visits. Information for the TFC will be acquired from both the patient and companion, and input of the companion to the rating will be recorded electronically.

4.5.9.3 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 to 124, with a higher score representing more severe impairment. The TMS takes approximately 15 minutes to administer and will be completed at clinic visits.

4.5.9.4 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 clinic visits and can be completed in less than 5 minutes. It will also be administered at specified timepoints indicated in Appendix 7 on the Roche HD mobile app (via electronic SDMT).

4.5.9.5 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 indicated in Appendix 7 on the Roche HD mobile app (via electronic SWR).

4.5.9.6 UHDRS Functional Assessment

The UHDRS Functional Assessment is a checklist of 25 common daily tasks. The investigator indicates if the patient can perform the task by giving a score of 1 to all "yes" replies. The checklist is then summed, and scores can range from 0 (inability to do any task) to 25 (ability to do all tasks on the checklist). The UHDRS FA can be completed in 15 minutes.

4.5.9.7 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 and at specified timepoints. It is a subscale of the UHDRS. The scale consists of 19 discrete levels ranging from 10 to 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 bed care.

4.5.9.8 HD Daily Activities Scale

The HD-DAS assesses patients' daily function. Following a semi-structured interview with the patient and study companion, 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.

4.5.9.9 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 (NRS), 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 postbaseline 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.

4.5.9.10 Patient Global Impression, Severity and Change Scales

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

The PGI-C is a single-item measure of change in global status (since starting the study) and is completed by the patient at specified post-baseline visits. The PGI-C has seven response options: "very much worse," "much worse," "minimally worse," "no change," "minimally improved," "much improved," and "very much improved." 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. The PGI-C can be completed in approximately 2 minutes.

4.5.9.11 Companion-Reported Global Impression, Severity and Change Scales

The Companion-Reported Global Impression–Severity (CrGI-S) is a single-item measure of current global severity and is completed by the companion (about the patient) at specified clinic visits. The CrGI-S can be completed in approximately 2 minutes. The CrGI-S is assessed using an 11-point NRS, where higher scores indicate greater severity.

The Companion-Reported Global Impression–Change (CrGI-C) is a single-item measure of change in global status (since starting the study) and is completed by the companion (about the patient) at specified post-baseline visits. The CrGI-C has seven response options: "very much worse," "much worse," "minimally worse," "no change," "minimally improved," "much improved," and "very much improved." 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. The CrGI-C can be completed in approximately 2 minutes.

4.5.9.12 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. It will be used in this study to characterize patients at screening and longitudinally to assess cognitive status at regular intervals throughout the study. It takes approximately 10 minutes to administer.

4.5.9.13 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 NRS, 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) and by the study companion (about him/herself). It will be completed at specified timepoints remotely by the patient on the Roche HD mobile app and by the study companion on an electronic device.

4.5.9.14 Apathy Evaluation Scale

The AES is an 18-item assessment of apathy, including overt behavior, cognitive aspects of motivation, and emotional responsivity. Each item is scored on a 4-point Likert scale, from 1 ("Not at all") to 4 ("A lot"). A total score is created by summing the 18 items (scores range from 18 to 72; 3 items are reverse scored), with higher scores indicating greater apathy. The AES takes approximately 10 minutes to complete and will be completed by the patient and study companion at specified clinic visits.

4.5.9.15 Neuro-Qol Cognition Function Short Form, Version 2

The Neuro-Qol Cognition Function Short Form contains 8 items (including "trouble concentrating" and difficulty "learning new tasks or instructions"), each assessed using a 5-point Likert scale, where lower scores indicate greater difficulty (4 items) or greater frequency (4 items). The raw sum score is converted to a T-score distribution (mean = 50, standard deviation = 10). The Neuro-Qol Cognition Function Short Form takes approximately 5 minutes to complete and will be completed by the patient at specified clinic visits.

4.5.9.16 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.

4.5.9.17 Symptoms of Major Depressive Disorder Scale

The SMDDS is a newly developed, valid, and reliable self-report assessment of depression (McCarrier et al. 2016). It contains 16 items, measuring concepts such as sadness, irritability, worry, and sleep disturbance. Each item is assessed on a 5-point Likert scale, from "Not at all" to "Extremely" (9 items) and from "Never" to "Always" (7 items). Item scores from 15 of the items (the least severe of the two eating items is not included) are summed to create a 0–60 score, where higher scores indicate more severe depressive symptomatology. The SMDDS takes approximately 10 minutes to complete and will be completed by the patient at specified clinic visits.

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.

4.5.9.18 HD Companion-Reported Irritability and Angry Outbursts Scale

The HD-CIAOS is a study companion-reported assessment of the patient's irritability and angry outbursts over the past 7 days and will be completed at specified timepoints remotely by the companion on an electronic device. It consists of three items: frequency of irritable behavior (6-point Likert scale: "Not at all" to "Always"), frequency of angry outbursts (number of occurrences), and severity of the worst outburst (4-point Likert scale "Mild" to "Very severe"). The HD-CIAOS takes about 2 minutes to complete.

4.5.9.19 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 both by the patient (about him/herself) and by the study companion (about him/herself) at baseline and at specified post-baseline clinic visits on an electronic device. In addition, it will be completed remotely at specified timepoints by the patient on the Roche HD mobile app and by the study companion on an electronic device.

4.5.9.20 Health Utilities Index Mark 2 and Mark 3

The HUI® is a multi-attribute system of health status (Feeny et al. 1995). The HUI2 and HUI3 questionnaire (commonly referred to as HUI2/3) contains 15 items with Likert-type response options. From these items, two scores can be produced: HUI2 (7 items) and HUI3 (8 items). Both scores are health utility indexes, where 0 = death, and 1 = perfect health.

The HUI2/3 will be completed by the companion, both about him/herself and as a proxy report of the patient's HRQoL. The HUI2/3 will be completed at specified timepoints at clinic visits and remotely on an electronic device.

4.5.9.21 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. FDA draft guidance for assessment of suicidality in clinical trials (FDA 2012). The C-SSRS will be used to assess eligibility for the study (full version at baseline, 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).

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.

4.5.9.22 Optional Exit Interviews

Optional exit interviews will be conducted with a subset of patients (up to 60 patients) at select sites within approximately 1 week after the end-of-treatment visit. The semi-structured interviews will be conducted by an external vendor and can be conducted by telephone but may be completed by an in-clinic videotaped session. The interviews will enable patients to provide details about changes they observe in their symptoms, as well as any impacts on daily life.

Interviews will be transcribed verbatim, and themes emerging from these transcripts will be interpreted in relation to changes in patients' clinical outcome assessment scores. All participants in this optional study interview will be asked which arm they thought they were assigned to (120 mg Q8W, 120 mg Q16W, or placebo). Of note, patients *and* staff will remain blind to patient treatment assignment during the study. *Following the Sponsor's decision to permanently discontinue study treatment, the Sponsor will become unblinded to treatment assignment,* as outlined in Section 4.2.

Additional consent for this optional portion of the study will be included in the relevant Informed Consent Form.

4.5.9.23 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). Each patient will receive a preconfigured smartphone and wrist-worn wearable with installed software for the Roche HD mobile app assessments. 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 provided with devices and trained on their use during screening. Patients will also have in-clinic assessments of the digital platform that are supervised as indicated in Appendix 7. Outside of the clinic, patients will be instructed to conduct 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, voice) and non-motor symptoms (processing speed, voice). Testing will usually last approximately 5 minutes in total on a typical day of testing. Not all tests are daily. Additional information on the tasks and schedule is specified in Appendix 7.

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. Companions will receive their own independent electronic device at screening, which is different from the patient smartphone.

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 Wi-Fi. Patients will be asked to charge the devices overnight. If patients have a Wi-Fi network at home, they will be encouraged to connect their smartphone to enable data transfer. If no Wi-Fi network is available, the sensor data will be transferred during clinic visits or after the devices have been returned.

Roche HD mobile app "baseline" data will consist of all data collected prior to and including the baseline visit (up to 28 days). Baseline data will be collected for at least the 7 days up to and including Day 1.

4.5.9.24 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. At specified clinic visits, patients will be asked to conduct the "active test" tasks under the supervision of trained site staff, as shown in Appendix 7.

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. At the time of study completion or early termination, patients will be asked to complete a pen-and-paper satisfaction survey about their experience using the smartphone and wrist-worn wearable.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7234292, the HTT protein, HD or other diseases, or drug safety:

- Blood and serum samples collected at baseline and at Weeks 37, 69, and 101
- Leftover blood, plasma, and CSF samples and any derivatives thereof (e.g., proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, 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 on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF.

If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review,

and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

Due to the Sponsor's decision to discontinue the 120-mg Q4W dosing regimen and replace this with a 120-mg Q16W dosing regimen in Protocol Version 4, all patients who enrolled prior to implementation of Protocol Version 4 will be prematurely discontinued from the study by the Sponsor and will complete their end-of-treatment visit prior to entry into Study BN40955.

Effective 22 March 2021, all patients will be discontinued from study treatment.

Patients who discontinue study treatment and do not withdraw consent for continued participation in the study will follow the existing ETT schedule of assessments, outlined in Appendix 1a and Appendix 1b. Patients who do not consent to version 6 of the protocol should be discontinued from the study.

An excessive rate of withdrawals (either study treatment discontinuation or withdrawal from the study) can render the study results non-interpretable. Therefore, all efforts should be taken to motivate patients to comply with all study-specific procedures and to be followed until the end of the 101-week, placebo-controlled treatment period.

Investigators should explore all possible options to contact patients for visits, especially end-of-treatment visits. The site must document all attempts to try to contact the patient in the patient's medical records and source documents.

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
- Loss of capacity to consent, if legal guardian consent is not possible

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

All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) for collection of *clinical outcome* data for the primary

and secondary endpoints (see Sections 2.1.1, 2.1.2, 2.2, *and Appendix 1b*). If the early treatment termination visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only early treatment termination will be considered. Patients will also attend the scheduled end-of-treatment *(EoT for ETT)* visit at Week 101. *Further clarification on the ETT schedule is provided in Section 3.1.1.1 and Appendix 1b.*

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

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 adverse events 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. The known safety risks for the lumbar puncture 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 adverse events. Guidelines for managing adverse events, 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 through 5.1.1.3) are potential risks associated with lumbar puncture.

In the completed Phase I/IIa study, the most commonly reported adverse events across all treatment groups (RO7234292, n=34; placebo, n=12) were procedural pain (54% of patients) and post–lumbar puncture 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-LP syndrome (14% each).

As of 7 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 lumbar puncture can be avoided by the mandatory use of a 24G atraumatic needle with a stylet, adherence to procedural

guidelines (see lumbar puncture manual and instructional video), and careful assessment of the patient, including neurologic examination with fundoscopy both prior to and post–lumbar puncture procedure. Lumbar puncture should be avoided when a contraindication is present.

CSF 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 lumbar puncture, 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 lumbar puncture and increased intracranial pressure.

There are specific contraindications to performing lumbar puncture. These include unstable cardiorespiratory status, where positioning patient for lumbar puncture 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, lumbar puncture (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. Previous lumbar surgery is an exclusion criterion for this study.

In the setting of HD, for the purposes of lumbar puncture 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 lumbar puncture injection. Post–lumbar puncture syndrome (e.g., headaches, nausea, vomiting, infection, hemorrhage, nerve irritation pain) can occur with IT administration. Experience to date with post–lumbar puncture 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 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 7 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–lumbar procedure (see Section 4.3.2.1). *However*, if a patient develops a headache after the lumbar puncture 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 lumbar puncture. Patients may present with headache, meningism, photophobia, neck stiffness, and pyrexia. Guidelines for management of patients with suspected meningitis are provided in Table 3.

5.1.2 Potential Risks Associated with RO7234292

The potential risks identified below have been considered in relation to clinical data available as of *7 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 to 8 hours following dosing, in the 13-week and in

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 MAD study (ISIS 443139-CS1), no adverse trends in neurological examinations were detected and only a few drug-related neurological adverse events 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 by the investigator not to be 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 intrathecal 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 4 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 lumbar puncture. See Table 3 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 3.

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 other clinically significant hepatic abnormality has been observed.

Liver enzymes will be monitored at each study visit. Guidelines for management of patients who develop decreased liver function are provided in Table 3.

5.1.2.6 Hydrocephalus

Hydrocephalus is included as a warning in the labelling 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 Investigator's 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 (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 Columbia-Suicide Severity Rating Scale (C-SSRS) and the Montreal Cognitive Assessment 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. ASO-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 blinded study drug per injection on a Q8W basis).

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 adverse events are outlined in Table 3. 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 3 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 three 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 twice 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 3 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Thrombocytopenia	• If platelet count is $\leq 100{,}000/mm^3$: o Monitor platelet count weekly • If platelet count is $\leq 75{,}000/mm^3$ and $> 50{,}000/mm^3$ in the absence of major bleeding or clinically relevant non-major bleeding: o Withhold study drug until the platelet count has recovered to $> 100{,}000/mm^3$. o The suitability of the patient for continued dosing and frequency of monitoring should be discussed with the Medical Monitor. • If platelet count is $\leq 50{,}000/mm^3$: o Permanently discontinue study drug. o 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. o Treatment per standard of care should be considered for patients whose platelet count is $< 25{,}000/mm^3$.
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: o eGFR or CrCl (using Cockcroft-Gault) < 60 mL/min o 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 $>3\times$ ULN: o Monitor weekly until ALT and AST return to $\leq 1.2\times$ ULN. o 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): o ALT or AST $>5\times$ ULN o ALT or AST $>3\times$ ULN, combined with total bilirubin $>2\times$ ULN or INR > 1.5 o ALT or AST $>3\times$ ULN coinciding with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia. o 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 adverse events, including serious adverse events and adverse events of special interest, 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 adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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 serious adverse event is any adverse event that meets any of the following criteria:

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

  This does not include any adverse event 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 adverse event 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 adverse event (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 adverse event 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 adverse events (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 adverse event 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 adverse events at each patient contact. All adverse events, 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 serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 5 months after the final dose of study drug or until the patient receives his or her first dose in the OLE study (BN40955), at which time reporting will occur per the new study requirements. *For patients consented to version 6 of the protocol, who have discontinued study treatment and have entered the ETT schedule of assessments, AEs will be reported until 5 months after the last dose of study drug or until the EoT for ETT Week 101 visit (whichever is longer). For patients consented to version 6 of the protocol, who have received their last dose of study treatment less than 5 months before the scheduled Week 101 EoT for ETT visit, an additional safety telephone call should be performed 5 months after the last dose.*

Instructions for reporting adverse events that occur after the adverse event 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 adverse event 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 4 will be used for assessing adverse event severity. Laboratory values determined as an adverse event should be graded as per Appendix 6, which is based on the NCI CTCAE (v5.0).

Table 4 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 adverse event 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 5):

- 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 5 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 adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event 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 adverse events 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 adverse events based on signs and symptoms should be nullified and replaced by one adverse event 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, adverse events 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 adverse event 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 three 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 adverse events 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 adverse event 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 adverse event 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 serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event 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 adverse event. A laboratory test result must be reported as an adverse event 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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP 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 adverse event. 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 adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event 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 adverse event.

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 adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$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 adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ 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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event 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 adverse event 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 adverse event 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 screening 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 adverse event 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 adverse events. 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 adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event 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 adverse event or a serious adverse event:

- 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 adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event 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 adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event 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 or placebo, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with RO7234292 or placebo, regardless of whether they result in an adverse event, 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 or Observer-Reported Outcome Data

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

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 serious adverse events to the local health authority 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 serious adverse events 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 email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 5 months after the final dose of study drug *or until the EoT for ETT Week 101 visit (whichever is longer).* 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 email 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 serious adverse events 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 email 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 serious adverse events 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 Informed Consent Form 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 email 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

A spontaneous abortion should be classified as a serious adverse event (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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event,

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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

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 serious adverse event, 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 adverse event 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 serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (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 serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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 serious adverse event that occurs after the end of the adverse event reporting period (defined as greater than 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 email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event 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

All patients enrolled prior to Version 4 of the protocol will not be included for any efficacy analysis. The safety data collected for these patients up to and including the end of treatment visit in Protocol BN40423 will be analyzed separately.

The primary efficacy analysis will be conducted at the end of the study (see Section 3.2). Treatment assignments will be unblinded to the Sponsor at the end of the study after the data have been cleaned and verified and the database has been locked.

Details of the planned statistical analyses mentioned below will be fully specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking and unblinding of the study database.

Unless otherwise specified, all the p-values considered in Section 6 are two-sided.

6.1 ANALYSIS POPULATIONS

The intent-to-treat (ITT) population will consist of all patients enrolled after implementation of Protocol Version 4 who received any study treatment. Randomized patients who receive 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 primary and secondary efficacy variables.

The safety population for the trial will consist of all patients who enroll after implementation of Version 4 of the protocol and also receive 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.

The PK population will include all patients randomized after implementation of Protocol Version 4 who received at least one dose, and had sufficient sampling to permit PK evaluation.

6.2 DETERMINATION OF SAMPLE SIZE

The planned sample size is adequate to capture meaningful clinical decline on both the TFC and cUHDRS and was estimated on the basis of data available from non-interventional studies (TRACK-HD, COHORT, ENROLL-HD) and a randomized placebo-controlled study (2CARE). Based on these data, using the anticipated trial population, a meta-analysis for the change from baseline at 24 months in TFC score suggested a natural decline of 1.36 points and a corresponding pooled standard deviation of 1.78. A conservative treatment discontinuation rate at Week 101 for patients receiving placebo or active is assumed to be 20% and 15%, respectively. Using these assumptions, the simulation described below was performed to estimate the sample size.

Description of Simulations to Derive the Sample Size

The design used for the simulation was simplified to consider only 2 treatment arms (placebo and active) and 2 postbaseline timepoints (Week 49 and Week 101). These simplifications are justifiable given that:

- The overall alpha level 5% will be split to 2.5%, such that each active treatment will be tested against placebo independently. Within each testing chain, a hierarchical procedure will be used to test the primary endpoint and secondary endpoints (see Section 6.3).
- The difference on the derived sample size for considering more than two postbaseline timepoints would be minimal.

The following algorithm was run and repeated 500,000 times:

1. Generate change from baseline values in TFC at Week 49 and Week 101 for N active patients according to the following bivariate normal distribution:

$$\begin{pmatrix} y\_wk49 \\ y\_wk101 \end{pmatrix} = N\left(\mu = \begin{pmatrix} 0.47 \\ 0.82 \end{pmatrix}, \sum = \begin{pmatrix} 1.56^2 & 1.8 \\ 1.8 & 1.78^2 \end{pmatrix}\right)$$

where y_wk49 and y_wk101 is the change from baseline in TFC, respectively, at Week 49 and Week 101, μ is the assumed true change at those two timepoints, and $\sum$ is the variance-covariance matrix. Subsequently:

- set to missing, due to study drug–related (SDR) reasons, both values at Week 49 and Week 101 for 5% of the N patients. Set to missing, due to non–study drug–related (NSDR) reasons, both values at Week 49 and Week 101 for additional 2.5% of the N active patients.

- set to missing, due to SDR reasons, only the value at Week 101 for additional 5% of the N active patients. Set to missing, due to NSDR reasons, only the value at Week 101 for additional 2.5% of the N active patients.

2. Generate change from baseline values in TFC at Week 49 and Week 101 for N placebo patients according to the following bivariate normal distribution:

$$\begin{pmatrix} y\_wk49 \\ y\_wk101 \end{pmatrix} = N\left(\mu = \begin{pmatrix} 0.79 \\ 1.36 \end{pmatrix}, \sum = \begin{pmatrix} 1.56^2 & 1.8 \\ 1.8 & 1.78^2 \end{pmatrix}\right)$$

where y_wk49 and y_wk101 is the change from baseline in TFC, respectively, at Week 49 and Week 101, μ is the assumed true change at those two timepoints, and $\sum$ is the variance-covariance matrix. Subsequently:

- set to missing both values at Week 49 and Week 101 for 10% of the N placebo patients

- set to missing only the value at Week 101 for additional 10% of the N placebo patients

Given how missing data will be imputed, it is not relevant to differentiate missing data into SDR versus NSDR reasons for placebo patients.

3. Apply multiple imputations and derive 20 complete datasets. Missing data on placebo patients were imputed from the placebo arm. Missing data on active patients, depending on if due to NSDR or SDR reasons, were imputed respectively from the active or the placebo arm.

4. Use a t-test to compare active versus placebo at Week 101 for each completed dataset and pool the result (Rubin 1987) to derive an estimate of the treatment effect, including a p-value.

Across the 500,000 simulations, the power achieved, with the N patients per arm was calculated by dividing the number of times the p-value (in above Step 4) was below 2.5%

by 500,000. The above procedure was repeated by only changing the N until the calculated power was close to 80%.

It was estimated that 267 patients per arm will provide approximately 80% power, at a two-sided $\alpha = 0.025$ level, to detect a 40% slowing of clinical decline for RO7234292 as compared with placebo at 101 weeks. This treatment effect translates into an expected average decline of ~0.82 points at 101 weeks for the RO7234292 arms. The minimal detectable difference with these assumptions is ~0.38 points.

6.3 TESTING STRATEGY AND MULTIPLICITY ADJUSTMENT

The overall alpha level 5% will be split to 2.5% for testing each active treatment against placebo. A hierarchical approach will be used for multiple adjustments that accounts for multiple endpoints (the primary and secondary endpoints).

Within each testing chain (RO7234292 Q8W and RO7234292 Q16W), the endpoint will be tested only if the preceding endpoint is significant at the alpha level 2.5%. Details of the order for secondary endpoints will be detailed in the SAP.

6.4 SUMMARIES OF CONDUCT OF STUDY

The numbers 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. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.5 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, CAG repeat length, CAP, HD stage, education) 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.

6.6 EFFICACY ANALYSES

To ensure the treatment groups under comparison are concurrent and that treatment regimens are comparable across the entire dosing period of the 25-month study, for all efficacy analyses, patients enrolled prior to implementation of Protocol Version 4 will not be included and will be offered the option to enroll into Study BN40955 before reaching the primary endpoint assessment in the current study.

6.6.1 Estimands

Following the very recent estimand framework outlined in the ICH-E9 draft addendum (FDA 2017), the attributes of the estimand for the primary endpoint are defined as follows:

- Population: ITT population (see Section 6.1)
- Variable: Change from baseline in cUHDRS score at Week 101
  - Note: cUHDRS scale will be replaced by TFC scale for the FDA.
- Intercurrent events (ICEs):
  - Treatment discontinued for study drug–related reasons (e.g., treatment-related adverse event or lack of efficacy):
    - After treatment discontinuation, the actual off-treatment values will be used in the analysis.
  - Treatment discontinued for NSDR reasons (e.g., lost to follow-up):
    - After treatment discontinuation, imputed hypothetical values as if patients had continued receiving study drug will be used in the analysis. In this instance, any data collected after treatment discontinuation will not be included in the analysis.
- Population level summary: Difference in mean change from baseline at Week 101 between each active arm and the placebo arm

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE.

The Sponsor will emphasize to investigators the importance of collecting data for the primary endpoint through Week 101, even if patients discontinue study drug but do not withdraw study consent, as well as the importance of providing detailed reasons for treatment discontinuation. The primary estimator, described by the statistical model in Section 6.6.2, will be applied on the dataset produced after multiple imputation of any missing value. In principle,

- missing data as well as off-treatment data from patients who discontinued treatment for NSDR reasons will be imputed from patients with available data from the same treatment arm collected while on treatment
- missing data from patients who discontinued treatment for SDR reasons will be imputed from:
  - patients with available data from the placebo arm collected either while on treatment or off treatment and
  - patients with available data from the same treatment arm collected while off treatment

Multiple imputation of missing data values will be performed as follows:

1. Imputation step: Missing data values will be imputed "m" times leading to "m" complete datasets.
2. Analysis step: Each of the resulting "m" datasets will be analyzed using the statistical model described in Section 6.6.2, which will provide an estimate of treatment difference.
3. Pooling step: The results from the "m" datasets will be combined (Rubin 1987) leading to an overall estimate of the treatment effect and associated 95% confidence intervals and p-values.

Full details of the algorithm for multiple imputation (e.g., which reference population to use for each missing data pattern, number of imputed datasets, method for imputation, etc.) will be provided in the SAP.

A supplementary estimand may be considered (and will be defined in the SAP).

6.6.2 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in cUHDRS score at Week 101. This is defined as the attribute "variable" of the primary estimand in Section 6.6.1.

Note: The primary efficacy endpoint for the U.S. FDA will be change from baseline in the TFC score at Week 101. TFC will be analyzed the same way as the cUHDRS.

The primary efficacy analysis for this study will compare each active treatment arm, RO7234292 Q8W and RO7234292 Q16W, against the placebo arm.

To account for the multiple comparison, an appropriate procedure will be used to maintain the overall two-sided type I error at 5% (details will be given in the SAP).

The analysis of the primary endpoint will be performed by means of analysis of covariance (ANCOVA). The model will include the corresponding endpoint baseline score, CAG repeat length, baseline CAP score (defined in Section 4.1.1), and treatment as covariates. On the basis of this analysis, least squares mean for the treatment differences at Week 101 and corresponding 95% CIs will be derived.

The robustness of the primary method of estimation described above may be explored by alternative sensitivity estimators based on varying assumptions underlying the multiple imputation strategy. These sensitivity analyses will be described in the SAP.

6.6.3 Secondary Efficacy Analyses

The secondary efficacy endpoints are identified in Section 2.1.2.

Similar hypotheses as for the primary efficacy endpoint will be tested for the secondary continuous efficacy endpoints.

Categorical endpoints, such as CGI-C and the proportion of progressors, will be analyzed by means of logistic regression and will include treatment (categorical), CAG repeat length, and CAP score as covariates.

Methods for controlling type I error in the testing of the secondary endpoints will be described in the SAP.

6.6.4 Subgroup Analyses

The results of selected efficacy variables will be summarized within subgroups using descriptive statistics. The following variables will be used to define subgroups:

- Sex (male vs. female)
- Age at baseline (< 45 vs. ≥ 45 years)
- CAG repeat length (< 43 vs. ≥ 43)
- Stage at baseline (I, II, III)
  - Stage III will be considered only if there are enough patients.

Additional exploratory analyses of efficacy results may be performed using an ANCOVA model, similar to the primary analysis, based on change from baseline for the variable of interest, with baseline score (not for analysis by baseline stage), CAP score, CAG repeat length (not for analysis by CAG repeat length), treatment, subgroup, and treatment-by-subgroup interaction as covariates.

6.6.5 Exploratory Efficacy Analysis

The exploratory efficacy endpoints are identified in Section 2.1.3.

The exploratory endpoints will be summarized using tables, listings, and graphs, as appropriate. Additional statistical modeling may be considered (e.g., ANCOVA, logistic regression).

6.6.6 Historical Controls

Should the treatment discontinuation rate in the placebo arm be significantly higher than expected, the Sponsor may consider the use of historical controls for efficacy analysis. In this scenario, the use of historical controls will be deemed supportive analyses.

Prior to database lock, the Sponsor may select historical controls from ENROLL-HD. These historical controls may be selected to match patients with regard to important baseline characteristics (e.g., gender, CAG, age, IS, International Standard Classification of Education). The objective for use and exact algorithm for selecting historical controls will be specified in the SAP. If implemented, the actual selection will

be made before database lock and unblinding of treatment allocation and will be documented and stored in the Sponsor's database.

Whether the Sponsor will decide to use those the historical controls, the exact algorithm for borrowing and for deriving an overall treatment effect will be described in the SAP before unblinding.

Additionally, given that some of the patients who will be enrolled in this study may have been part of ENROLL-HD, the Sponsor may explore a within-patient comparison for the rate of decline in cUHDRS or TFC score, before treatment with RO7234292 (prior to randomization, using ENROLL-HD registry data) and after treatment with RO7234292 (after randomization, using study data), for patients who were randomized to the active arm and had follow-up in ENROLL-HD of at least 1 year's duration prior to randomization into this study.

6.7 SAFETY ANALYSES

The safety population (see Section 6.1) will be the primary population for all analyses of safety data. Incorrect treatment assignments (patients who received a treatment different than their planned randomized treatment) will be summarized and the impact on the safety assessment will be discussed.

For all safety analyses, patients enrolled prior to implementation of the Version 4 of the protocol will be summarized separately.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms. The adverse event severity grading scale indicated in Table 4 will be used for assessing adverse event severity. Laboratory values determined as an adverse event should be graded as per Appendix 6, which is based on the NCI CTCAE (v5.0).

All safety data, including adverse events, laboratory tests, CSSR-S, 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 adverse events will be summarized on the basis of body systems and dictionary preferred terms. The incidence of adverse events by severity and relationship to study drug or study procedure and incidence of marked abnormal laboratory test results will be provided.

The iDMC will review safety data throughout the study. Analyses required for the iDMC data review will be performed as described in the iDMC Charter.

6.8 PHARMACOKINETIC ANALYSES

For all patients in the PK population (Section 6.1), 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., area under the plasma concentration–time curve, average trough plasma concentration) will be computed and used to explore exposure-response relationship on primary and key secondary 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.

6.9 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 or, if no treatment is received prior to study discontinuation, according to treatment assigned.

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 for patients on active treatment only. 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).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported via descriptive statistics.

6.10 BIOMARKER ANALYSES

The biomarker endpoints are described in Section 2.5.

A mixed-effects model repeat measurement model will be used to model the change in each primary and secondary biomarker endpoint, adjusting for the baseline endpoint, CAG repeat length, CAP score, treatment, visit, and treatment-by-visit interaction (the final list of covariates and details of the model will be specified in the SAP).

6.11 HEALTH STATUS UTILITY ANALYSIS

The health status utility endpoints are described in Section 2.6.

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

6.12 OPTIONAL INTERIM ANALYSES

The Sponsor may choose to conduct one or more interim analyses for efficacy. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct an interim analysis, along with the rationale, specification of the endpoint (e.g., clinical and/or biomarker endpoint), number of patients, and statistical details for each analysis, will be introduced via a future protocol amendment, which will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of an interim analysis, and the iDMC Charter will be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of an interim analysis of efficacy data, the type I error rate will be controlled to ensure statistical validity is maintained. Additional criteria for recommending that the study be stopped for positive efficacy will be added to a future protocol amendment.

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.

eCRFs 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.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs 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. eCRFs 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. eCRFs 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-, CLINICIAN-, AND OBSERVER-REPORTED OUTCOME DATA

Electronic devices will be used to capture PRO, ClinRO, ObsRO, and PerfO data. The devices are 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 MONITORING PLATFORM

During "active tests" and "passive monitoring," the smartphone and wrist-worn wearable record 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 Wi-Fi. 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 health authorities.

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 health authority 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, ClinRO, ObsRO (if applicable), and PerfO data (if applicable), Informed Consent Forms, 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 health authorities, 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 health authorities, 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 United States 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 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 Informed Consent Form (and ancillary sample Informed Consent Forms) 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 Informed Consent Forms 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 health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form 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 before his or her participation in the study. The study companion must also sign and date a consent form prior to 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.

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 health authority 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 patient should lose capacity to consent during the study (i.e., after enrollment), as judged by the investigator, a legally authorized representative may sign on behalf of the patient.

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 United States, 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 Informed Consent Forms, 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 adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority 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 health authority 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 Informed Consent Form (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 on 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 health authorities, 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, 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. 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 health authorities. 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, Informed Consent Forms, 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 health authorities. 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., adverse event 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 health authorities; 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 110 sites globally, which may include The Republic of China, will participate to enroll approximately 801 patients after implementation of Version 4 of the protocol. 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.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

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 web site:

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).

10. REFERENCES

Andrzejewski KL, Dowling AV, Stamler D, et al. Wearable sensors in Huntington disease: a pilot study. J Huntington's Dis 2016;5.2:199–206.

Adams JL, Dinesh K, Xiong M,et al. Multiple wearable sensors in parkinson and Huntington disease individuals: a pilot study in clinic and at home. Digit Biomark 2017:1:52–63

Baig SS, Strong M, Quarrell OW. The global prevalence of Huntington's disease: a systematic review and discussion. Neurodegener Dis Manag 2016;6:331–43.

Beglinger LJ, Prest L, Mills JA, et al. Clinical predictors of driving status in Huntington's disease. Mov Disord 2012;27:1146–52.

Bohanna I, Georgiou-Karistianis N, Sritharan A, et al. Diffusion tensor imaging in Huntington's disease reveals distinct patterns of white matter degeneration associated with motor cognitive deficits. Brain Imaging Behav 2011;5:171–80.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Cerritelli SM, Crouch RJ. Ribonuclease H: the enzymes in eukaryotes. FEBS J 2009;276:1494–505.

Crooke ST, Bennett CF. Progress in antisense oligonucleotide therapeutics. Annu Rev Pharmacol Toxicol 1996;36:107–29.

Dogan I, Eickhoff CR, Fox PT, et al. Functional connectivity modeling of consistent cortico-striatal degeneration in Huntington's disease. Neuroimage Clin 2015;7:640–52.

Douaud G, Gaura V, Ribeiro MJ, et al. Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study. Neuroimage 2006;32:1562–75.

Duyao M, Ambrose C, Myers R, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat Genet 1993;4:387–92.

Espinoza FA, Turner JA, Vergara VM, et al. Whole-brain connectivity in a large study of Huntington's disease gene mutation carriers and healthy controls. Brain Connect 2018;8:166–78.

EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

[FDA] Food and Drug Administration. Guidance for industry: suicidal ideation and behavior: prospective assessment of occurrence in clinical trials [resource on the Internet] 2012 [cited 28 February 2018]. Available from: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm315156.htm.

[FDA] Food and Drug Administration. E9(R1) statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials. [resource on the Internet] 2017 [cited 1 August 2018]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582738.pdf.

Feeny D, Furlong W, Boyle M, et al. Multi-attribute health status classification systems. Health utilities index. Pharmacoeconomics 1995;7:490–502.

Genetic Modifiers of Huntington's Disease Consortium. Identification of genetic factors that modify clinical onset of Huntington's disease. Cell 2015;162:516–26.

Harrington DL, Long JD, Durgerian S, et al. Cross-sectional and longitudinal multimodal structural imaging in prodromal Huntington's disease. Mov Disord 2016;31:1664–75.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Hogarth P, Kayson E, Kieburtz K, et al. Interrater agreement in the assessment of motor manifestations of Huntington's disease. Mov Disord 2005;20:293–7.

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

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Johnson EB, Byrne LM, Gregory S, et al. Neurofilament light protein in blood predicts regional atrophy in Huntington disease. Neurology 2018;90:e717–23.

Kordasiewicz HB, Stanek LM, Wancewicz EV, et al. Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron 2012;74:1031–44.

Lipsmeier F, Taylor KI, Kilchenmann T, et al. Evaluation of smartphone-based tsting to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. Mov Disord 2018. doi : 10.1002/mds.27376. Epub ahead of print.

Liu JP, Zeitlin SO. Is huntingtin dispensable in the adult brain? J Huntingtons Dis 2017;6:1–17.

Liu W, Yang J, Chen K, et al. Resting-state fMRI reveals potential neural correlates of impaired cognition in Huntington's disease. Parkinsonism Relat Disord 2016;27:41–6.

Maetzler W, Domingos J, Srulijes K, et al. Quantitative wearable sensors for objective assessment of Parkinson's disease. Mov Disord 2013;28:1628–37.

McCarrier KP, Deal LS, Abraham L, et al. Patient-centered research to support the development of the Symptoms of Major Depressive Disorder Scale (SMDDS): initial qualitative research. Patient 2016;9:117–34.

Moumné L, Betuing S, Caboche J. Multiple aspects of gene dysregulation in Huntington's disease. Front Neurol 2013;4:127.

Nance M, Paulsen JS, Rosenblatt A, et al. A physician's guide to the management of Huntington's disease, 3rd edition. Huntington's Disease Society of America, 2011.

Novak MJ, Seunarine KK, Gibbard CR, et al. Basal ganglia-cortical structural connectivity in Huntington's disease. Hum Brain Mapp 2015;36:1728–40.

Paulsen JS, Long JD, Ross CA, et al. Prediction of manifest Huntington's disease with clinical and imaging measures: a prospective observational study. Lancet Neurol 2014;13:1193–201.

Paulson HL, Albin RL. Huntington's disease: clinical features and routes to therapy. In: Lo DC, Hughes RE, editors. Neurobiology of Huntington's disease: applications to drug discovery. Boca Raton (FL): CRC Press/Taylor & Francis; 2011: Chapter 1.

Peinemann A, Schuller S, Pohl C, et al. Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study. J Neurol Sci 2005;239:11–9.

Penney JB, Young AB, Shoulson I, et al. Huntington's disease in Venezuela: 7 years of follow-up on symptomatic and asymptomatic individuals. Movement Disorders 1990;5:93–9.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266–77.

Ross CA, Pantelyat A, Kogan J, et al. Determinants of functional disability in Huntington's disease: role of cognitive and motor dysfunction. Mov Disord 2014;29:1351–8.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons. 1987.

Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. Neurology 2017;89:2495–2502.

Schoch KM, Miller TM. Antisense oligonucleotides: translation from mouse models to human neurodegenerative diseases. Neuron 2017;94:1056–70.

Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1–3.

Smith, A. Symbol Digit Modalities Test (SDMT). Manual (rev.). Los Angeles: Western Psychological Services, 1982.

Sorensen SA, Fenger K. Causes of death in patients with Huntington's disease and in unaffected first degree relatives. J Med Genet 1992;29:911–4.

Stanek LM, Yang W, Angus S, et al. Antisense oligonucleotide-mediated correction of transcriptional dysregulation is correlated with behavioral benefits in the YAC128 mouse model of Huntington's disease. J Huntingtons Dis 2013;2:217–28.

Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol 2012;11:42–53.

Van Raamsdonk JM, Pearson J, Rogers DA, et al. Loss of wild-type huntingtin influences motor dysfunction and survival in the YAC128 mouse model of Huntington disease. Hum Mol Genet 2005;14:1379–92.

Walker FO. Huntington's disease. Semin Neurol 2007;27:143–50.

Werner CJ, Dogan I, Saß C, et al. Altered resting-state connectivity in Huntington's disease. Hum Brain Mapp 2014;35:2582–93.

Wexler NS, Young AB, Tanzi RE, et al. Homozygotes for Huntington's disease. Nature 1987;326:194–7.

Wild EJ, Boggio R, Langbehn D, et al. Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. J Clin Invest 2015;125:1979–86.

Wild EJ, Tabrizi SJ. Therapies targeting DNA and RNA in Huntington's disease. Lancet Neurol 2017;16:837–47.

Zhang Y, Long JD, Mills JA, et al. Indexing disease progression at study entry with individuals at-risk for Huntington disease. Am J Med Genet B Neuropsychiatr Genet 2011;156:751–63.

Appendix 1a Schedule of Activities for Patients Enrolled after Implementation of Protocol Version 4

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT [b]	Safety Follow-Up Calls [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	−4 to −1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	−28 to −2	−1	1	(±3)	(±7) [dd]												(±7)	(±7)	(≤56)	
Signed informed consent [c]	x																			
Review of inclusion and exclusion criteria	x																			
Demographic data	x																			
Medical history and baseline conditions [d]	x	x[e]																		
Blood sample for CAG repeat length	x																			
Viral serology [f]	x																			
Thyroid panel [g]	x																			
Vital signs [h]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Complete physical examination [i]	x	x[e]			x			x				x				x			x	x
Neurologic examination [j]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
ECG [k]	x	x[e]			x			x				x				x	x		x	x
Hematology [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Chemistry [m]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Pregnancy test [n]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

Appendix 1a: Schedule of Activities for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT [b]	Safety Follow-Up Calls [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	−4 to −1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	−28 to −2	−1	1	(±3)	(±7) [dd]												(±7)	(±7)	(≤56)	
Local INR and/or PT, aPTT, platelet count [x]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	
Urinalysis [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	*x*		x	x
Plasma sample for PK			x		x	x		x [p]		x		x		x		x			x	
Plasma sample for immunogenicity testing			x		x	x		x		x		x		x		x	*x*		x	x
Plasma sample for biomarkers			x		x	x		x		x		x		x		x	*x*		x	x
Blood sample for clinical genotyping			x[e]																	
CSF sample for PK/safety/biomarkers			x	x	x	x	x	x	x	x	x	x	x	x	x	x[y]	*x*		x	
MRI [q]	x				x			x				x				x	x			
HD-DAS	x				x		x		x		x		x		x					
Independence Scale	x		x	x		x		x		x		x		x		x	x		x	
MoCA	x		x	x		x		x		x		x		x		x	x		x	
C-SSRS [r]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
UHDRS FA			x	x		x		x		x		x		x		x	x		x	

Appendix 1a: Schedule of Activities for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT [b]	Safety Follow-Up Calls [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	−4 to −1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	−28 to −2	−1	1	(±3)	(±7) [dd]												(±7)	(±7)	(≤56)	
TFC [s]			x	x		x		x		x		x		x		x	x		x	
TMS [s, cc]	x		x	x		x		x		x		x		x		x	x		x	
CGI-S			x	x		x		x		x		x		x		x	x		x	
CGI-C				x		x		x		x		x		x		x	x		x	
SDMT [s]			x	x		x		x		x		x		x		x	x		x	
SWR [s]			x	x		x		x		x		x		x		x	x		x	
AES			x		x		x		x		x		x		x	x	x			
SMDDS			x		x		x		x		x		x		x	x	x			
NeuroQoL			x	x		x		x		x		x		x		x	x		x	
EQ-5D-5L (in-clinic)			x	x		x		x		x		x		x		x	x		x	
PGI-S			x	x		x		x		x		x		x		x	x		x	
PGI-C				x		x		x		x		x		x		x	x		x	
Roche HD mobile app in-clinic assessments	x		x	x						x						x	x		x	
Roche HD mobile app remote data collection		Continuous remote data collection [t]																	x	
Optional exit interview [u]																x	x			
CRQ: EQ-5D-5L, HUI-self, HUI-proxy, CrGI-S			x	x		x		x		x		x		x		x	x		x	

Appendix 1a: Schedule of Activities for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT [b]	Safety Follow-Up Calls [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	−4 to −1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	−28 to −2	−1	1	(±3)	(±7) [dd]												(±7)	(±7)	(≤56)	
CRQ: AES			x		x		x		x		x		x		x	x	x			
CRQ: CrGI-C				x		x		x		x		x		x		x	x		x	
Remote data collection of CRQ (EQ-5D-5L, HUI-self, HUI-proxy, HD-CIAOS, WPAI)		Remote data collection (see Appendix 4)																	x	
Blood sample for RBR DNA (optional) [v]			x																	
Blood sample for RBR RNA (optional) [v]			x					x				x				x			x	
Serum sample for RBR (optional) [v]			x					x				x				x			x	
Change in medical information since previous visit [w]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lumbar puncture [x]			x	x	x	x	x	x	x	x	x	x	x	x	x	x [y]	x [y]		x [y]	
Study drug administration			x	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]					
Concomitant medications [aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; AES = Apathy Evaluation Scale; BL = baseline; CGI-C = Clinical Global Impression, Change; CGI-S = Clinical Global Impression, Severity; CrGI-C = Companion-Reported Global Impression, Change; CrGI-S = Companion-Reported Global Impression, Severity; CRQ = Companion-reported questionnaire; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; cUHDRS = composite

Appendix 1a: Schedule of Activities for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

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; ETT = early treatment termination; FA = Functional Assessment; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HD = Huntington disease; HD-CIAOS=Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale; HD-DAS = HD Daily Activities Scale; HUI = Health Utilities Index; *LP = lumbar puncture;* MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; Neuro-Qol = Quality of Life in Neurological Disorders; PGI-C = Patient Global Impression, Change; PGI-S = Patient Global Impression, Severity; PK = pharmacokinetic; Q8W = every 8 weeks; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up; SMDDS = Symptoms of Major Depressive Disorder Scale; SWR = Stroop Word Reading; TFC = Total Functional Capacity Scale; TMS = Total Motor Score; UHDRS = Unified Huntington's Disease Rating Scale.

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] A maximum of one 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). If re-screening is required, CAG repeat length testing from the initial screening does not need to be repeated (historical values will not be accepted). The screening MRI and viral serology from the initial screening, including for other Roche studies, may be acceptable as part of the re-screening assessments, if performed within 12 weeks of the baseline visit.

[b] Patients who complete the treatment period will return to the clinic for a treatment completion visit at Week 101 (i.e., the EoT visit). All patients enrolled in Study BN40423 who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study *(including all patients from 22 March 2021)* will *follow the ETT visit schedule (see Appendix 1b and Section 3.1.1.1)*. Study visits should be planned as per the study schedule, however under exceptional circumstances, *a* time window of ±7 days can be utilized. *The ETT visit should take place within 56 days of the decision to discontinue the study treatment.*

Patients enrolled prior to implementation of Version 4 of the protocol: all patients will be prematurely discontinued from the Study BN40423 and will complete their EoT visit for early treatment termination prior to entry into Study BN40955.

[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, HD history (including past hospitalizations [i.e., number, duration, and reason]), over the last 2 years, reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline.

[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. All data should be recorded on the appropriate eCRF.

Appendix 1a: Schedule of Activities for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

[i] A complete physical examination, performed at screening and other specified visits, 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. 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 measured at screening and baseline only.

[j] A neurologic examination (including fundoscopy), performed at screening 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. 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. *At visits when an LP is performed and study treatment is not administered, the neurological examination should be performed prior to the LP.* Weight should also be measured at each visit. Any abnormality identified at baseline (Week 1) 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.

[k] Triplicate ECG are to be performed within approximately 5 minutes of each other, after the patient has been in a supine position for approximately 10 minutes. ECGs for each patient should be obtained from the same machine whenever possible. At screening, baseline (Day −1 or Day 1) and other visits, pre-dose ECG should be performed prior to any blood draws and where applicable before the lumbar puncture. For patients in Japan, additional triplicate ECG monitoring will be performed at 2 (± 30 minutes), 4 (± 30 minutes), and 6 (± 30 minutes) hours following the first administration of study drug (Day 1).

[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] At the Week 37 visit, PK samples will be collected prior to dosing and at 1, 2, and 4 hours post-dose. All patients will remain in clinic at least 4 hours after lumbar puncture.

[q] MRI 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 QC and the results must be available before the patient can be enrolled in the study. At Weeks 13, 37, 69, 101 and at the EoT for ETT visit the MRI should be scheduled to occur before the lumbar puncture. The MRI scan should be performed 7−14 days prior to the lumbar puncture 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 lumbar puncture, then it can be conducted the day after the lumbar puncture, as long as there are no post-lumbar puncture contraindications and it occurs within 2 weeks of the original scan.

[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).

[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] Optional exit interviews will be conducted for patients who consent from the selected sites within approximately 1 week after the EoT visit; these interviews can be conducted by telephone but may be completed by an in-clinic videotaped session.

[v] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[w] At the time of each study drug administration, *non-dosing visit,* and safety follow-up telephone calls, an interval medical history should be obtained and any changes in medications, any major procedures or hospitalizations, and any physician visits for HD or general medical care should be recorded.

Appendix 1a: Schedule of Activities for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

[x] Prior to performing each scheduled lumbar puncture, 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 lumbar puncture. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, 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. Depending on institutional guidelines, local anesthesia should be used for the procedure. Sedation may not be used. Spinal ultrasound may be used for the lumbar puncture procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. Patients will be discouraged from resting supine after the lumbar puncture 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 the case of a failed IT bolus dosing *or a failed CSF collection procedure* (e.g., due to an inadequate establishment of access to the IT space), a second attempt may occur up to 7 days after the originally scheduled attempt. For this additional visit, safety and tolerability evaluations on the day of LP administration will be performed, including neurological examination *(predose and postdose, or pre-procedure if no study treatment is being administered)*, vital signs, and a review of adverse events and concomitant medication. If the second attempt occurs more than 3 days after the first attempt, 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.

[y] CSF samples will be obtained at the Week 101 EoT*, Week 101 EoT for ETT, and ETT visits*, but no study drug will be administered.

[z] Patients in Q16W arm will receive placebo at these visits.

[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 screening to the study completion/discontinuation visit.

[bb] 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, 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] 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.

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

[ee] *During the treatment period, a* safety follow-up telephone call will be conducted for the months in which no clinic visits are. A safety follow-up call will also be conducted approximately 2 months after the Week 101 visit. Telephone safety follow-up calls will assess any changes to ongoing adverse events or occurrence of new adverse events and changes to concomitant medication. Unscheduled visits can occur based on the outcome of this safety follow-up call.

Appendix 1b Schedule of Activities for Early Treatment Termination (Applicable to all Patients from 22 March 2021)

Visit	*ETT* [a]	*FU Week 53* [a]	*FU Week 69* [a]	*EoT for ETT (Week 101)* [a]	*Safety Follow-Up Calls* [b]
Month		*13*	*17*	*25*	
Window (days)	*≤ 56 days after the decision to discontinue study treatment*	*(± 7)*	*(± 7)*	*(± 7)* [c]	*(± 7)*
Vital signs [d]	*x*				
Complete physical examination [e]	*x*				
Neurologic examination [f]	*x*			*x*	
ECG [g]	*x*			*x*	
Hematology [h]	*x*			*x*	
Chemistry [i]	*x*			*x*	
Pregnancy test [j]	*x*			*x*	
Local INR and/or PT, aPTT, platelet count [k]	*x*			*x*	
Urinalysis [l]	*x*			*x*	
Plasma sample for PK	*x*				
Plasma sample for immunogenicity testing	*x*			*x*	
Plasma sample for biomarkers	*x*			*x*	
CSF sample for safety/biomarkers	*x*			*x*	
MRI [m]				*x*	
Independence Scale	*x*	*x*	*x*	*x*	
MoCA	*x*	*x*	*x*	*x*	
C-SSRS [n]	*x*	*x*	*x*	*x*	
UHDRS FA	*x*	*x*	*x*	*x*	

Appendix 1b: Schedule of Activities for Early Treatment Termination (Applicable to all Patients from 22 March 2021) (cont.)

Visit	*ETT* [a]	*FU Week 53* [a]	*FU Week 69* [a]	*EoT for ETT (Week 101)* [a]	*Safety Follow-Up Calls* [b]
Month		*13*	*17*	*25*	
Window (days)	*≤ 56 days after the decision to discontinue study treatment*	*(± 7)*	*(± 7)*	*(± 7)* [c]	*(± 7)*
TFC [o]	*x*	*x*	*x*	*x*	
TMS [o]	*x*	*x*	*x*	*x*	
CGI-S	*x*	*x*	*x*	*x*	
CGI-C	*x*	*x*	*x*	*x*	
SDMT [o]	*x*	*x*	*x*	*x*	
SWR [o]	*x*	*x*	*x*	*x*	
AES				*x*	
SMDDS				*x*	
NeuroQoL	*x*			*x*	
EQ-5D-5L (in-clinic)	*x*			*x*	
PGI-S	*x*			*x*	
PGI-C	*x*			*x*	
Roche HD mobile app in-clinic assessments	*x*			*x*	
Roche HD mobile app remote data collection	*Continuous remote data collection* [p]				
Optional exit interview				*x*	
CRQ: EQ-5D-5L, HUI-self, HUI-proxy, CrGI-S	*x*			*x*	
CRQ: AES				*x*	
CRQ: CrGI-C	*x*			*x*	
Remote data collection of CRQ (EQ-5D-5L, HUI-self, HUI-proxy, HD-CIAOS, WPAI)	*Remote data collection*				

Appendix 1b: Schedule of Activities for Early Treatment Termination (Applicable to all Patients from 22 March 2021) (cont.)

Visit	ETT [a]	FU Week 53 [a]	FU Week 69 [a]	EoT for ETT (Week 101) [a]	Safety Follow-Up Calls [b]
Month		13	17	25	
Window (days)	≤ 56 days after the decision to discontinue study treatment	(± 7)	(± 7)	(± 7) [c]	(± 7)
Blood sample for RBR RNA (optional) [r]	x				
Serum sample for RBR (optional) [r]	x				
Change in medical information since previous visit [s]	x	x	x	x	
Lumbar puncture [k]	x [t]			x [t]	
Concomitant medications [u]	x	x	x	x	
Adverse events [v]	x	x	x	x	

AES = Apathy Evaluation Scale; CGI-C = Clinical Global Impression, Change; CGI-S = Clinical Global Impression, Severity; CrGI-C=Companion-Reported Global Impression, Change; CrGI-S=Companion-Reported Global Impression, Severity; CRQ=Companion-reported questionnaire; CSF = cerebrospinal fluid; C–SSRS = Columbia-Suicide Severity Rating Scale; 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; ETT = early treatment termination; FA = Functional Assessment; FU = follow-up; HD = Huntington disease; HD-CIAOS=Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale; HUI = Health Utilities Index; LP = lumbar puncture; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; Neuro-QoL = Quality of Life in Neurological Disorders; PGI-C = Patient Global Impression, Change; PGI-S = Patient Global Impression, Severity; PK = pharmacokinetic; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; SMDDS = Symptoms of Major Depressive Disorder Scale; SWR = Stroop Word Reading; TFC = Total Functional Capacity Scale; TMS = Total Motor Score; UHDRS = Unified Huntington's Disease Rating Scale.

Notes: Unscheduled safety assessments (MRI, ECG, safety laboratory assessments, vital signs) can be performed if clinically indicated.

[a] All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study (this includes all patients from 22 March 2021) will attend a minimum of two and up to four in-clinic visits depending on which visits have already been completed at the time of study drug discontinuation (see Figure 3). Patients will complete an ETT visit within 56 days (8 weeks) of the decision to discontinue study treatment (i.e., 22 March 2021). Patients will also return to the clinic for FU study visits at Weeks 53 and 69 (if not already completed) for collection of clinical outcome data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, 2.2 and the table above). If the ETT visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only the ETT visit should be performed. Patients will also attend the scheduled EoT for ETT visit at Week 101. Study visits should be planned as per the study schedule, however under exceptional circumstances, a time window of ±7 days can be utilized where shown.

Appendix 1b: Schedule of Activities for Early Treatment Termination (Applicable to all Patients from 22 March 2021) (cont.)

[b] *After study treatment discontinuation, a safety follow-up telephone call should be conducted every 8 weeks between the clinic visits. For patients consented to version 6 of the protocol who received their last dose of study treatment less than 5 months before the scheduled Week 101 EoT for ETT visit, an additional safety telephone call should be performed 5 months after the last dose. Telephone safety follow-up calls will assess any changes to ongoing adverse events or occurrence of new adverse events and changes to concomitant medication which should be documented in the eCRF. Unscheduled visits can occur based on the outcome of this safety follow-up call.*

[c] *Excluding MRIs, which have a visit window of –14 to –7 days.*

[d] *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. All data should be recorded on the appropriate eCRF.*

[e] *The 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. 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.*

[f] *A neurologic examination (including fundoscopy) 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. At visits when an LP is performed and study treatment is not administered, the neurological examination should be performed prior to the LP. 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.*

[g] *Triplicate ECG are to be performed within approximately 5 minutes of each other, after the patient has been in a supine position for approximately 10 minutes. ECGs for each patient should be obtained from the same machine whenever possible. The ECG should be performed prior to any blood draws and before the lumbar puncture.*

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

[i] *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.*

[j] *Urine pregnancy tests will be performed at specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.*

Appendix 1b: Schedule of Activities for Early Treatment Termination (Applicable to all Patients from 22 March 2021) (cont.)

[k] *Prior to performing each scheduled lumbar puncture, 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 lumbar puncture. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 5 mL should be collected over a maximum of 60 minutes, once CSF flow has been established. 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 lumbar puncture procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. Patients will be discouraged from resting supine after the lumbar puncture 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 the case of a failed CSF collection procedure (e.g., due to an inadequate establishment of access to the IT space), a second attempt may occur up to 7 days after the originally scheduled attempt. For this additional visit, safety and tolerability evaluations on the day of LP administration will be performed, including a pre-procedure neurological examination, vital signs, and a review of adverse events and concomitant medication. If the second attempt occurs more than 3 days after the first attempt, 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.*

[l] *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).*

[m] *The MRI should be scheduled to occur before the lumbar puncture. The MRI scan should be performed 7–14 days prior to the lumbar puncture 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 lumbar puncture, then it can be conducted the day after the lumbar puncture, as long as there are no post-lumbar puncture contraindications and it occurs within 2 weeks of the original scan.*

[n] *The C-SSRS will be used to monitor the patients (follow-up version, requiring approximately 5 minutes to administer, assuming absence of suicidal ideation and no change in clinical status from previous administration).*

[o] *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.*

[p] *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.*

[q] *Optional exit interviews will be conducted for patients who consent from the selected sites within approximately 1 week after the EoT for ETT visit; these interviews can be conducted by telephone but may be completed by an in-clinic videotaped session.*

[r] *Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.*

Appendix 1b: Schedule of Activities for Early Treatment Termination (Applicable to all Patients from 22 March 2021) (cont.)

[s] *An interval medical history should be obtained at each clinic visit and safety telephone call and any changes in medications, any major procedures or hospitalizations, and any physician visits for HD or general medical care should be recorded.*

[t] *CSF samples will be obtained at the Week 101 EoT for ETT, and ETT visits but no study drug will be administered.*

[u] *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 screening to the study completion/discontinuation visit.*

[v] *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 (see Section 5.6).*

Appendix 2 Clinician-Reported Outcomes for Patients Enrolled after Implementation of Protocol Version 4

Assessment	Name	Items	Concepts	Approx. Duration	Timing
FA	UHDRS Functional Assessment	25	Daily function	15 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
IS	Independence Scale	1	Functional disability	3 min	Screening, baseline, and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TFC	Total Functional Capacity Scale	5	Overall function	10 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TMS	Total Motor Score	31	Motor function	15 min	DCL only: Screening TMS without DCL: Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
C-SSRS	Columbia-Suicide Severity Scale	5	Suicidal ideation and behavior	20 min full version; 5 min follow-up version	Full version at screening in clinic; follow-up version at baseline and all post-baseline clinic visits
CGI-S	Clinical Global Impression, Severity	1	Overall severity of patient status	2 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
CGI-C	Clinical Global Impression, Change	1	Overall change in patient status	2 min	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
HD-DAS	Huntington's Disease Daily Activities Scale	25	Daily function	25 min	Screening and Weeks 13, 29, 45, 61, 77, and 93

DCL = diagnostic confidence level.

Appendix 3 Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled after Implementation of Protocol Version 4

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
AES	Apathy Evaluation Scale	18	Apathy	10	PRO + ObsRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
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	5	Sensor data, PRO, PerfO	Daily + at clinic visits (Screening, baseline and Weeks 5, 53, and 101 and ETT visits)	Roche HD mobile app
CrGI-C	Companion-Reported Global Impression, Change	1	Overall change in patient status	2	ObsRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
CrGI-S	Companion-Reported Global Impression, Severity	1	Overall severity of patient status	2	ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire	6	Health utilities	5	PRO + ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						Weekly	Roche HD mobile app; electronic device

Appendix 3: Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
HD-SDI	Huntington's Disease Speaking Difficulty Item	1	Speech	1	PRO	Weekly	Roche HD mobile app
HD-CIAOS	Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale	3	Irritability and angry outbursts	2	ObsRO	Weekly	Electronic device
HUI®	Health Utilities Index	15	Health-related quality of life	10	ObsRO	Baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
						Weekly	Electronic device
MoCA	Montreal Cognitive Assessment	11	Overall cognitive status	10	PerfO	Screening, baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
Neuro-Qol Cog Func	Neuro-Qol Cognitive Function Short Form	8	Cognition	5	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101	In-clinic
PGI-C	Patient Global Impression, Change	1	Overall change in patient status	2	PRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
PGI-S	Patient Global Impression, Severity	1	Overall severity of patient status	2	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic

Appendix 3: Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
SDMT/ eSDMT	Symbol Digit Modalities Test	Max number in 90 seconds	Cognitive	5	PerfO	SDMT at baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						eSDMT monthly + at clinic visits (screening, baseline, Weeks 5, 53,101, and ETT)	Roche HD mobile app (eSDMT)
SMDDS	Symptoms of Major Depressive Disorder Scale	16	Depression, anxiety, irritability, sleep	10	PRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
SWR/eSWR	Stroop Word Reading Test	Max numbers in 45 seconds	Cognitive	5	PerfO	SWR at baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						eSWR monthly + at clinic visits (screening, baseline, Weeks 5, 53, and 101 and ETT)	Roche HD mobile app (eSWR)
WPAI	Work Productivity and Activity Impairment	6	Work productivity	5	PRO + ObsRO	Baseline and then monthly	Roche HD mobile app and electronic device

app = application; ETT = early treatment termination; HD = Huntington disease; ObsRO = observer-reported outcome; PerfO = performance outcome; PRO = patient-reported outcome.

Appendix 4 Clinical Assessments Order and Duration for Patients Enrolled after Implementation of Protocol Version 4

Table 1 Screening Visit Clinical Assessments

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Diagnostic Confidence Level [a] Huntington's Disease Daily Activities Scale Independence Scale MoCA C-SSRS	~60	Qualified study physician
Break (if needed)		~20-30	
2	Roche HD mobile application	~20	Qualified study personnel

C-SSRS = Columbia-Suicide Severity Rating Scale; DCL = Diagnostic Confidence Level; HD = Huntington disease; 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 4: Clinical Assessments Order and Duration for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

Table 2 Baseline and Week 101 Clinical Assessments (for Primary Analysis)

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change (post-baseline visits only)	~60	Qualified study physician
Break (if needed)		~20–30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10–20	
4 [a]	Neuro-Qol Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change (post-baseline visits only)	~20	Qualified study personnel
Break (if needed)		~10–20	
5 [a]	Roche HD mobile application	~20	Qualified study personnel

HD = Huntington disease; MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale.

[a] At the baseline visit and at Week 101, Blocks 3, 4, and 5 can be completed on the same day after Blocks 1 and 2, or on the following day, but must be completed predose at the baseline visit.

Appendix 4: Clinical Assessments Order and Duration for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

Table 3 Follow-Up Clinical Assessments at Weeks 5, 21, 37, 53, 69, and 85

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change	~60	Qualified study physician
Break (if needed)		~20-30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3	Neuro-Qol Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change	~30	Qualified study personnel
4	Roche HD mobile application [a]	~20	Qualified study personnel

MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale

[a] These assessments will take place only at Weeks 5 and 53.

Appendix 4: Clinical Assessments Order and Duration for Patients Enrolled after Implementation of Protocol Version 4 (cont.)

Table 4 Follow-Up Clinical Assessments at Weeks 13, 29, 45, 61, 77, and 93

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10	
2	Huntington's Disease-Daily Activities Scale	~25	Qualified study physician

[a] To be completed prior to safety assessments.

Appendix 5 Guidelines for Order of Assessments

This guidance is in addition to what is mandated throughout this protocol, including from Section 4.5.9.

- Screening Visits: Screening assessments can be performed over several days through the 28-day screening period. Blood sample for CAG repeat testing and the MRI scans should be taken as early as possible to enable the results to be available in time for randomization. The electronic clinical outcome assessments (eCOAs) can be done after eligibility has been confirmed for all other parameters, so that patients and sites are not spending unnecessary time on eCOAs before knowing if the patient will fulfill all the other eligibility criteria.
- All eCOA blocks should always be done in a sequential order as per Appendix 2, Appendix 3, and Appendix 4. One block cannot be done before the previous block is completed (i.e., the blocks should be completed sequentially as Block 1, Block, 2, Block 3, Block 4, and Block 5).
- Within a block, the protocol order should be kept to prevent bias. All the assessments have been ordered by importance for the primary and secondary study endpoints.
- eCOA blocks can be split over 2 consecutive days. When eCOA blocks are split over 2 consecutive days, Blocks 1 and 2 should always be completed together on the same day. As such, either Blocks 1–5 or just 1 and 2 can be done the day before dosing.
- The same methodology should be kept for an individual patient's eCOAs, to prevent intra-patient variability. For example, if the blocks are done all together, they should be performed that way for all visits, but at a minimum for baseline and Week 101 visits.
- The same timings should be kept for each patient's eCOAs at each visit, but especially for Day 1 and Week 101 visits.
- Blood sampling (all or just coagulation) can be done before Block 1 or after Block 5 or between blocks, but only as follows:
    - The eCOAs are separated into 2 consecutive days
    - The blood sampling should be done after Block 2 but should not be done before Block 3 on the following day.

Therefore, blood sampling can occur the day before (before Block 1, after Block 2, or after Block 5) depending on which eCOAs are done the day before dosing. Alternatively, blood sampling can be done before Block 1 on the day of dosing. Again the same methodology should be used for the patient throughout the study but in particularly for the Day 1 and Week 101 visits.

Appendix 6 Grading Scale for Adverse Events Relating to Laboratory Abnormalities for All Patients

The following grading recommendations for adverse events relating to lab 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

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

Appendix 6: Grading Scale for Adverse Events Relating to Laboratory Abnormalities for All Patients (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[t]
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

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

Appendix 6: Grading Scale for Adverse Events Relating to Laboratory Abnormalities for All Patients (cont.)

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)

Appendix 7 Roche HD Mobile Application for Patients Enrolled after Implementation of Protocol Version 4: Active Test

The following tasks are part of the "active tests" conducted on the Roche Huntington's Disease (HD) mobile application by the patient.

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 (eSDMT)
The Cognitive Test asks participants to match symbols with numbers according to a key as quickly and accurately as possible. The key, symbols, numbers are all displayed on a smartphone screen. The test assesses visuo-motor integration, and measures visual attention and motor speed. It is modelled on the pen and paper Symbol Digit Modalities Test (SDMT) (Smith, 1968). The SDMT has been shown to be sensitive to symptom changes in early HD patients (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 modelled on the Stroop Word Reading (SWR) (Ridley 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 modelled 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 early HD patients. It is modelled 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 two points that are at least four steps apart, while wearing the smartphone and wrist-worn wearable. They need to make at least five turns. The test is designed to assess gait and lower-body bradykinesia, which are also assessed by the UHDRS. It is modelled 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 done in 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).

Tasks are automatically scheduled as shown below in Figure 1 and take no more than 5 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., EuroQol 5-Dimension, 5 Level Questionnaire, Work Productivity and Activity Impairment, Huntington's Disease Speaking Difficulty Item, 2-Minute Walk Test) are rolled over to the next time the active test is completed.

References

Bechtel N, Scahill RI, Rosas HD, et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. Neurology 2010;75:2150–60.

Berg KO, Wood-Dauphinee SL, Williams JI, et al. Measuring balance in the elderly: validation of an instrument. Can J Public Health 1992;83(Suppl 2):S7–11.

Busse ME, Wiles CM, Rosser AE. Mobility and falls in people with Huntington's disease. J Neurol Neurosurg Psychiatry 2009;80:88–90.

Dalton A, Khalil H, Busse M, et al. Analysis of gait and balance through a single triaxial accelerometer in presymptomatic and symptomatic Huntington’s disease. Gait Posture 2013;37:49–54.

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136–42.Kegelmeyer et al. 2017

Rao AK, Muratori L, Louis ED, et al. Clinical measurement of mobility and balance impairments in Huntington's disease: validity and responsiveness. Gait Posture 2009;29:433–6.

Reilmann R, Bohlen S, Kirsten F, et al. Assessment of involuntary choreatic movements in Huntington's disease—toward objective and quantitative measures. Mov Disord 2011;26:2267–73.

Reilmann R, Bohlen S, Klopstock T, et al. Grasping premanifest Huntington's disease - shaping new endpoints for new trials. Mov Disord 2010;25:2858–62.

Say MJ, Jones R, Scahill R, et al. Visuomotor integration deficits precede clinical onset in Huntington's disease. Neuropsychologia 2011;49:264–70.

Smith A. The symbol-digit modalites test: a neuropsychologic test of learning and other cerebral disorders. In: Helmuth J, editor. Learning disorders. Seattle: Special Child Publications; 1968:83–91.

Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.

Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. The Lancet Neurology 2012;11.1:42–53.

Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12:637–49.

Figure 1 Timing of Assessments

	Screening, Baseline, Week 5, 53, 101, ETT	Timing of assessments in 4-week rotation (day)																											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
PROs																													
2 Daily Questions (Physical, Mood)	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
EQ-5D-5L		o							o							o							o						
WPAI					o																								
HD-SDI							o							o							o							o	
Cognitive Tests																													
eSDMT	o																	o											
Word reading test	o																	o											
Motor tests																													
Speeded tapping Test (L+R)	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Draw shape Test (L+R)	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Chorea Test (L+R)	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Balance Test	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
U-Turn Test	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Walking																													
2 Minute Walk Test		o							o							o							o						

EQ-5D-5L = EuroQol 5-Dimension, 5 Level Questionnaire; eSDMT = electronic Symbol Digit Modalities Test; HD-SDI = Huntington's Disease Speaking Difficulty Item; L = left; PRO = patient-reported outcome; R = right; WPAI=Work Productivity and Activity Impairment Questionnaire.

Appendix 8 Diagnostic Confidence Level for All Patients

The Diagnostic Confidence Level is calculated as shown below (from UHDRS Total Motor Score 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 9 Guidance for Neurological Examination for All Patients

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 and study treatment is not administered, the neurological examination should be performed prior to the lumbar puncture.*

Appendix 10 Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	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	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
Signed informed consent [c]	x																														
Review of inclusion and exclusion criteria	x																														
Demographic data	x																														
Medical history and baseline conditions [d]	x	x [e]																													
Blood sample for CAG repeat length	x																														
Viral serology [f]	x																														
Thyroid panel [g]	x																														
Vital signs [h]	x	x [e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Complete physical examination [i]	x	x [e]				x						x								x								x		x	x
Neurologic examination [j]	x	x [e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG [k]	x	x [e]				x						x								x								x	x	x	x
Hematology [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

Appendix 10: Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	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	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
Chemistry [m]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Pregnancy test [n]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Local INR, aPTT, PT platelet count [x]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Urinalysis [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Plasma sample for PK			x			x		x				x [p]				x				x				x				x		x	
Plasma sample for immunogenicity testing			x			x		x				x				x				x				x				x		x	x
Plasma sample for biomarkers			x			x		x				x				x				x				x				x		x	x
Blood sample for clinical genotyping		x[e]																													
CSF sample for PK/safety/biomarkers			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[y]		x	
MRI [q]	x					x						x								x								x	x		
HD-DAS	x					x				x				x				x				x				x					
Independence Scale	x		x	x				x				x				x				x				x				x	x	x	
MoCA	x		x	x				x				x				x				x				x				x	x	x	
C-SSRS [r]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 10: Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	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	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
UHDRS FA			x	x				x				x				x				x				x				x	x	x	
TFC [s]			x	x				x				x				x				x				x				x	x	x	
TMS [s, cc]	x		x	x				x				x				x				x				x				x	x	x	
CGI-S			x	x				x				x				x				x				x				x	x	x	
CGI-C				x				x				x				x				x				x				x	x	x	
SDMT [s]			x	x				x				x				x				x				x				x	x	x	
SWR [s]			x	x				x				x				x				x				x				x	x	x	
AES			x			x				x				x				x				x				x		x	x		
SMDDS			x			x				x				x				x				x				x		x	x		
NeuroQoL			x	x				x				x				x				x				x				x	x	x	
EQ-5D-5L (in-clinic)			x	x				x				x				x				x				x				x	x	x	
HUI® (in-clinic)			x	x				x				x				x				x				x				x	x	x	
PGI-S			x	x				x				x				x				x				x				x	x	x	
PGI-C				x				x				x				x				x				x				x	x	x	
Roche HD mobile app in-clinic assessments	x		x						x						x						x							x	x	x	
Roche HD mobile app remote data collection	Continuous remote data collection [t]																														

Appendix 10: Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	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	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
Optional exit interview [u]																												x	x		
Blood sample for RBR DNA (optional) [v]			x																												
Blood sample for RBR RNA (optional) [v]			x									x								x								x		x	
Serum sample for RBR (optional) [v]			x									x								x								x		x	
Change in medical information since previous visit [w]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lumbar puncture [x]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [y]		x [y]	
Study drug administration			x	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]				
Concomitant medications [aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; AES = Apathy Evaluation Scale; BL = baseline; 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; ETT = early treatment termination; FA = Functional Assessment; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HD = Huntington disease; HD-DAS = HD Daily Activities Scale; HUI = Health Utilities Index; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; Neuro-Qol = Quality of Life in Neurological Disorders; PGI-C = Patient Global Impression,

Appendix 10: Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

Change; PGI-S = Patient Global Impression, Severity; PK = pharmacokinetic; Q8W = every 8 weeks; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up; SMDDS = Symptoms of Major Depressive Disorder Scale; SWR = Stroop Word Reading; TFC = Total Functional Capacity Scale; TMS = Total Motor Score; UHDRS = Unified Huntington's Disease Rating Scale.

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] A maximum of one 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). If re-screening is required, CAG repeat length testing does not need to be repeated and 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 baseline visit.

[b] Patients who complete the treatment period will return to the clinic for a treatment completion visit at Week 101 (i.e., the EoT visit). All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) and at Week 101 (i.e., the EoT for ETT visit) for collection of at least the data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). If the ETT visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only ETT will be considered. The ETT visit should be performed 28 days (±3 days) after the last dose. Patients will also attend the scheduled EoT for ETT visit at Week 101 for limited assessments including the collection of the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). Study visits should be planned as per the study schedule, however under exceptional circumstances, time window of ±3 days can be utilized.

[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, HD history (including past hospitalizations [i.e., number, duration, and reason]), over the last 2 years, reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline.

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

[f] Viral serology: HBsAg and HCV antibody

[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 baseline (Day -1 or Day 1) 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, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems (including fundoscopy); 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. 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 measured at screening only.

Appendix 10: Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

[j] A neurologic examination, performed at screening and at every clinical visit, should include assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, 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. Weight should also be measured at each visit. Any abnormality identified at baseline 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.

[k] Triplicate ECG are to be performed after the patient has been in a supine position for approximately 10 minutes. ECGs for each patient should be obtained from the same machine whenever possible. At screening, baseline (Day −1 or Day 1) and other visits, pre-dose ECG should be performed prior to any blood draws and where applicable before the lumbar puncture.

[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 (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[p] At the Week 37 visit, PK samples will be collected prior to dosing and at 1, 2, and 4 hours post-dose. All patients will remain in clinic at least 4 hours after lumbar puncture.

[q] At Weeks 13, 37, and 69 and at the EoT visit, the MRI should be scheduled to occur before the lumbar puncture. It can be scheduled in the days prior to the lumbar puncture (provided it occurs within the visit window). After patient enrollment, the MRI scan should be performed 7−14 days prior to the lumbar puncture to allow time for re-scanning if the quality of the initial MRI is inadequate. MRI should take place as early as possible within the screening window but may take place at any time during screening. Results must be available before the patient can be enrolled in the study.

[r] The C-SSRS will be used to assess eligibility for the study (full version at baseline, 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).

[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.

Appendix 10: Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

[u] Optional exit interviews will be conducted within approximately 1 week after the EoT visit; these interviews can be conducted by telephone.

[v] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[w] At the time of each study drug administration, an interval medical history should be obtained and any changes in medications, any major procedures or hospitalizations, and any physician visits for HD or general medical care should be recorded.

[x] Prior to performing each scheduled lumbar puncture, local laboratory analysis of coagulation factors (INR, aPTT, PT) 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 lumbar puncture. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 5 mL should be collected over a maximum of 60 minutes. 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 Whitacre (atraumatic) needle 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 lumbar puncture procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. Patients will be discouraged from resting supine after the lumbar puncture procedure and will be encouraged to mobilize immediately by walking around at a minimum and, if feasible, walking briskly.

[y] The last CSF sample will be obtained at the Week 101 EoT visit, but no study drug will be administered.

[z] Patients in Q8W arm will receive placebo at these visits.

[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 screening to the study completion/discontinuation visit.

[bb] 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, 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] 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.

[dd] Excluding MRIs, which have a visit window of −14 days.

Appendix 11 Clinician-Reported Outcomes for Patients Enrolled before Implementation of Protocol Version 4

Assessment	Name	Items	Concepts	Approx. Duration	Timing
FA	UHDRS Functional Assessment	25	Daily function	15 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
IS	Independence Scale	1	Functional disability	3 min	Screening, baseline, and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TFC	Total Functional Capacity Scale	5	Overall function	10 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TMS	Total Motor Score	31	Motor function	15 min	DCL only: Screening TMS without DCL: Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
C-SSRS	Columbia-Suicide Severity Scale	5	Suicidal ideation and behavior	20 min full version; 5 min follow-up version	Full version at screening in clinic; follow-up version at baseline and all post-baseline clinic visits
CGI-S	Clinical Global Impression, Severity	1	Overall severity of patient status	2 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
CGI-C	Clinical Global Impression, Change	1	Overall change in patient status	2 min	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
HD-DAS	Huntington's Disease Daily Activities Scale	25	Daily function	25 min	Screening and Weeks 13, 29, 45, 61, 77, and 93

DCL = diagnostic confidence level.

Appendix 12 Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
AES	Apathy Evaluation Scale	18	Apathy	10	PRO + ObsRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
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	5	Sensor data, PRO, PerfO	Daily + at clinic visits (Screening, baseline and Weeks 25, 49, 73, and 101 and ETT visits)	Roche HD mobile app
CrGI-C	Companion-Reported Global Impression, Change	1	Overall change in patient status	2	ObsRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
CrGI-S	Companion-Reported Global Impression, Severity	1	Overall severity of patient status	2	ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire	6	Health utilities	5	PRO + ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						Weekly	Roche HD mobile app; electronic device

Appendix 12: Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
HD-SDI	Huntington's Disease—Speaking Difficulty Item	1	Speech	1	PRO	Weekly	Roche HD mobile app
HD-CIAOS	Huntington's Disease—Companion-Reported Irritability and Angry Outbursts Scale	3	Irritability and angry outbursts	2	ObsRO	Weekly	Electronic device
HUI®	Health Utilities Index	15	Health-related quality of life	10	ObsRO	Baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
						Weekly	Electronic device
MoCA	Montreal Cognitive Assessment	11	Overall cognitive status	10	PerfO	Screening, baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
Neuro-Qol Cog Func	Neuro-Qol Cognitive Function Short Form	8	Cognition	5	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101	In-clinic
PGI-C	Patient Global Impression, Change	1	Overall change in patient status	2	PRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
PGI-S	Patient Global Impression, Severity	1	Overall severity of patient status	2	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic

Appendix 12: Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
SDMT/ eSDMT	Symbol Digit Modalities Test	Max number in 90 seconds	Cognitive	5	PerfO	SDMT at baseline and Weeks 5, 21, 37, 53, 61 69, 85, and 101 and ETT visits	In-clinic
						eSDMT at screening, baseline, and Week 101 in last block post-SDMT assessment	Roche HD mobile app (eSDMT)
SMDDS	Symptoms of Major Depressive Disorder Scale	16	Depression, anxiety, irritability, sleep	10	PRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
SWR/eSWR	Stroop Word Reading Test	Max numbers in 45 seconds	Cognitive	5	PerfO	SWR at baseline and Weeks 5, 21, 37, 53, 61 69, 85, and 101 and ETT visits	In-clinic
						eSWR at screening, baseline, and Week 101 in last block post-SWR assessment	Roche HD mobile app (eSWR)
WPAI	Work Productivity and Activity Impairment	6	Work productivity	5	PRO + ObsRO	Monthly	Roche HD mobile app and electronic device

app = application; ETT = early treatment termination; HD = Huntington disease; ObsRO = observer-reported outcome; PerfO = performance outcome; PRO = patient-reported outcome.

Appendix 13 Clinical Assessments Order and Duration for Patients Enrolled before Implementation of Protocol Version 4

Table 1 Screening Visit Clinical Assessments

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Diagnostic Confidence Level Huntington's Disease Daily Activities Scale Independence Scale MoCA C-SSRS	~60	Qualified study physician
Break (if needed)		~20-30	
2	Roche HD mobile application	~20	Qualified study personnel

C-SSRS = Columbia-Suicide Severity Rating Scale; HD = Huntington disease; MoCA = Montreal Cognitive Assessment.

Table 2 Baseline and Week 101 Clinical Assessments (for Primary Analysis)

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change (post-baseline visits only)	~60	Qualified study physician
Break (if needed)		~20–30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10–20	
4 [a]	Neuro-Qol Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change (post-baseline visits only)	~20	Qualified study personnel
Break (if needed)		~10–20	
5 [a]	Roche HD mobile application	~20	Qualified study personnel

HD = Huntington disease; MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale.

[a] At the baseline visit and at week 101, Blocks 3, 4, and 5 can be completed on the same day after Blocks 1 and 2, or on the following day, but must be completed predose at the baseline visit.

Table 3 Follow-Up Clinical Assessments at Weeks 5, 21, 37, 53, 69, and 85

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change	~60	Qualified study physician
Break (if needed)		~20-30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3	Neuro-Qol Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change	~30	Qualified study personnel

MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale

Table 4 Follow-Up Clinical Assessments at Weeks 13, 29, 45, 61, 77, and 93

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10	
2	Huntington's Disease-Daily Activities Scale	~25	Qualified study physician

[a] To be completed prior to safety assessments.

Table 5 Digital Monitoring Platform Assessment Supervised by Study Staff in Clinic at Weeks 25, 49, 73

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Roche HD mobile application	~20	Qualified study personnel

HD = Huntington disease.

Appendix 14 Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4: Active Test

The following tasks are part of the "active tests" conducted on the Roche Huntington's Disease (HD) mobile application by the patient.

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 (eSDMT)
The Cognitive Test asks participants to match symbols with numbers according to a key as quickly and accurately as possible. The key, symbols, numbers are all displayed on a smartphone screen. The test assesses visuo-motor integration, and measures visual attention and motor speed. It is modelled on the pen and paper Symbol Digit Modalities Test (SDMT) (Smith, 1968). The SDMT has been shown to be sensitive to symptom changes in early HD patients (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 modelled on the Stroop Word Reading (SWR) (Ridley 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 modelled 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 early HD patients. It is modelled 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 two points that are at least four steps apart, while wearing the smartphone and wrist-worn wearable. They need to make at least five turns. The test is designed to assess gait and lower-body bradykinesia, which are also assessed by the UHDRS. It is modelled 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 done in 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).

Tasks are automatically scheduled as shown below in Figure 1 and take no more than 5 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., EuroQol 5-Dimension, 5 Level Questionnaire, Work Productivity and Activity Impairment, Huntington's Disease Speaking Difficulty Item, 2-Minute Walk Test) are rolled over to the next time the active test is completed.

References

Bechtel N, Scahill RI, Rosas HD, et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. Neurology 2010;75:2150–60.

Berg KO, Wood-Dauphinee SL, Williams JI, et al. Measuring balance in the elderly: validation of an instrument. Can J Public Health 1992;83(Suppl 2):S7–11.

Busse ME, Wiles CM, Rosser AE. Mobility and falls in people with Huntington's disease. J Neurol Neurosurg Psychiatry 2009;80:88–90.

Dalton A, Khalil H, Busse M, et al. Analysis of gait and balance through a single triaxial accelerometer in presymptomatic and symptomatic Huntington's disease. Gait Posture 2013;37:49–54.

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136–42.Kegelmeyer et al. 2017

Rao AK, Muratori L, Louis ED, et al. Clinical measurement of mobility and balance impairments in Huntington's disease: validity and responsiveness. Gait Posture 2009;29:433–6.

Reilmann R, Bohlen S, Kirsten F, et al. Assessment of involuntary choreatic movements in Huntington's disease—toward objective and quantitative measures. Mov Disord 2011;26:2267–73.

Reilmann R, Bohlen S, Klopstock T, et al. Grasping premanifest Huntington's disease - shaping new endpoints for new trials. Mov Disord 2010;25:2858–62.

Say MJ, Jones R, Scahill R, et al. Visuomotor integration deficits precede clinical onset in Huntington's disease. Neuropsychologia 2011;49:264–70.

Smith A. The symbol-digit modalites test: a neuropsychologic test of learning and other cerebral disorders. In: Helmuth J, editor. Learning disorders. Seattle: Special Child Publications; 1968:83–91.

Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.

Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. The Lancet Neurology 2012;11.1:42–53.

Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12:637–49.

Figure 1 Timing of Assessments

	Baseline, Month 25	Screening, Month 6, 12, 18	Timing of assessments in 4-week rotation (day)																											
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
PROs																														
2 Daily Questions (Physical, Mood)			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
EQ-5D-5L			o							o							o							o					
WPAI						o																								
HD-SDI								o							o							o						o	
Cognitive Tests																														
eSDMT	o																													
Word reading test	o																													
Motor tests																														
Speeded tapping Test (L+R)	o	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Draw shape Test (L+R)	o	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Chorea Test (L+R)	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Balance Test	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
U-Turn Test	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Walking																														
2 Minute Walk Test									o							o							o							o

EQ-5D-5L = EuroQol 5-Dimension, 5 Level Questionnaire; eSDMT = electronic Symbol Digit Modalities Test; HD-SDI = Huntington's Disease Speaking Difficulty Item; L = left; PRO = patient-reported outcome; R = right; WPAI.

PROTOCOL

TITLE:	**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**
PROTOCOL NUMBER:	BN40423
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-002987-14
IND NUMBER:	137873
TEST PRODUCT:	RO7234292
MEDICAL MONITOR:	[redacted], *M.D., Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 18 September 2018
DATES AMENDED:	Version 2 (European Union): 13 December 2018 Version 3 (VHP): 24 January 2019 Version 4: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	16-Apr-2019 22:13:46

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

The Study BN40423 protocol has been amended following a 9-month data review from the ongoing open-label extension (OLE) Study BN40697 (ISIS 443139-CS2). Preliminary data—including cerebrospinal fluid (CSF) mutant huntingtin (mHTT) protein, exploratory fluid biomarkers, and safety/tolerability—show that a 120 mg every-8-week (Q8W; every 2 months) dosing regimen of RO7234292 achieves 47% median CSF mHTT lowering at trough (i.e., sample taken immediately before the next dose) and the 120 mg every-4-week (Q4W; monthly) dosing regimen achieves 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 ~40% median lowering observed in the completed Phase I/IIa study.

Safety and tolerability data for RO7234292 from the Phase II OLE Study BN40697 suggest that relative to the Q4W treatment regimen, the Q8W treatment regimen may be more suitable for chronic intrathecal (IT) dosing, as evidenced by improved adherence to the less frequent regimen. There have been no acute safety concerns meriting a change to the ongoing Study BN40697. However, given the 9-month CSF mHTT results, which suggest a longer than anticipated duration of effect of RO7234292 on CSF mHTT lowering, it is not necessary to use Q4W paradigm to test the existing dose rationale in this study.

The existing dose rationale tests a more frequent dosing regimen, which is anticipated to maintain trough CSF mHTT reduction of at least ~40% (i.e., Q8W 120 mg arm from present data), and a less frequent regimen, 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 ~20% is maintained in a 120-mg Q16W paradigm). Thus, this protocol for the 25-month pivotal Phase III study (BN40423) has been amended to replace the Q4W arm with an every-16-week (Q16W; every 4 months) arm, while continuing the Q8W arm and placebo.

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

- The Q4W dosing regimen has been removed from this study design based on preliminary data from Study BN40697. The 120-mg Q8W arm will be continued in the protocol, and a less frequent regimen of 120 mg Q16W has been added. The underlying dose rationale remains the same for the program, namely testing a more frequent dosing regimen that maintains a higher magnitude trough reduction of at least ~40% (i.e., Q8W 120-mg arm from present data) versus a less frequent dosing regimen that allows for a lower magnitude trough reduction, which is still anticipated to lower mHTT acutely, but will allow more recovery of HTT levels between doses (from present data trough CSF mHTT reduction of ~20% is maintained in a 120-mg Q16W paradigm (Sections 1.2, 3.1, 3.3.1, 4.6, and 6). The timings of study assessments have been updated accordingly (Appendix 1).

- Treatment regimen descriptions have been updated. Patients who enrolled in Study BN40423 before this amendment (Version 4) will be given the option of enrolling in the long-term OLE Study BN40955 after approval of the OLE study by the relevant competent authority and Ethics Committee/Investigational Review Board (Sections 3.1, 3.3.3, and 4.2). Those patients will be discontinued from Study BN40423 at the point of enrollment into Study BN40955.
- Description of study companion requirements has been revised (Section 4.1.1).
- Exclusion criteria have been revised to further describe drug and/or alcohol abuse (Sections 4.1.2 and 4.5.2). In addition, clarification has been made for exclusions for scoliosis and antiretroviral medications (Section 4.5.5).
- Additional details have been provided for administration of study drug by lumbar puncture (Section 4.3.2.1). Clarification has also been made that patients should not perform any activity associated with a change in the ambient air pressure for at least 72 hours post–study drug administration (Section 4.5.5).
- Sedation and anti-anxiety medication have been further detailed in the prohibited therapy section (Section 4.4.2).
- A CSF sample for differential cell counts, where feasible, has been added to the local laboratory samples section (Section 4.5.6).
- Preservation of biomarkers samples has been updated from 5 years to 10 years (Section 4.5.6).
- Loss of capacity to consent (if legal guardian consent is not possible) has been added as a possible reason for study treatment discontinuation (Section 4.6.1).
- The potential risks section has been updated to include hydrocephalus based upon observed findings from another intrathecal bolus–administered 2'MOE ASO and changes in CSF protein observed with RO7234292. Additional updates from the ongoing Study BN40697 have been made. The safety monitoring plan and management guidelines for patients who experience adverse events have been further clarified but principally remain the same (Section 5.1).
- The name and contact phone number for the Medical Monitor has been revised (Section 5.4.1).
- Language has been added to clarify that, after withdrawal of consent for participation in the RBR, remaining RBR samples will be destroyed or will no longer be linked to the patient (Section 4.5.10.6).
- Text has been modified to account for the fact that special situations (i.e., accidental overdoses and medication errors) are not required to be reported within 24 hours (Sections 5.3.5.12 and 5.4). Note that serious adverse events associated with special situations are still required to be reported within 24 hours.
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).

- Language has been revised to clarify that data posting will not be limited to two clinical trial registries and to clarify that redacted CSRs are provided only if requirements of Roche's global policy on data sharing have been met (Section 9.5).
- Appendices 1–4 and 6 describe study assessments relevant solely to patients enrolled after implementation of Protocol Version 4. Appendices 9–13 describe study assessments relevant solely to patients enrolled before implementation of Protocol Version 4.
- Guidance for neurological examination has been added as Appendix 8.

This amendment includes cumulative changes to the protocol from Versions 2 (EU) and 3 (VHP), which were created following comments from the Voluntary Harmonization Process (VHP) review. Protocol Versions 2 and 3 were previously only implemented in EU countries, as they were local amendment requests following the European Medicines Agency (EMA) review.

Changes brought forward from the Version 2 amendment are summarized below:

- Additional wording has been added as per Clinical Trial Facilitation Group guidance to clarify that a vasectomized man must undergo a medical assessment of surgical success before he can be considered surgically sterile (Section 4.1.1).
- The inclusion criterion referring to the estimated glomerular filtration rate has been corrected by using the correct unit (mL/min) (Section 4.1.1).
- The exclusion criterion regarding current use of antidepressants or benzodiazepine has been amended to change from 112 weeks to 12 weeks (Section 4.1.2).
- Additional information has been provided in the statistical section around the testing strategy for the primary endpoint, how missing data will be imputed, clarity around the use of historical controls, and details on how the sample size has been calculated, as requested (Sections 6.2, 6.3, and 6.6).

Changes brought forward from the Version 3 amendment are summarized below:

- Clarification has been added to Section 6.12. An Interim Analysis (IA) will be performed only after a future protocol amendment outlining a detailed plan of the IA.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**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**
PROTOCOL NUMBER:	BN40423
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-002987-14
IND NUMBER:	137873
TEST PRODUCT:	RO7234292
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:	**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**
PROTOCOL NUMBER:	BN40423
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-002987-14
IND NUMBER:	137873
TEST PRODUCT:	RO7234292
PHASE:	Phase III
INDICATION:	Huntington's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of RO7234292 compared with placebo in patients with manifest Huntington's disease (HD). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score at Week 101

  Note: The primary efficacy endpoint for the U.S. Food and Drug Administration (FDA) will be change from baseline in the Total Functional Capacity (TFC) score at Week 101

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in scores for the following individual scales at Week 101:
  - TFC
  - Total Motor Score (TMS)
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading Test (SWR)

    Note: For the U.S. FDA, the first secondary endpoint will be change from baseline in the cUHDRS score at Week 101 instead of TFC, as TFC will be the primary endpoint.

- Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S) score at Week 101

- Proportion of patients with a decrease from baseline of ≥ 1 point on the TFC at Week 101
- Proportion of patients with a decline from baseline of ≥ 1.2 points on the cUHDRS at Week 101
- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline at Week 101

Exploratory Efficacy Objective

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

- Change from baseline in the Apathy Evaluation Scale (AES) score at Week 101
- Change from baseline in the Symptoms of Major Depressive Disorder Scale (SMDDS) score at Week 101
- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score at Week 93
- Change from baseline in the Patient Global Impression, Severity Scale (PGI-S) score at Week 101
- Change from baseline in the Quality of Life in Neurological Disorders (Neuro-Qol) Cognition Function Short Form at Week 101
- Change from baseline in the Huntington's Disease Speaking Difficulty Item Scale (HD-SDI) score at Week 101
- Change from baseline in the Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale (HD-CIAOS) score at Week 101
- Change from baseline in the in-clinic patient-reported EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-score and visual analogue scale (VAS) at Week 101
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) at Week 101

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of RO7234292 compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale
- Change from baseline in Montreal Cognitive Assessment (MoCA)
- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory results
- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct

Pharmacokinetic Objectives

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

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

The exploratory pharmacokinetic/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 plasma profiles and/or trough CSF concentrations of PK parameters for RO7234292 and efficacy endpoints

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

Immunogenicity Objectives

The immunogenicity objective for this study is 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
- Titer and antibody subtype, determined if ADAs are identified

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Biomarker Objectives

Primary Biomarker Objective

The primary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in CSF mHTT protein level at Week 101

Secondary Biomarker Objective

The secondary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in whole and regional brain volumes (caudate, whole brain, and ventricular), as determined by structural magnetic resonance imaging (MRI), at Week 101
- Change from baseline in CSF neurofilament light chain (NfL) protein level at Week 101

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to RO7234292 (i.e., predictive biomarkers), 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 adverse events or can lead to improved adverse event 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 in blood, plasma, and CSF and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers (e.g., putamen, cortical grey matter, cortical white matter volumes, resting state functional MRI signal) 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- and companion-reported EQ-5D-5L Index and VAS scores at specified timepoints
- Change from baseline in companion self-reported and proxy-reported Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) scores at specified timepoints
- Change from baseline in patient- and companion-reported Work Productivity and Activity Impairment (WPAI) scores at specified timepoints

Study Design

Description of Study

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

Prospective patients will undergo screening assessments during a 4-week screening period. A maximum of one re-screening will be allowed within 8 weeks of the initial screening failure for patients who fail the initial screening.

Upon completion of the screening period, eligible patients will be randomly allocated in a 1:1:1 ratio to receive RO7234292 every *8* weeks (*Q8W*; RO7234292 *Q8W* arm), RO7234292 every *16* weeks (*Q16W*; RO7234292 *Q16W* arm), or placebo *Q8W* (placebo arm) by IT injection. To maintain the study blind and integrity, patients in the RO7234292 *Q16W* arm will also receive placebo (i.e., alternating doses of active drug and placebo).

During scheduled clinic visits, patients will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, MoCA, C-SSRS, neuroimaging assessments (neurologic safety sequences), and *a review of any* adverse events including related concomitant medications, as detailed in the schedule of activities.

If there is the occurrence of a failed IT bolus dosing procedure due to inadequate establishment of access to the IT space, a second dosing attempt may occur up to 7 days after the originally scheduled dosing visit. At this additional visit, safety and tolerability evaluations will be performed as described in the schedule of activities.

A telephone safety follow-up call will be conducted for the months in which no clinic visits are scheduled to check for any change in patient status (i.e., adverse events, concomitant medications) since the patient's last visit. Where deemed appropriate, an unscheduled clinic visit should be arranged for safety follow-up; no dosing will occur at these unscheduled visits. During the telephone follow-up call, patients will be reminded of their next follow-up visit.

Patients who complete the treatment period will return to the clinic for an end-of-treatment visit at Week 101. Patients will then be given the option on an individual basis of receiving RO7234292 in an OLE study (BN40955) upon completion of Study BN40423, provided they meet eligibility criteria and the data from the ongoing RO7234292 program support continued development. Approval of the OLE study must also be granted by the relevant competent authority and Ethics Committee (EC)/Investigational Review Board (IRB).

All patients *enrolled in Study BN40423* who *choose to* discontinue study treatment prematurely, but do not withdraw consent for continued participation in the study, will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) for collection of at least the data for the primary and secondary endpoints. If the early treatment termination visit falls within ± 30 days of either scheduled visits at Week 53 or Week 69, then only the early treatment termination visit will be considered. The early treatment termination visit should be performed 28 days (± 3 days) after the last dose. Patients will also attend the scheduled end-of-treatment visit at Week 101.

An independent Data Monitoring Committee (iDMC) and independent Data Coordinating Center (iDCC) will be employed to monitor and evaluate patient safety throughout the study as well as to evaluate evidence of early efficacy.

Study Design Overview for Patients Enrolled prior to Implementation of Protocol Version 4

All patients enrolled in Study BN40423 prior to implementation of the Version 4 protocol amendment will be prematurely discontinued by the Sponsor from this study and will be offered treatment in the OLE Study BN40955, once approval has been granted by the relevant competent authority and ECs/IRBs. Patients will continue to receive treatment in Study BN40423 until the OLE study has been approved at their study site. Patients who discontinue treatment or study prior to Sponsor discontinuation will not be eligible for the OLE Study BN40955.

Patients who choose to enroll in the OLE will complete an end-of-treatment visit in Study BN40423, which can also serve as the inclusion visit for Study BN40955. All patients who are prematurely discontinued by the Sponsor who choose not to consent to Study BN40955 will additionally undergo a 5-month postdose safety follow-up visit.

Number of Patients

Approximately 660 patients with HD will be enrolled in this global study *from the implementation of Protocol Version 4 and onwards. This is in addition to patients who enrolled prior to Version 4, who will be discontinued from this study and offered participation in OLE Study BN40955.*

Target Population

Inclusion Criteria

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

- Signed Informed Consent Form
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form *and at the time of first dose administration*
- Manifest HD diagnosis, defined as a diagnostic confidence level (DCL) score of 4
- Independence Scale (IS) score ≥ 70
- Genetically confirmed disease by direct DNA testing with a CAP score > 400 (Zhang et al. 2011), calculated as follows:

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

- 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 lumbar punctures
- Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min (Cockcroft-Gault formula)
- Ability and willingness, in the investigator's judgment, to comply with all aspects of the protocol including completion of interviews and questionnaires for the duration of the study
- Ability and willingness, in the investigator's judgment, to carry a smartphone, wear a digital monitoring device, and complete smartphone-based tasks
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment
- Signed study companion consent for participation, if a study companion is available, who fulfills all of the following criteria:
  - Age ≥ 18 years
  - Reliable and competent, in the investigator's judgment
  - Sufficiently knowledgeable of the patient's condition to complete study companion assessments of the patient, and likely to remain sufficiently knowledgeable throughout the study, in the investigator's judgment
  - Able to comment on study participant's symptoms and functioning experience

    Note: Companions *must have no cognitive, behavioral or motor change*, in the opinion of the investigator, that would question the validity of the acquired observer-reported data.

    All effort should be made to retain the study companion; however, should this not be possible, a study companion can be replaced and new consent obtained.

- 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 two 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 (≥ 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.

Exclusion Criteria

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 done by an appropriately qualified mental health professional to assess whether it is safe for the patient to participate in the study. Mild passive suicidal ideation (i.e., occasional thoughts that life is not worth living or is hard) without history of attempts or hospitalization over the past 12 months is generally acceptable for study participation, but final decision on participation should be made carefully and in consultation with 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
- Clinical diagnosis of chronic migraines
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study drug

Women of childbearing potential must have a negative serum pregnancy test result *at baseline and a confirmatory urine pregnancy test* prior to initiation of study drug.

- Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Positive for hepatitis C virus (HCV) antibody or hepatitis B surface antigen (HBsAg) at screening
- Known HIV infection
- Current or previous use of an antisense oligonucleotide (including small interfering RNA)
- Current or previous use of anti-psychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks from initiation of study treatment
- Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) and/or tetrabenazine, valbenazine, or deutetrabenazine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
- Current use of supplements (e.g., coenzyme Q10, vitamins, creatine) at a dose that has not been stable for at least 6 weeks prior to screening or is anticipated to change during the study
- Current use of an antidepressant or benzodiazepine at a dose that has not been stable for at least *12* weeks prior to screening or is anticipated to change between screening and treatment initiation
- Treatment with investigational therapy within 4 weeks or 5 drug-elimination half-lives prior to screening, whichever is longer
- Antiplatelet or anticoagulant therapy within 14 days prior to screening or anticipated use during the study, including, but not limited to, aspirin (unless ≤81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- History of bleeding diathesis or coagulopathy
- Platelet count less than the lower limit of normal

  Platelet counts between 125,000 and 150,000 mm3 are permissible as long as the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.
- History of gene therapy, cell transplantation, or any experimental brain surgery
- Concurrent or planned concurrent participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions (e.g., lumbar puncture)

  Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
- Drug (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
- Antiretroviral medications*, including antiretroviral medication taken as prophylaxis*
- 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 structural brain lesion (e.g., tumor, arterio-venous malformation) 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 approximately 117 weeks (29 months) after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4.5 years.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are RO7234292 and RO7234292 placebo.

Test Product (Investigational Drug)

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), two 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, preparation, and handling of RO7234292, refer to the pharmacy manual.

Placebo

RO7234292 placebo will be supplied by the Sponsor as a sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL RO7234292 placebo drug product for IT injection. The liquid is no different in color than the active drug.

For a 20 mL dosing volume, two vials containing 10 mL of RO7234292 placebo will have to be pooled by drawing them up into the same injection syringe containing 20 mL of placebo drug product.

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

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change from baseline in cUHDRS score at Week 101. This is defined as the attribute "variable" of the primary estimand.

Note: The primary efficacy endpoint for the U.S. FDA will be change from baseline in the TFC score at Week 101. TFC will be analyzed the same way as the cUHDRS.

The primary efficacy analysis for this study will compare each active treatment arm, RO7234292 $Q8W$ and RO7234292 $Q16W$, against the placebo arm. To account for the multiple comparison, an appropriate procedure will be used to maintain the overall two-sided type I error at 5% (details will be given in the SAP).

The analysis of the primary endpoint will be performed by means of analysis of covariance (ANCOVA). The model will include the corresponding endpoint baseline score, CAG repeat length, baseline CAP score, and treatment as covariates; the final list of covariates will be defined in the SAP. On the basis of this analysis, least squares mean for the treatment differences at Week 101 and corresponding 95% CIs will be derived.

The robustness of the primary method of estimation described above may be explored by alternative sensitivity estimators based on varying assumptions underlying the multiple imputation strategy. These sensitivity analyses will be described in the SAP.

Determination of Sample Size

The planned sample size is adequate to capture meaningful clinical decline on both the TFC and cUHDRS and was estimated on the basis of data available from non-interventional studies (TRACK-HD, COHORT, ENROLL-HD) and a randomized placebo-controlled study (2CARE). Based on these data, using the anticipated trial population, a meta-analysis for the change from baseline at 24 months in TFC score suggested a natural decline of 1.36 points and a corresponding pooled standard deviation of 1.78. *A conservative treatment discontinuation rate at Week 101 for patients receiving placebo or active is assumed to be 20% and 15%,*

respectively. Using these assumptions, the simulation described in the protocol was performed to estimate the sample size.

It was estimated that 220 patients per arm will provide approximately 80% power, at a two-sided $\alpha = 0.05$ level, to detect a 40% slowing of clinical decline for RO7234292 as compared with placebo at 101 weeks. This treatment effect translates into an expected average decline of ~0.82 points at 101 weeks for the RO7234292 arms. The minimal detectable difference with these assumptions is ~0.38 points.

Optional Interim Analyses

The Sponsor may choose to conduct one or more interim analyses for efficacy. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct an interim analysis, along with the rationale, specification of the endpoint (e.g., clinical and/or biomarker endpoint), number of patients, and statistical details for each analysis, will be *introduced via a future protocol amendment*, which will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of an interim analysis, and the iDMC Charter will be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of an interim analysis of efficacy data, the type I error rate will be controlled to ensure statistical validity is maintained. Additional criteria for recommending that the study be stopped for positive efficacy will be added to *a future protocol amendment*.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ANCOVA	analysis of covariance
AES	Apathy Evaluation Scale
app	application
ASO	antisense oligonucleotide
CAP	CAG–Age Product
CGI-C	Clinical Global Impression–Change
CGI-S	Clinical Global Impression–Severity
ClinRO	clinician-reported outcome
CrGI-C	Companion-Reported Global Impression–Change
CrGI-S	Companion-Reported Global Impression–Severity
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
cUHDRS	composite Unified Huntington's Disease Rating Scale
DCL	diagnostic confidence level
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
EMA	*European Medicines Agency*
FDA	Food and Drug Administration
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HD	Huntington's disease
HD-CIAOS	Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale
HD-DAS	Huntington's Disease Daily Activities Scale
HDID	Huntington's Disease Identification Number
HD-SDI	Huntington's Disease Speaking Difficulty Item
HIPAA	Health Insurance Portability and Accountability Act

HRQoL	health-related quality of life
HTT	huntingtin (gene)
HTT	huntingtin (protein)
HUI	Health Utilities Index
HUI2	HUI Mark 2
HUI3	HUI Mark 3
ICE	intercurrent event
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IS	Independence Scale
IT	intrathecal
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
mHTT	mutant huntingtin (protein)
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
Neuro-Qol	Quality of Life in Neurological Disorders
NfL	neurofilament light chain (protein)
NRS	numeric rating scale
NSDR	*non–study drug–related (reasons)*
ObsRO	observer-reported outcome
OLE	open-label extension
PD	pharmacodynamic
PerfO	performance outcome
PGI-C	Patient Global Impression–Change
PGI-S	Patient Global Impression–Severity
PK	pharmacokinetic
PRO	patient-reported outcome
Q4W	every 4 weeks
Q8W	every 8 weeks
Q16W	*every 16 weeks*

QTc	corrected QT interval
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities Test
SDR	*study drug–related (reasons)*
SMDDS	Symptoms of Major Depressive Disorder Scale
SWR	Stroop Word Reading
TFC	Total Functional Capacity Scale
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
VAS	visual analogue scale
WES	whole exome sequencing
WGS	whole genome sequencing
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 CAG repeats in exon 1 of the Huntingtin *HTT* gene on chromosome 4, which encodes for a mutant huntingtin (mHTT) protein. Based upon nonclinical and clinical evidence, mHTT is considered the primary driver of HD pathophysiology (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 to 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). Motor onset is typically confirmed through use of the 15-item motor examination of the Unified Huntington's Disease Rating Scale (UHDRS). After completion of the examination, a certified motor rater assigns a diagnostic confidence level (DCL) score. Scores range from 0 to 4, with 0 representing no impairment and 4 representing unequivocal motor signs of HD ($\geq$99% confidence). Among the considerable clinical phenotypic heterogeneity of the disease, motor onset is one of the more robust and consistently-agreed-upon disease features. Behavioral features, including emotional disorders and personality changes, do not have a uniform presentation, are episodic in nature, and do not usually progress steadily over time (Ross et al. 2014).

Individuals with HD can be categorized as having either premanifest disease (diagnosed prior to motor onset) or manifest disease (diagnosed on the basis of motor onset). The premanifest disease period can be subdivided into presymptomatic and prodromal periods. During the presymptomatic period, from birth to young adulthood, individuals are not clinically distinguishable from controls. During the prodromal period, which can last many years before threshold clinical motor diagnosis, subtle motor changes and variable cognitive and behavioral changes appear but are not sufficient to make the clinical diagnosis of HD.

The manifest disease period can be subdivided into five 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 five clinical stages are defined by the score on the 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 et al. 1979).

Currently approved treatments aim to reduce the burden of symptoms, maximize function, and improve the patient's quality of life (Nance et al. 2011). Tetrabenazine and deutetrabenazine target abnormal involuntary movements (i.e., chorea) associated with HD, and these symptomatic therapies have a challenging benefit–risk profile. These drugs have been linked to many significant adverse events, including parkinsonism, akathisia, sedation, 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).

To date, there are no approved treatments able *to* slow or stop the clinical progression of HD.

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 ISIS443139 and IONIS-HTTRx. 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 (Crooke and Bennett 1996; Cerritelli and Crouch 2009), including cells of interest in the CNS (e.g., neurons and neuroglia). Reduction of the *HTT* gene mRNA, which in turn limits translation of the wild-type and mutant huntingtin protein, could potentially inhibit all downstream toxic effects 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 and non-human primates, 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 (Kordasiewicz et al. 2012; Stanek et al. 2013).

Nonclinical proof-of-concept studies with ASOs targeting mutant *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, bacterial artificial chromosome (BAC)HD 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 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 and 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) four 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 intrathecally 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 support 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 Phase II open-label extension (OLE) study for patients who participated in Study ISIS 443139-CS1.

Nine-month clinical data from the ongoing, 15-month, Phase II OLE Study BN40697—including CSF mHTT protein, exploratory fluid biomarkers, and safety/tolerability data—are available for reporting. All individuals in Study BN40967 have reached the 9-month timepoint of the planned 15-month study, and several

individuals have now received RO7234292 for over 1 year on both regimens. Study BN40697 will be continued until its anticipated completion by December 2019.

Preliminary data show that a 120 mg every-8-week (Q8W; every 2 months) dosing regimen of RO7234292 achieves 47% median CSF mHTT lowering at trough (i.e., sample taken immediately before the next dose) and the 120 mg Q4W dosing regimen achieves 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.

Further details on nonclinical and clinical studies can be found in the RO7234292 Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

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 manifest HD. Building on the completed Phase I/IIa study and the ongoing Phase II OLE study, this Phase III, double-blind, placebo-controlled study (BN40423) will collect longer-term clinical efficacy and safety data to definitively evaluate the benefit and potential risks of RO7234292 when administered by IT bolus injection *Q8W* or every *16* weeks (*Q16W; every 4 months*) over a 25-month (2-year) period to patients with manifest HD.

Review of safety and tolerability 9-month data for RO7234292 from the Phase II OLE suggests 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 adverse events, decreased proportion of patients with moderate adverse events, and fewer adverse events considered possibly related to study drug in the Q8W regimen compared to the Q4W regimen (for details see the RO7234292 Investigator's Brochure).

There have been no acute safety concerns meriting a change to the ongoing Phase II OLE study protocol (BN40697). However, given the 9-month CSF mHTT results, which suggest 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 justify a change in Study BN40423 to explore less frequent dosing regimens by continuing the Q8W RO7234292 and placebo arms, 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 ~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 ~20% is maintained in a 120-mg Q16W paradigm.

The known potential risks associated with RO7234292 and additional risks related to lumbar punctures are elaborated, along with mitigation measures, in Section 5.1. Taking into account the measures to minimize risk to patients participating in this study, the potential risks identified for IT administration of RO7234292 are justified by the anticipated benefits that may be afforded to patients with HD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of RO7234292 compared with placebo in patients with manifest HD. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score at Week 101

  Note: The primary efficacy endpoint for the U.S. Food and Drug Administration (FDA) will be change from baseline in the TFC score at Week 101.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in scores for the following individual scales at Week 101:
  - TFC
  - Total Motor Score (TMS)
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading (SWR) Test

  Note: For the U.S. FDA, the first secondary endpoint will be change from baseline in the cUHDRS score at Week 101 instead of TFC, as TFC will be the primary endpoint.

- Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S) score at Week 101

- Proportion of patients with a decrease from baseline of ≥ 1 point on the TFC at Week 101
- Proportion of patients with a decline from baseline of ≥ 1.2 points on the cUHDRS at Week 101
- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline at Week 101

2.1.3 Exploratory Efficacy Objective

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

- Change from baseline in the Apathy Evaluation Scale (AES) score at Week 101
- Change from baseline in the Symptoms of Major Depressive Disorder Scale (SMDDS) score at Week 101
- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score at Week 93
- Change from baseline in the Patient Global Impression, Severity Scale (PGI-S) score at Week 101
- Change from baseline in the Quality of Life in Neurological Disorders (Neuro-Qol) Cognition Function Short Form at Week 101
- Change from baseline in the Huntington's Disease Speaking Difficulty Item Scale (HD-SDI) score at Week 101
- Change from baseline in the Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale (HD-CIAOS) score at Week 101
- Change from baseline in the in-clinic patient-reported EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-score and visual analogue scale (VAS) at Week 101
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) at Week 101

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of RO7234292 compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale (see Table 4)
- Change from baseline in Montreal Cognitive Assessment (MoCA)
- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory results
- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit, including

detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct

2.3 PHARMACOKINETIC OBJECTIVES

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

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

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

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is 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
- Titer and antibody subtype, determined if ADAs are identified

The exploratory immunogenicity objective for this study is 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 BIOMARKER OBJECTIVES

2.5.1 Primary Biomarker Objective

The primary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in CSF mHTT protein level at Week 101

2.5.2 Secondary Biomarker Objective

The secondary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in whole and regional brain volumes (caudate, whole brain, and ventricular), as determined by structural magnetic resonance imaging (MRI), at Week 101
- Change from baseline in CSF neurofilament light chain (NfL) protein level at Week 101

2.5.3 Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to RO7234292 (i.e., predictive biomarkers), 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 adverse events or can lead to improved adverse event 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 in blood, plasma, and CSF (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers (e.g., putamen, cortical grey matter, cortical white matter volumes, resting state functional MRI signal) (see Section 4.5.7) 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- and companion-reported EQ-5D-5L Index and VAS scores at specified timepoints
- Change from baseline in companion self-reported and proxy-reported Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) scores at specified timepoints
- Change from baseline in patient- and companion-reported Work Productivity and Activity Impairment (WPAI) scores at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

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

Prospective patients will undergo screening assessments during a 4-week screening period. A maximum of one re-screening will be allowed within 8 weeks of the initial screening failure for patients who fail the initial screening (see Section 4.5.1).

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

in *Table 1*. To maintain the study blind and integrity, patients in the RO7234292 *Q16W* arm will also receive placebo (i.e., alternating doses of active drug and placebo).

Table 1 Treatment Regimens *after Implementation of Protocol Version 4*

Arm	*Treatment Regimen*
RO7234292 Q8W arm	*RO7234292 loading dose: 120 mg at Days 1 and 29 (2 doses)* *RO7234292: 120 mg Q8W from Week 13 to Week 93 (11 doses)*
RO7234292 Q16W arm	*RO7234292 loading dose: 120 mg at Days 1 and 29 (2 doses)* *RO7234292: 120 mg Q16W from Week 21 to Week 85 (5 doses)* *Placebo: Q16W from Week 13 to Week 93 (6 doses)*
Placebo arm	*Placebo: at Days 1 and 29 (2 doses) and Q8W from Week 13 to Week 93 (11 doses)*

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

During scheduled clinic visits, patients will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, MoCA, C-SSRS, neuroimaging assessments (neurologic safety sequences), and *a review of any* adverse events including related concomitant medications, as detailed in Appendix 1.

If there is the occurrence of a failed IT bolus dosing procedure due to inadequate establishment of access to the IT space, a second dosing attempt may occur up to 7 days after the originally scheduled dosing visit. At this additional visit, safety and tolerability evaluations will be performed as described in Appendix 1.

A telephone safety follow-up call will be conducted for the months in which no clinic visits are scheduled to check for any change in patient status (i.e., adverse events, concomitant medications) since the patient's last visit. Where deemed appropriate, an unscheduled clinic visit should be arranged for safety follow-up; no dosing will occur at these unscheduled visits. During the telephone follow-up call, patients will be reminded of their next follow-up visit.

Patients who complete the treatment period will return to the clinic for an end-of-treatment visit at Week 101. Patients will then be given the option on an individual basis of receiving RO7234292 in an OLE study (BN40955) upon completion of Study BN40423, provided they meet eligibility criteria and the data from the ongoing RO7234292 program support continued development. Approval of the OLE study must also be granted by the relevant competent authority and Ethics Committee (EC)/Investigational Review Board (IRB).

All patients *enrolled in Study BN40423* who *choose to* discontinue study treatment prematurely, but do not withdraw consent for continued participation in the study, will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) for

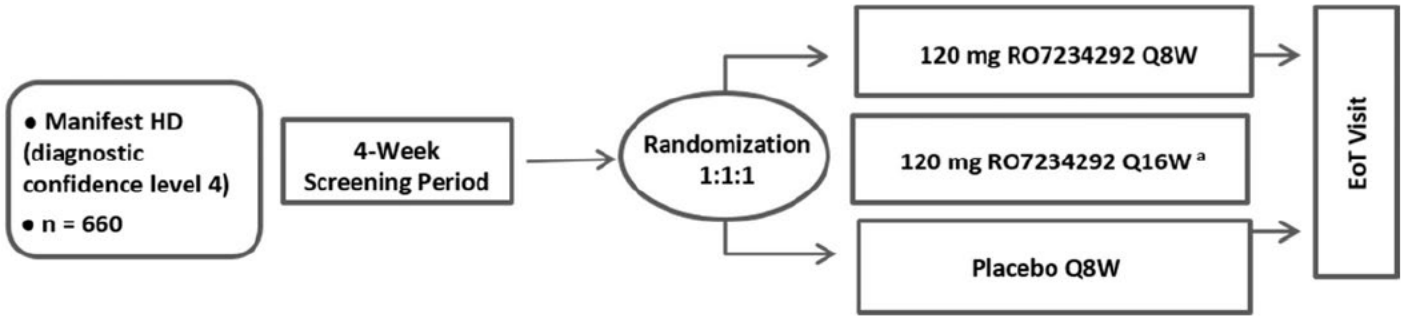
collection of at least the data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). If the early treatment termination visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only the early treatment termination visit will be considered. The early treatment termination visit should be performed 28 days (±7 days) after the last dose. Patients will also attend the scheduled end-of-treatment visit at Week 101.

An independent Data Monitoring Committee (iDMC) and independent Data Coordinating Center (iDCC) will be employed to monitor and evaluate patient safety throughout the study as well as to evaluate evidence of early efficacy (see Section 3.1.2).

The Sponsor may choose to conduct one or more interim analyses during the study (further details are given in Section 6.12).

Figure 1 and Figure 2 present the study schema *and* overview of the dosing schedule *respectively, for patients enrolled in Study BN40423 after implementation of Protocol Version 4.* A schedule of activities is provided in *Appendix 1*.

Figure 1 Study Schema *for Patients Enrolled after Implementation of Protocol Version 4*

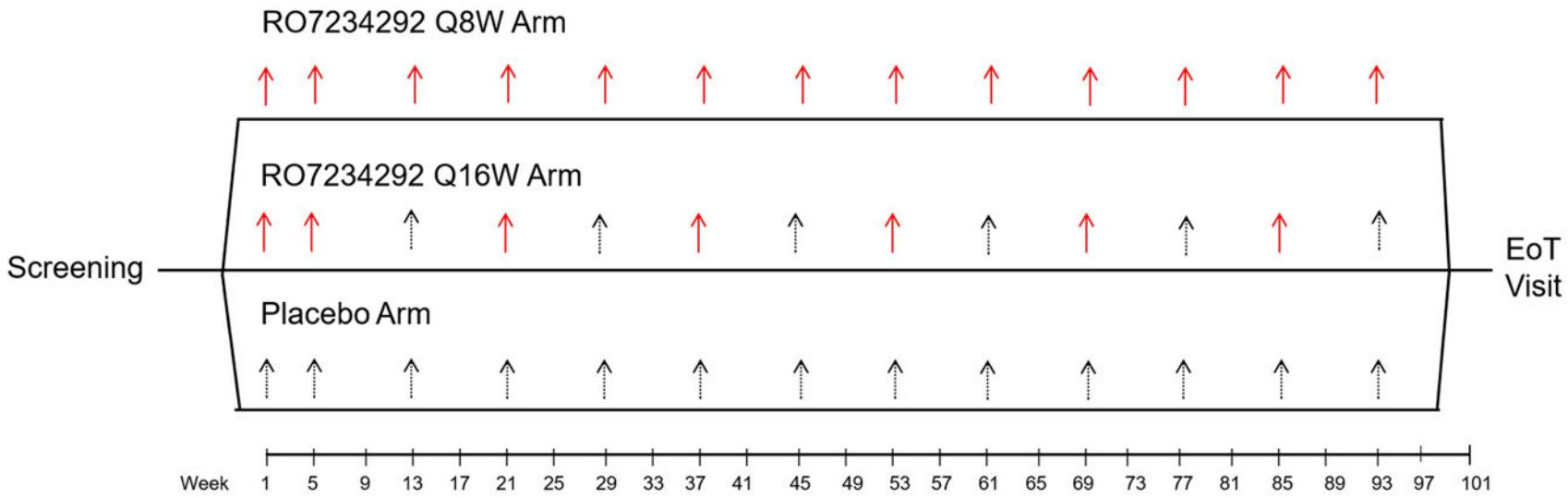


EoT = end of treatment; HD = Huntington disease; Q8W = every 8 weeks; *Q16W = every 16 weeks.*

Note: After study completion, patients may be eligible to participate in an open-label extension study (BN40955). Patients who complete the treatment period will return to the clinic for an end-of-treatment visit at Week 101. All patients *enrolled in Study BN40423* who *choose to* discontinue study treatment prematurely, but do not withdraw consent for continued participation in the study, will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) for collection of at least the data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). If the early treatment termination visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only the early treatment termination visit will be considered. Patients will also attend the scheduled end-of-treatment visit at Week 101.

[a] Patients in the RO7234292 *Q16W* arm will receive placebo at alternating visits to keep the double blind, as shown in *Figure 2 and* Appendix 1.

Figure 2 Dosing Schema *for Patients Enrolled after Implementation of Protocol Version 4*



EoT = end of treatment; Q8W = every 8 weeks; *Q16W = every 16 weeks*.

Notes: Red, solid arrows indicate study drug administration, while black, dotted arrows indicate placebo administration. Patients in the RO7234292 Q8W arm will receive a loading dose of RO7234292 on Days 1 and 29 (loading period), followed by *active study drug Q8W. Patients in the RO7234292 Q16W arm will receive a loading dose of RO7234292 on Days 1 and 29 (loading period), followed by* alternating *Q8W* doses of placebo and active study drug.

3.1.1.1 *Study Design Overview for Patients Enrolled prior to Implementation of Protocol Version 4*

All patients enrolled in Study BN40423 prior to implementation of the Version 4 protocol amendment will be prematurely discontinued by the Sponsor from this study and will be offered treatment in the OLE Study BN40955, once approval has been granted by the relevant competent authority and ECs/IRBs. Patients will continue to receive treatment in Study BN40423 until the OLE study has been approved at their study site. Patients who discontinue treatment or study prior to Sponsor discontinuation will not be eligible for the OLE Study BN40955.

Patients who choose to enroll in the OLE will complete an end-of-treatment visit in Study BN40423, which can also serve as the inclusion visit for Study BN40955. All patients who are prematurely discontinued by the Sponsor who choose not to consent to Study BN40955 will additionally undergo a 5-month postdose safety follow-up visit.

Table 2 presents the treatment regimen for all patients before implementation of the Version 4 protocol.

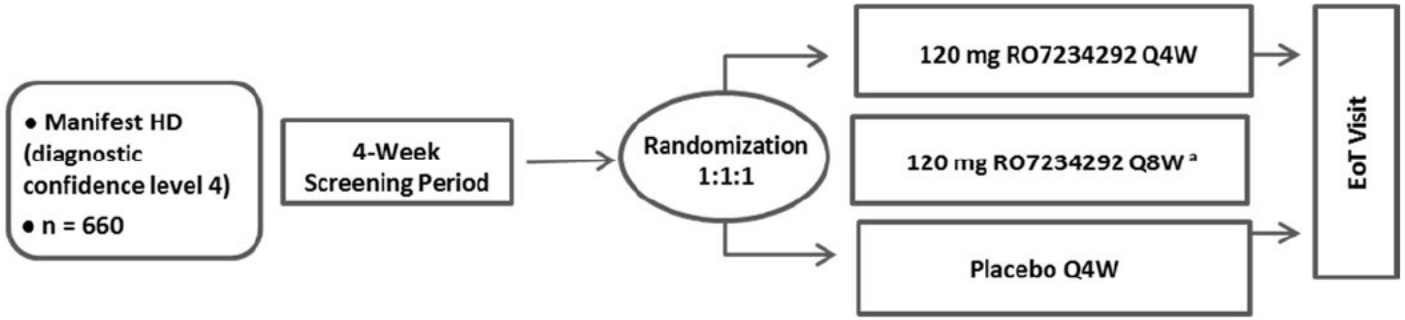
Table 2 Treatment Regimens prior to Implementation of Protocol Version 4

Arm	*Treatment Regimen*
RO7234292 Q4W arm	*RO7234292: 120 mg Q4W from Week 1 to Week 97 (25 doses)*
RO7234292 Q8W arm	*RO7234292 loading dose: 120 mg at Days 1 and 29 (2 doses)* *Placebo: Q8W from Week 9 to Week 97 (12 doses)* *RO7234292: 120 mg Q8W from Week 13 to Week 93 (11 doses)*
Placebo arm	*Placebo: Q4W from Week 1 to Week 97 (25 doses)*

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

Figure 3 and Figure 4 present study schema and overviews of the dosing schedule, respectively. A schedule of activities is provided in Appendix 9, with additional assessments described in Appendix 10, Appendix 11, Appendix 12, and Appendix 13.

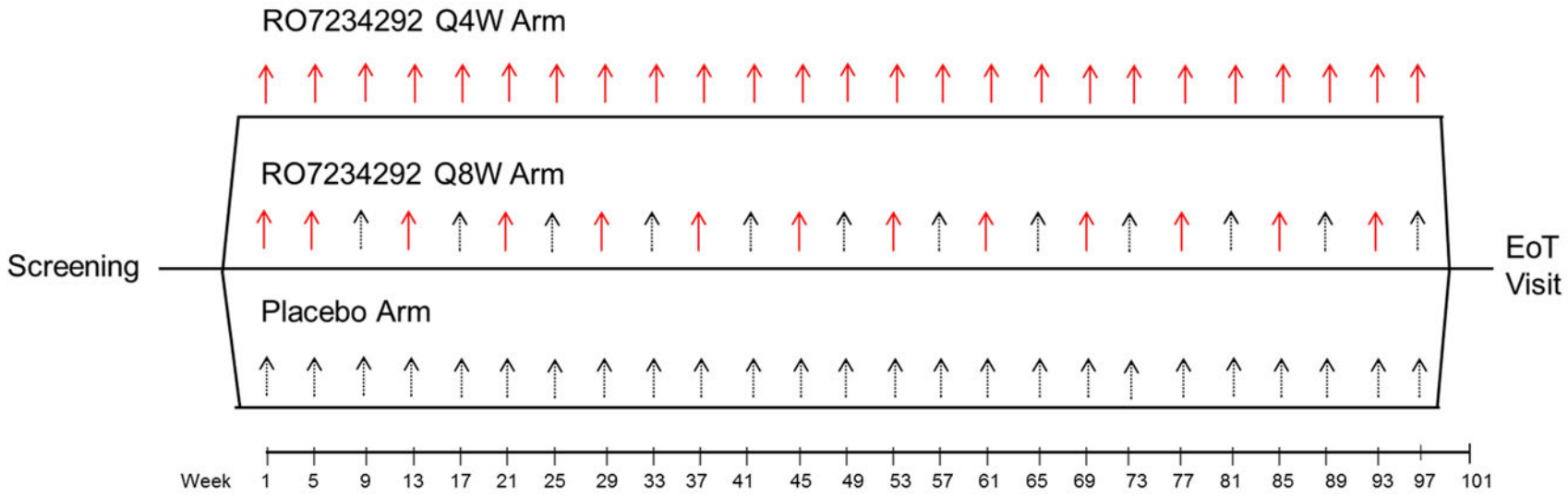
Figure 3 Study Schema for Patients Enrolled prior to Implementation of Protocol Version 4



EoT =end of treatment; HD =Huntington disease; Q4W =every 4 weeks; Q8W =every 8 weeks.

Notes: All patients who enroll prior to implementation of Protocol Version 4 will be prematurely discontinued from treatment by the Sponsor and offered treatment in the open-label extension study (BN40955). These patients will complete an EoT visit in Study BN40423, which can also serve as the screening visit for Study BN40955. All patients who are prematurely discontinued by the Sponsor who choose not to consent to Study BN40955 will additionally undergo a 5-month postdose safety follow-up visit. Patients in the Q8W arm will remain in the Q8W arm of the OLE study (BN40955). Patients in the placebo arm or Q4W arms will be randomly allocated to the Q8W or Q16W arms in Study BN40955.

Figure 4 Dosing Schema for Patients Enrolled prior to Implementation of Protocol Version 4



EoT =end of treatment; Q4W =every 4 weeks; Q8W =every 8 weeks.

Notes: Red, solid arrows indicate study drug administration, while black, dotted arrows indicate placebo administration. Patients in the RO7234292 Q8W arm will receive a loading dose of RO7234292 on Days 1 and 29 (loading period), followed by alternating doses of placebo and active study drug.

3.1.2 Independent Data Monitoring Committee

The incidence and nature of adverse events, serious adverse events, adverse events of special interest, and abnormalities from neuroimaging assessments; vital signs; ECG assessments; laboratory parameters; and any other relevant safety information will be reviewed on a regular basis by an iDMC in an unblinded fashion. This information may also include MRI data and exploratory CSF biomarkers, for example NfL and Tau. These reviews will occur approximately every 6 months or at the discretion of the iDMC.

The iDMC will also undertake evaluation of any interim analysis. Specific operational details, such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities, will be detailed in an iDMC Charter.

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 approximately 117 weeks (29 months) after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4.5 years.

In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for RO7234292 Dose and Schedule

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, two active dosing regimens and a placebo arm will be used in this study: RO7234292 $Q8W$ (RO7234292 $Q8W$ arm), RO7234292 $Q16W$ (RO7234292 $Q16W$ arm), and placebo $Q8W$ (placebo arm) by IT injection. To maintain the study blind and integrity, patients in the RO7234292 $Q16W$ arm will also receive placebo (i.e., alternating doses of active drug and placebo).

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 preclinical 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 intrathecally Q4W for four 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 five 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 three or four 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 Phase II OLE suggest 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 adverse events, decreased proportion of patients with moderate adverse events, and fewer adverse events 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 predicted the observed Q8W 9-month reductions (for details see the RO7234292 Investigator's Brochure). From this same model, a Q16W regimen is predicted to result in median CSF HTT trough lowering of 20%, within the range of the 20%–40% target for CSF mHTT lowering at trough and steady state.*

- *Acute lowering in this same model in the 120-mg Q16W regimen is 20% 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 intrathecally in clinical trials. IT 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.

A 25-month (2-year) study treatment length has been chosen because the signal-to-noise characteristics of the primary endpoint cUHDRS (TFC for U.S. FDA)—as investigated in prospective observational cohort studies and in placebo groups of prior clinical trials—suggest that this length is optimal for trial *efficacy*. A treatment duration of 25 months will also enable demonstration of sustained, durable benefit on slowing clinical progression as presumed to be achievable with RO7234292 (which is proposed to be administered as a chronic treatment to slow clinical progression). Studies with a shorter treatment duration, such as 18 months, would require a dramatically larger sample size (i.e., 50%) under the 30% slowing of clinical progression assumption. This would result in a potential risk of signal dilution due to inherent variability of a larger number of sites and clinical raters, resulting in a potential increased risk of type II error.

In summary, a 120-mg *Q8W* dosing regimen and the less frequent dosing regimen of 120 mg *Q16W* have been selected for this Phase III study to maximize CSF mHTT protein lowering acutely and to test the hypothesis of clinical efficacy, as a function of more versus less frequent dosing, while mitigating theoretical risks of long-term IT dosing *of 120 mg* and of non-allele specific lowering of HTT. The 25-month duration is also considered appropriate for providing evidence of the benefit–risk profile of RO7234292 and longer-term tolerability of IT administration.

3.3.2 Rationale for Patient Population

Patients with manifest HD (DCL score of 4 [i.e., motor abnormalities ≥99% likely to be due to HD]) who are ambulatory without assistance, verbal, and possess a CAG–Age

Product (CAP) score of >400 (Zhang et al. 2011; see Section 4.1.1) and an Independence Scale (IS) score of ≥ 70 will be included in this study. This patient population represents manifest disease where disability might be more plausibly reversed or slowed in response to a therapeutic intervention compared with patients with more advanced disease (Penney et al. 1990). This definition also corresponds to the patients most commonly recruited at present for clinical trials aiming to slow clinical progression. Such cohorts are known to have a longitudinal decline in clinical measures (Paulsen et al. 2014) over a timeframe appropriate for clinical trials.

3.3.3 Rationale for Control Group

Patients will be randomly allocated to receive active treatment (RO7234292 *Q8W* or *Q16W*) or placebo in this double-blind study because there are no disease-modifying standard-of-care treatments for patients with HD. The placebo arm will be compared with the RO7234292 treatment arms to enable a robust assessment of the primary endpoint and the benefit-risk profile. As each patient completes the study *or is prematurely discontinued by the Sponsor as a consequence of the changes to the study through Protocol Version 4*, they will be given the option of receiving RO7234292 in an OLE study (BN40955), provided they meet eligibility criteria and the data from the ongoing RO7234292 program support continued development. Approval of *Study BN40955* must also be granted by the relevant competent authority and EC/IRB.

3.3.4 Rationale for Biomarker Assessments

3.3.4.1 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). mHTT 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). NfL 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, 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.

3.3.4.2 Blood Biomarkers

NfL levels in blood correlate with NfL levels in CSF and could serve as prognostic blood biomarkers of disease onset and progression in HD (Wild and Tabrizi 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.

3.3.4.3 Genetic Testing to Determine CAG Repeat Length

HD is caused by mutation in exon 1 of the *HTT* gene located on chromosome 4, resulting in a polyglutamine (CAG) expansion in the huntingtin protein. Above 35 CAG repeats, the age of HD onset is inversely correlated with the length of the expansion (Duyao et al. 1993). CAG repeat length will be determined by direct DNA testing performed centrally.

3.3.4.4 Clinical Genotyping

Although CAG repeat length is inversely correlated to age of onset in HD, it only accounts for approximately 50% of the variance. Identification of other genetic modifiers of disease severity and disease progression in HD could provide important insights, as has been recently shown in the Genetic Modifiers of Huntington's Disease Consortium (2015), where relatively common single nucleotide polymorphisms in the HD population were found to be associated with either an accelerated or delayed age of motor onset. A blood sample will be collected to detect individual single nucleotide polymorphisms to explore, for example, their influence on progression rates, age of onset, disease severity, or response to treatment.

3.3.4.5 Magnetic Resonance Imaging

MRI 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. Structural MRI will be used to assess brain volume, diffusion-weighted MRI will be used to examine structural brain connectivity, and 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. 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.

Structural Magnetic Resonance Imaging

Numerous structural MRI studies have demonstrated wide-spread brain atrophy, including whole-brain, caudate, and ventricular changes in patients with premanifest and manifest HD (Douaud et al. 2006; Harrington et al. 2016). Brain volume correlates with cognitive function (Peinemann et al. 2005). Further, whole-brain, caudate, and ventricular volumes can predict and track progressive clinical decline in patients with HD and can also be associated with molecular biomarkers of neurodegeneration, such as NfL (Tabrizi et al. 2012).

Diffusion Magnetic Resonance Imaging

Widespread changes in basal ganglia–cortical structural connectivity have also been observed in patients with HD (Novak et al. 2015), including associations between striatum-sensorimotor cortex connections and UHDRS motor scale and TMS

(Bohanna et al. 2011), suggesting that the clinical phenotype in manifest HD may be a result of altered structural connectivity.

Resting-State Functional Magnetic Resonance Imaging

Resting-state functional MRI studies have generated evidence for functional connectivity alterations and their correlation to several clinical and cognitive measures in patients with HD (Werner et al. 2014; Dogan et al. 2015; Liu et al. 2016; Espinoza et al. 2018), implying that disrupted functional integrity of distinct brain networks may underlie clinical progression in HD.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 660 patients with HD will be enrolled in this global study *from the implementation of Protocol Version 4 and onwards. This is in addition to patients who enrolled prior to Version 4, who will be discontinued from this study and offered participation in OLE Study BN40955.*

4.1.1 Inclusion Criteria

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

- Signed Informed Consent Form
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form *and at the time of first dose administration*
- Manifest HD diagnosis, defined as a DCL score of 4 (see Appendix 7)
- Independence Scale (IS) score ≥ 70
- Genetically confirmed disease by direct DNA testing with a CAP score > 400 (Zhang et al. 2011), calculated as follows:

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

- 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 lumbar punctures

- Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min (Cockcroft-Gault formula)
- Ability and willingness, in the investigator's judgment, to comply with all aspects of the protocol including completion of interviews and questionnaires for the duration of the study
- Ability and willingness, in the investigator's judgment, to carry a smartphone, wear a digital monitoring device, and complete smartphone-based tasks
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment
- Signed study companion consent for participation*,* if a study companion is available*,* who fulfills all of the following criteria:
  - Age ≥ 18 years
  - Reliable and competent, in the investigator's judgment
  - Sufficiently knowledgeable of the patient's condition to complete study companion assessments of the patient, and likely to remain sufficiently knowledgeable throughout the study, in the investigator's judgment
  - Able to comment on study participant's symptoms and functioning experience, as required per Appendix 1

    Note: Companions *must have no cognitive, behavioral or motor change*, in the opinion of the investigator, that would question the validity of the acquired observer-reported data.

    All effort should be made to retain the study companion; however, should this not be possible, a study companion can be replaced and new consent obtained.
- 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 <u>two</u> 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 (≥ 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 <u>must</u> 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.

4.1.2 Exclusion Criteria

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 done by an appropriately qualified mental health professional to assess whether it is safe for the patient to participate in the study. Mild passive suicidal ideation (i.e., occasional thoughts that life is not worth living or is hard) without history of attempts or hospitalization over the past 12 months is generally acceptable for study participation, but final decision on participation should be made carefully and in consultation with 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

- Clinical diagnosis of chronic migraines
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study drug

  Women of childbearing potential must have a negative serum pregnancy test result *at baseline and a confirmatory urine pregnancy test* prior to initiation of study drug.
- Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Positive for hepatitis C virus (HCV) antibody or hepatitis B surface antigen (HBsAg) at screening
- Known HIV infection
- Current or previous use of an antisense oligonucleotide (including small interfering RNA)
- Current or previous use of anti-psychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks from initiation of study treatment
- Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) and/or tetrabenazine, valbenazine, or deutetrabenazine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
- Current use of supplements (e.g., coenzyme Q10, vitamins, creatine) at a dose that has not been stable for at least 6 weeks prior to screening or is anticipated to change during the study
- Current use of an antidepressant or benzodiazepine at a dose that has not been stable for at least *12* weeks prior to screening or is anticipated to change between screening and treatment initiation
- Treatment with investigational therapy within 4 weeks or 5 drug-elimination half-lives prior to screening, whichever is longer
- Antiplatelet or anticoagulant therapy within 14 days prior to screening or anticipated use during the study, including, but not limited to, aspirin (unless $\leq$ 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.
- History of gene therapy, cell transplantation, or any experimental brain surgery
- Concurrent or planned participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions

Observational studies (e.g., ENROLL-HD prospective study) are acceptable.

- 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
- Antiretroviral medications*, including antiretroviral medication taken as prophylaxis*
- 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 structural brain lesion (e.g., tumor, arterio-venous malformation) as assessed by a centrally read MRI scan during the screening period

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

All patients who were enrolled prior to implementation of Protocol Version 4 and have not already discontinued for another reason will be prematurely discontinued and offered treatment in OLE Study BN40955. The treatment assignments of these patients will remain blinded until at least after the entire cohort has been discontinued from Study BN40423. Patients will receive either the Q8W regimen or Q16W regimen in Study BN40955. These patients will not be included in the primary analysis for Study BN40423.

Patients enrolled after implementation of Protocol Version 4 will be randomly allocated to receive 120 mg of RO7234292 *Q8W*, 120 mg of RO7234292 *Q16W*, or placebo *Q8W*. An independent interactive voice or web-based response system (IxRS) provider will conduct randomization and hold the treatment assignment code.

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during the clinical trial. These roles include the unblinding group, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, iDMC members, and iDCC members.

While PK and ADA samples must be collected from patients assigned to the placebo arm to maintain the blinding of treatment assignment, PK and ADA assay results for

these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignment in order to identify appropriate samples for analysis. PK samples from patients assigned to the placebo arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples will be analyzed for all patients. Post-baseline ADA samples from patients assigned to the placebo arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment. The investigator, patient, and Sponsor personnel will remain blinded to treatment assignment, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above).

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are RO7234292 and RO7234292 placebo.

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), two 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, preparation, and handling of RO7234292, refer to the pharmacy manual.

4.3.1.2 Placebo

RO7234292 placebo will be supplied by the Sponsor as a sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL RO7234292 placebo drug product for IT injection. The liquid is no different in color than the active drug.

For a 20 mL dosing volume, two vials containing 10 mL of RO7234292 placebo will have to be pooled by drawing them up into the same injection syringe containing 20 mL of placebo drug product.

For information on the formulation, preparation, and handling of RO7234292 placebo, 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 adverse events, should be reported as described in Section 5.3.5.12

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

4.3.2.1 RO7234292 and Placebo

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

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

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (RO7234292 or placebo) will be provided by the Sponsor. 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 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 web site:

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

Patients may be eligible to receive RO7234292 as part of an OLE study (BN40955), as described in Section 3.1.

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 screening to the end-of-treatment visit for patients who enter OLE Study BN40955 or the safety follow-up visit for patients who do not enroll in the OLE study. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Contraceptive agents
- Supplements (e.g., coenzyme Q10, vitamins, creatine) if the dose has been stable for at least 6 weeks prior to screening and the dose is not anticipated to change during the study
- Antipsychotics only if prescribed for motor symptoms or for mood stabilization (i.e., irritability or aggressiveness) and/or tetrabenazine/deutetrabenazine/valbenazine if the dose has been stable for at least 12 weeks prior to screening and the dose is not anticipated to change between screening and the start of study treatment

  If clinically indicated, dose changes or medication stopping or starting can occur as per investigator judgment during the course of the study.
- Antidepressant or benzodiazepine if the dose has been stable for at least 12 weeks prior to screening and the dose is not anticipated to change between screening and the start of study treatment

  If clinically indicated, dose changes or medication stopping or starting can occur as per investigator judgment during the course of the study.
- Anti-epileptics if given for mood stabilization*, pain, restless legs, or insomnia*
- Aspirin at doses ≤ 81 mg/day
- Local anesthesia for the lumbar puncture procedure, depending on institutional guidelines

  Sedation may not be used for lumbar puncture.

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 lumbar puncture or IT bolus procedures in the study

  Depending on institutional guidelines, local anesthesia is permissible for the lumbar puncture procedure
- Use of anti-anxiety medication is discouraged during scheduled MRI scans in the study. Anti-anxiety medication used *to prevent movement disorder to allow successful MRI scan is not permitted in this study, as movement disorder too severe to scan under drug-free conditions is an overall study exclusionary criterion.*

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. 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.

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 screening evaluations). Informed Consent Forms for patients and study companions (if available) 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's capacity is confirmed, the investigator may proceed with signing of the Informed Consent Form.

All screening 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 screened and to confirm eligibility or record reasons for screening failure, as applicable.

A maximum of one 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). If re-screening is required, CAG repeat length testing does not need to be repeated (historical values will not be accepted) and the screening MRI and viral serology from the initial screening*, including from other Roche studies,* may be acceptable as part of the re-screening assessments if performed within 12 weeks of the baseline visit.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, HD history (including past hospitalizations [i.e., number, duration, and reason]) over the last 2 years, reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline. *Alcohol and/or drug 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. Daily use of any drug (i.e., cannabinoid, opioid, stimulant, hallucinogen, designer) or daily alcohol use that meets criteria for either abuse or psychological or physiological dependence is not permitted and is exclusionary. Occasional use that does not meet the criteria for abuse is permissible in this study.*

In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from screening to the end-of-treatment visit for patients who enter OLE Study BN40955 or the safety follow-up visit for patients who do not enroll in the OLE study will be recorded. At the time of each study drug administration *and telephone safety follow-up calls*, an interval medical history should be obtained and any changes in medications and any physician visits for HD or general medical care 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. Demographic data and social status data (e.g., relationship to patient and employment status) will also be collected for the study companion. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment.

A unique HD identification number (HDID) will be collected from patients who already have an 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 screening and other specified visits (see Appendix 1), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems (including fundoscopy); 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. Height will be measured at baseline only.

A neurologic examination, performed at screening 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 8)*. The

neurologic examination 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. Weight should also be measured at each visit.

Any abnormality identified at baseline *(Week 1)* 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.

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 approximately 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 lumbar puncture, local laboratory analysis of coagulation factors (INR *and/or PT*, aPTT) and platelets must be conducted and the results reviewed. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, 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 manual,* should be used to minimize risk of post–lumbar puncture 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 lumbar puncture procedure if deemed necessary, but ultrasound is not required. Ultrasound guidance may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. For details on the lumbar puncture and IT bolus dosing procedure, please refer to the *LP procedure and CSF collection guidelines* manual and instructional video.

Administration will occur via a lumbar puncture 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, unless patient-specific factors require 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.

Patients will be discouraged from resting supine after the lumbar puncture 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 72 hours postdose (e.g., air travel, scuba diving, or hot air balloons).

Lumbar punctures will be performed as specified in the schedule of activities (see Appendix 1), with the last CSF sample obtained at the Week 101 end-of-treatment visit. 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).

- CSF for safety: cell count *(including RBCs and WBCs),* glucose, and protein
- *CSF sample for differential cell counts (absolute or percentage), where feasible*

The following samples 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
- Thyroid panel: thyroid-stimulating hormone and free thyroxine (also known as T4) levels
- Viral serology: HBsAg and HCV antibody
- Serum pregnancy test

  Serum pregnancy tests will be performed for women of childbearing potential at screening. *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)
- CSF and blood (plasma) samples for PK analyses and metabolite identification
- Blood (plasma) samples for immunogenicity analyses
- Blood sample for determination of CAG repeat length in *HTT* for patient eligibility
- CSF samples for analysis of mHTT and NfL levels to evaluate the effects of RO7234292 compared with placebo (primary and secondary biomarker endpoints)
- Blood, plasma, and CSF samples for exploratory research on biomarkers and biomarker assay development

Exploratory biomarker research may include, but will not be limited to, total HTT protein, tau, and other proteins related to HD, neurodegeneration, and inflammation. Research may involve extraction of DNA and analysis of mutations, single nucleotide polymorphisms, and other genetic variations. Research will not be aimed at distinguishing germline mutations from somatic mutations.

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Blood, 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.
- Blood (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; therefore, these samples will 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, including data on mutations, 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 on study data publication.

4.5.7 Magnetic Resonance Imaging

Structural MRI will be used to assess brain volume, diffusion-weighted MRI will be used to examine structural brain connectivity, and 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. All scans are mandatory unless a site does not have the capability to perform a resting-state functional MRI or diffusion-weighted MRI. For these cases, the Medical Monitor should be consulted; approval to continue without these scans would 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. MRI scans will be managed by a central laboratory to monitor and ensure the integrity and quality of the acquired data. The screening MRI will be evaluated by the central laboratory to determine patient eligibility. Local neuroradiologists will still be responsible for assessing MRI-related ongoing safety monitoring. During central review, the Sponsor and/or site staff will be notified of any unexpected findings requiring clinical follow-up.

MRI 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 QC and the results* must be available before the patient can be enrolled in the study.

After patient enrollment at specified timepoints, the MRI must be scheduled to occur before the lumbar puncture (see Appendix 1). The MRI scan should be performed 7–14 days prior to the lumbar puncture to allow time for re-scanning if the quality of the initial MRI is inadequate.

4.5.8 Electrocardiograms

Triplicate ECG recording will be obtained at specified timepoints*, within approximately 5 minutes of each other*, as outlined in the schedule of activities (see Appendix 1), 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. ECG recording must be performed after the patient has been resting in a supine position for at least 10 minutes. 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.

4.5.9 Patient-Reported, Clinician-Reported, Study Observer-Reported, and Performance Outcomes

Patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) data will be collected in the clinic to document the change from baseline over time. Additionally, PRO, ObsRO, and PerfO data will be collected remotely. 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 health authority 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 lumbar puncture procedure.

Patients, clinicians, and study companions (if participating) will use an electronic device to capture outcome 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. *Paper must not be used to capture clinical outcome data, unless it is for performance outcome measures (e.g., SDMT and MoCA). Performance measure outcomes must be completed in ink and not pencil.*

Patients will use a smartphone and wrist-worn wearable to capture outcome data remotely and at specified visits (see Section 4.5.9.22). Study companions will use an electronic device to capture data remotely and at specified visits. The electronic devices and/or instructions for completing the questionnaires electronically will be provided to patients and study companions by site staff. Study companion device data will be transmitted to a centralized database maintained by the electronic device vendor. The patient device data will be transmitted to a centralized database maintained by the Sponsor. The data will be available for access by appropriate study personnel. If the device is lost, a replacement will be sent. All devices are encrypted and password protected. See Appendix 1 for the schedule of activities, and Appendix 3 and Appendix 4 for a summary of timing and duration of each PRO, ClinRO, ObsRO, and PerfO assessment. Appendix 5 shows the order and approximate timing of assessments at each clinic visit. *Appendix 9 through Appendix 13 show relevant information for patients who enrolled in Study BN40423 before implementation of Protocol Version 4.*

4.5.9.1 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).

4.5.9.2 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 and the study companion (if available). The TFC score ranges from 0 to 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 clinic visits.

4.5.9.3 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 to 124, with a higher score representing more severe impairment. The TMS takes approximately 15 minutes to administer and will be completed at clinic visits.

4.5.9.4 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 clinic visits and can be completed in less than 5 minutes. It will also be administered at specified timepoints *indicated in Appendix 6* on the Roche HD mobile app (via electronic SDMT).

4.5.9.5 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 *indicated in Appendix 6* on the Roche HD mobile app (via electronic SWR).

4.5.9.6 UHDRS Functional Assessment

The UHDRS Functional Assessment is a checklist of 25 common daily tasks. The investigator indicates if the patient can perform the task by giving a score of 1 to all "yes" replies. The checklist is then summed, and scores can range from 0 (inability to do any task) to 25 (ability to do all tasks on the checklist). The UHDRS FA can be completed in *15* minutes.

4.5.9.7 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 and at specified timepoints. It is a subscale of the UHDRS. The scale consists of 19 discrete levels ranging from 10 to 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 bed care.

4.5.9.8 HD Daily Activities Scale

The HD-DAS assesses patients' daily function. Following a semi-structured interview with the patient and/or study companion, 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.

4.5.9.9 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 (NRS), 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 postbaseline 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.

4.5.9.10 Patient Global Impression, Severity and Change Scales

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

The PGI-C is a single-item measure of change in global status (since starting the study) and is completed by the patient at specified post-baseline visits. The PGI-C has seven response options: "very much worse," "much worse," "minimally worse," "no change," "minimally improved," "much improved," and "very much improved." 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. The PGI-C can be completed in approximately 2 minutes.

4.5.9.11 Companion-Reported Global Impression, Severity and Change Scales

The Companion-Reported Global Impression–Severity (CrGI-S) is a single-item measure of current global severity and is completed by the companion (about the patient) at specified clinic visits. The CrGI-S can be completed in approximately 2 minutes. The CrGI-S is assessed using an 11-point NRS, where higher scores indicate greater severity.

The Companion-Reported Global Impression–Change (CrGI-C) is a single-item measure of change in global status (since starting the study) and is completed by the companion (about the patient) at specified post-baseline visits. The CrGI-C has seven response options: "very much worse," "much worse," "minimally worse," "no change," "minimally improved," "much improved," and "very much improved." 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. The CrGI-C can be completed in approximately 2 minutes.

4.5.9.12 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. It will be used in this study to characterize patients at screening and longitudinally to assess cognitive status at regular intervals throughout the study. It takes approximately 10 minutes to administer.

4.5.9.13 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 NRS, 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) and by the study companion (if available, about him/herself). It will be completed at specified timepoints remotely by the patient on the Roche HD mobile app and by the study companion (if available) on an electronic device.

4.5.9.14 Apathy Evaluation Scale

The AES is an 18-item assessment of apathy, including overt behavior, cognitive aspects of motivation, and emotional responsivity. Each item is scored on a 4-point Likert scale, from 1 ("Not at all") to 4 ("A lot"). A total score is created by summing the 18 items (scores range from 18 to 72; 3 items are reverse scored), with higher scores indicating greater apathy. The AES takes approximately 10 minutes to complete and will be completed by the patient and study companion (if available) at specified clinic visits.

4.5.9.15 Neuro-Qol Cognition Function Short Form, Version 2

The Neuro-Qol Cognition Function Short Form contains 8 items (including "trouble concentrating" and difficulty "learning new tasks or instructions"), each assessed using a 5-point Likert scale, where lower scores indicate greater difficulty (4 items) or greater frequency (4 items). The raw sum score is converted to a T-score distribution (mean = 50, standard deviation = 10). The Neuro-Qol Cognition Function Short Form takes approximately 5 minutes to complete and will be completed by the patient at specified clinic visits.

4.5.9.16 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.

4.5.9.17 Symptoms of Major Depressive Disorder Scale

The SMDDS is a newly developed, valid, and reliable self-report assessment of depression (McCarrier et al. 2016). It contains 16 items, measuring concepts such as sadness, irritability, worry, and sleep disturbance. Each item is assessed on a 5-point Likert scale, from "Not at all" to "Extremely" (9 items) and from "Never" to "Always" (7 items). Item scores from 15 of the items (the least severe of the two eating items is not included) are summed to create a 0–60 score, where higher scores indicate more severe depressive symptomatology. The SMDDS takes approximately 10 minutes to complete and will be completed by the patient at specified clinic visits.

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.

4.5.9.18 HD Companion-Reported Irritability and Angry Outbursts Scale

The HD-CIAOS is a study companion-reported assessment of the patient's irritability and angry outbursts over the past 7 days and will be completed at specified timepoints remotely by the companion (if available) on an electronic device. It consists of three items: frequency of irritable behavior (6-point Likert scale: "Not at all" to "Always"), frequency of angry outbursts (number of occurrences), and severity of the worst outburst

(4-point Likert scale "Mild" to "Very severe"). The HD-CIAOS takes about 2 minutes to complete.

4.5.9.19 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 both by the patient (about him/herself) and by the study companion (if available, about him/herself) at baseline and at specified post-baseline clinic visits on an electronic device. In addition, it will be completed remotely at specified timepoints by the patient on the Roche HD mobile app and by the study companion on an electronic device.

4.5.9.20 Health Utilities Index Mark 2 and Mark 3

The HUI® is a multi-attribute system of health status (Feeny et al. 1995). The HUI2 and HUI3 questionnaire (commonly referred to as HUI2/3) contains 15 items with Likert-type response options. From these items, two scores can be produced: HUI2 (7 items) and HUI3 (8 items). Both scores are health utility indexes, where 0 = death, and 1 = perfect health.

The HUI2/3 will be completed by the companion, both about him/herself and as a proxy report of the patient's HRQoL. The HUI2/3 will be completed at specified timepoints at clinic visits and remotely on an electronic device.

4.5.9.21 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. FDA draft guidance for assessment of suicidality in clinical trials (FDA 2012). The C-SSRS will be used to assess eligibility for the study (full version at baseline, 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).

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.

4.5.9.22 Optional Exit Interviews

Optional exit interviews will be conducted with a subset of patients (up to 60 patients) at select sites within approximately 1 week after the end-of-treatment visit. The semi-structured interviews will be conducted by an external vendor and can be conducted by telephone. The interviews will enable patients to provide details about changes they observe in their symptoms, as well as any impacts on daily life.

Interviews will be transcribed verbatim, and themes emerging from these transcripts will be interpreted in relation to changes in patients' clinical outcome assessment scores. All participants in this optional study interview will be asked which arm they thought they were assigned to (120 mg *Q8W*, 120 mg *Q16W*, or placebo). Of note, patients, staff, and the Sponsor will remain blind to patient treatment assignment during the study, as outlined in Section 4.2.

Additional consent for this optional portion of the study will be included in the relevant Informed Consent Form.

4.5.9.23 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). Each patient will receive a preconfigured smartphone and wrist-worn wearable with installed software for the Roche HD mobile app assessments. 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 provided with devices and trained on their use during screening. *Patients will also have in-clinic assessments of the digital platform that are supervised as indicated in Appendix 6. Outside of the clinic, patients* will be instructed to conduct 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, voice) and non-motor symptoms (processing speed, voice). Testing will usually last approximately 5 minutes in total on a typical day of testing. Not all tests are daily. Additional information on the tasks and schedule is specified in Appendix 6.

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. Companions (where available) will receive their own independent electronic device at screening, which is different from the patient smartphone.

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 Wi-Fi. Patients will be asked to charge the devices overnight. If patients have a Wi-Fi network at home, they will be encouraged to connect their smartphone to enable data transfer. If no Wi-Fi network is available, the sensor data will be transferred during clinic visits or after the devices have been returned.

Roche HD mobile app "baseline" data will consist of all data collected prior to and including the baseline visit (up to 28 days). Baseline data will be collected for at least the 7 days up to and including Day 1.

4.5.9.24 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. At specified clinic visits, patients will be asked to conduct the "active test" tasks under the supervision of trained site staff*, as shown in Appendix 6.*

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. At the time of study completion or early termination, patients will be asked to complete a pen-and-paper satisfaction survey about their experience using the smartphone and wrist-worn wearable.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7234292, the HTT protein, HD or other diseases, or drug safety:

- Blood and serum samples collected at baseline and at Weeks 37, 69, and 101
- Leftover blood, plasma, and CSF samples and any derivatives thereof (e.g., proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, 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 on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient.* However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF.

If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

Due to the Sponsor's decision to discontinue the 120-mg Q4W dosing regimen and replace this with a 120-mg Q16W dosing regimen in Protocol Version 4, all patients who enrolled prior to implementation of Protocol Version 4 will be prematurely discontinued from the study by the Sponsor and will complete their end-of-treatment visit prior to entry into Study BN40955.

An excessive rate of withdrawals (either study treatment discontinuation or withdrawal from the study) can render the study results non-interpretable. Therefore, all efforts should be taken to motivate patients to comply with all study-specific procedures and to be followed until the end of the 101-week, placebo-controlled treatment period.

Investigators should explore all possible options to contact patients for visits, especially end-of-treatment visits. The site must document all attempts to try to contact the patient in the patient's medical records and source documents.

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
- *Loss of capacity to consent, if legal guardian consent is not possible*

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

All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) for collection of at least the data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). If the early treatment termination visit falls within $\pm$30 days of either scheduled visits at Week 53 or Week 69, then only early treatment termination will be considered. Patients will also attend the scheduled end-of-treatment visit at Week 101 *window*.

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

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 adverse events 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. The known safety risks for the lumbar puncture 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 adverse events. Guidelines for managing adverse events, 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 through 5.1.1.3) are potential risks associated with lumbar puncture.

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

In the ongoing Phase II OLE Study BN40967 (9-month data), potential post–lumbar puncture adverse events (including procedural pain, post–lumbar puncture syndrome, post-procedural discomfort, headache, and migraine) occurring within 72 hours of drug administration were summarized per cohort. For the Q4W cohort (n=23), 28 events were reported in 13 (56%) of patients; for the Q8W cohort (n=23), 27 events were reported in 12 (52.2%) patients.

Many of the complications associated with lumbar puncture can be avoided by the mandatory use of a 24G *atraumatic* needle with a stylet, adherence to procedural guidelines (see lumbar puncture manual and instructional video), and careful assessment of the patient, including neurologic examination with fundoscopy both prior to and post–lumbar puncture procedure. Lumbar puncture should be avoided when a contraindication is present.

CSF 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 lumbar puncture, 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 lumbar puncture and increased intracranial pressure.

There are specific contraindications to performing lumbar puncture. These include unstable cardiorespiratory status, where positioning patient for lumbar puncture 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, lumbar puncture (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. Previous lumbar surgery is an exclusion criterion for this study.

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

5.1.1.1 Post–Lumbar Puncture Syndrome

RO7234292 will be delivered directly to the CNS by IT lumbar puncture injection. Post–lumbar puncture syndrome (e.g., headaches, nausea, vomiting, infection, hemorrhage, nerve irritation pain) can occur with IT administration. Experience to date with post–lumbar puncture 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 ongoing Phase II OLE Study BN40967 (9-month*

data), 4 events of post lumbar puncture syndrome were reported in the Q4W cohort (17.4%) and 3 in the Q8W cohort (13.0%). All these events were rated as mild and resolved without treatment with the exception of 1 event in the Q4W cohort that required treatment (mild and resolved).

Patients should walk post–lumbar procedure, to assist drug distribution (see Section 4.3.2.1); however, if a patient develops a headache after the lumbar puncture with characteristic features, which makes walking intolerable, the patient should be encouraged to first sit down and if the headache persists then 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 lumbar puncture. Patients may present with headache, meningism, photophobia, neck stiffness, and pyrexia. Guidelines for management of patients with suspected meningitis are provided in Table 3.

5.1.2 Potential Risks Associated with RO7234292

The potential risks identified below have been considered in relation to clinical data available as of 30 January 2019, including the completed Phase I/IIa study and ongoing Phase II OLE study (9-month datacut).

5.1.2.1 *Neurologic Changes*

In cynomolgus monkeys, acute, transient deficits in lower spinal reflexes (patellar reflex in particular) were typically observed 2 to 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 MAD study (ISIS 443139-CS1), no adverse trends in neurological examinations were detected and only a few drug-related neurological adverse events were observed in ≥2 patients. See the RO7234292 Investigator's Brochure for more information.

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 intrathecal bolus injection of RO7234292.

5.1.2.2 Elevations in CSF WBCs *and Protein*

Mild elevations in CSF WBCs have been observed during the Phase I/IIa, dose-escalation study (Study ISIS 443139-CS1) and its respective OLE study (Study ISIS 443139-CS2 [Study BN40697]) at various timepoints that are sometimes associated with changes in CSF protein without signs of *inflammation*. The majority of patients have counts under 10 WBCs, with several patients with higher elevations observed to date in the OLE study. Patients with CSF WBC elevations have generally been asymptomatic. One case with elevations in CSF WBCs and CSF protein presented with ankle hyporeflexia after the seventh dose of 120 mg monthly with enhancement of the cauda equina noted on MRI of the spine, with no other clinical sequelae noted.

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.

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 was observed in the completed RO7234292 Phase I/IIa study. In the ongoing phase II OLE study (BN40697), no events of thrombocytopenia have been reported to date (9-month data).

Platelet counts will be monitored at each study visit prior to lumbar puncture. See *Table 3* 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. *In the ongoing Phase II OLE study (BN40697), one case of moderate proteinuria considered related to the study drug has been reported in the Q4W cohort (resolved without any intervention); 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 3*.

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 *was 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. In the ongoing Phase II OLE study (BN40697), liver enzyme adverse events were reported in 2 patients in the Q4W cohort (one moderate event of gamma-glutamyltransferase increase, ongoing, and one mild hepatic enzyme increase which resolved without any intervention and were considered not related to RO7234292 by the investigator). No other clinically significant hepatic abnormality has been observed.*

Liver enzymes will be monitored at each study visit. Guidelines for management of patients who develop decreased liver function are provided in Table 3.

5.1.2.6 *Hydrocephalus*

Hydrocephalus is included as a warning in the labelling of one marketed IT-administered 2'-MOE chimeric ASO. No hydrocephalus was observed in the completed RO7234292 Phase I/IIa MAD study (ISIS 443139-CS2) and the ongoing Phase II OLE study (BN40697) to date.

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 (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 Columbia-Suicide Severity Rating Scale (C-SSRS) and the Montreal Cognitive Assessment 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 recent 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. ASO-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 per injection on a $Q8W$ basis).

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 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 adverse events are outlined in Table 3. 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 3 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*, or other acute neurologic symptoms*	• Withhold study drug if diagnosis of meningitis, radiculitis, arachnoiditis*, or acute neurologic symptoms* is suspected and initiate appropriate diagnostic work-up as indicated. • Clinical signs and symptoms (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 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 *WBC count* CSF elevations above 10 are present*, or a change from baseline in CSF proteins greater than twice baseline* or where there is uncertainty to discuss next steps of patient management in the study. • If diagnosis of suspected meningitis, radiculitis, arachnoiditis*, 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*, or acute neurologic symptom* diagnosis is confirmed, standard-of-care therapies should be instituted as indicated.

Thrombocytopenia	• If platelet count is $\leq$100,000/mm^3:
	  ○ Monitor platelet count weekly
	• If platelet count is $\leq$ 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 $\leq$ 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 3 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

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: o eGFR (using Cockcroft-Gault) or CrCl < 60 mL/min o 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: o Monitor weekly until ALT and AST return to ≤1.2×ULN. o 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): o ALT or AST >5×ULN o ALT or AST >3×ULN, combined with total bilirubin >2× ULN or INR >1.5 o 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. o 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 adverse events, including serious adverse events and adverse events of special interest, 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 adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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 serious adverse event is any adverse event that meets any of the following criteria:

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

  This does not include any adverse event 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 adverse event 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 adverse event (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 adverse event 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 adverse events (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 adverse event 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 adverse events at each patient contact. All adverse events, 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 serious adverse events caused by a protocol-mandated intervention (e.g., invasive

procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 5 months after the final dose of study drug or until the patient receives his or her first dose in the OLE study (BN40955), at which time reporting will occur per the new study requirements.

Instructions for reporting adverse events that occur after the adverse event 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 adverse event 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 4 will be used for assessing adverse event severity. Laboratory values determined as an adverse event should be graded as per Appendix 5, which is based on the NCI CTCAE (v5.0).

Table 4 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 adverse event 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 5):

- 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 5 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 adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event 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 adverse events 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 adverse events based on signs and symptoms should be nullified and replaced by one adverse event 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, adverse events 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 adverse event 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 three 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 adverse events 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 adverse event 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 adverse event 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 serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event 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 adverse event. A laboratory test result must be reported as an adverse event 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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP 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 adverse event. 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 adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event 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 adverse event.

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 adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$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 adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ 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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event 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 adverse event 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 adverse event 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 screening 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 adverse event 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 adverse events. 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 adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event 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 adverse event or a serious adverse event:

- 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 adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event 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 adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event 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 or placebo, adverse events associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with RO7234292 or placebo, regardless of whether they result in an adverse event, 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 or Observer-Reported Outcome Data

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

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 serious adverse events to the local health authority 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 serious adverse events 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 email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest 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 email 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 serious adverse events 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 email 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 serious adverse events 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 Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the final dose of study drug 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 email 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

A spontaneous abortion should be classified as a serious adverse event (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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

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 serious adverse event, 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 adverse event 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 serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (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 serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, 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 serious adverse event that occurs after the end of the adverse event reporting period (defined as greater than 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 email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event 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

All patients enrolled prior to Version 4 of the protocol will not be included for any efficacy analysis. The safety data collected for these patients up to and including the end of treatment visit in Protocol BN40423 will be analyzed separately.

The primary efficacy analysis will be conducted at the end of the study (see Section 3.2). Treatment assignments will be unblinded to the Sponsor at the end of the study after the data have been cleaned and verified and the database has been locked.

Details of the planned statistical analyses mentioned below will be fully specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to the locking and unblinding of the study database.

Unless otherwise specified, all the p-values considered in Section 6 are two-sided.

6.1 ANALYSIS POPULATIONS

The intent-to-treat (ITT) population will consist of all patients *enrolled after implementation of Protocol Version 4* who received any study treatment. Randomized patients who receive 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 primary and secondary efficacy variables.

The safety population for the trial will consist of all patients who enroll after implementation of Version 4 of the protocol and also receive 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.

The PK population will include all randomized patients who received at least one dose, and had sufficient sampling to permit PK evaluation.

6.2 DETERMINATION OF SAMPLE SIZE

The planned sample size is adequate to capture meaningful clinical decline on both the TFC and cUHDRS and was estimated on the basis of data available from non-interventional studies (TRACK-HD, COHORT, ENROLL-HD) and a randomized placebo-controlled study (2CARE). Based on these data, using the anticipated trial population, a meta-analysis for the change from baseline at 24 months in TFC score suggested a natural decline of 1.36 points and a corresponding pooled standard deviation of 1.78. *A conservative treatment discontinuation rate at Week 101 for patients receiving placebo or active is assumed to be 20% and 15%, respectively. Using these assumptions, the simulation described below was performed to estimate the sample size.*

Description of Simulations to Derive the Sample Size

The design used for the simulation was simplified to consider only 2 treatment arms (placebo and active) and 2 postbaseline timepoints (Week 49 and Week 101). These simplifications are justifiable given that:

- *A hierarchical procedure will be used to test the primary endpoint for the two regimens against placebo, with the Q8W regimen tested first (see Section 6.3).*
- *The difference on the derived sample size for considering more than two postbaseline timepoints would be minimal.*

The following algorithm was run and repeated 500,000 times:

1. *Generate change from baseline values in TFC at Week 49 and Week 101 for N active patients according to the following bivariate normal distribution:*

$$\begin{pmatrix} y\_wk49 \\ y\_wk101 \end{pmatrix} = N\left(\mu = \begin{pmatrix} 0.47 \\ 0.82 \end{pmatrix}, \sum = \begin{pmatrix} 1.56^2 & 0 \\ 0 & 1.78^2 \end{pmatrix}\right)$$

where y_wk49 and y_wk101 is the change from baseline in TFC, respectively, at Week 49 and Week 101, μ is the assumed true change at those two timepoints, and $\sum$ is the variance-covariance matrix. Subsequently:

- *set to missing, due to study drug–related (SDR) reasons, both values at Week 49 and Week 101 for 5% of the N patients. Set to missing, due to non–study drug–related (NSDR) reasons, both values at Week 49 and Week 101 for additional 2.5% of the N active patients.*

- *set to missing, due to SDR reasons, only the value at Week 101 for additional 5% of the N active patients. Set to missing, due to NSDR reasons, only the value at Week 101 for additional 2.5% of the N active patients.*

2. *Generate change from baseline values in TFC at Week 49 and Week 101 for N placebo patients according to the following bivariate normal distribution:*

$$\begin{pmatrix} y\_wk49 \\ y\_wk101 \end{pmatrix} = N\left(\mu = \begin{pmatrix} 0.79 \\ 1.36 \end{pmatrix}, \sum = \begin{pmatrix} 1.56^2 & 0 \\ 0 & 1.78^2 \end{pmatrix}\right)$$

where y_wk49 and y_wk101 is the change from baseline in TFC, respectively, at Week 49 and Week 101, μ is the assumed true change at those two timepoints, and $\sum$ is the variance-covariance matrix. Subsequently:

- *set to missing both values at Week 49 and Week 101 for 10% of the N placebo patients*
- *set to missing only the value at Week 101 for additional 10% of the N placebo patients*

Given how missing data will be imputed, it is not relevant to differentiate missing data into SDR versus NSDR reasons for placebo patients.

3. *Apply multiple imputations and derive 20 complete datasets. Missing data on placebo patients were imputed from the placebo arm. Missing data on active patients, depending on if due to NSDR or SDR reasons, were imputed respectively from the active or the placebo arm.*

4. *Use a t-test to compare active versus placebo at Week 101 for each completed dataset and pool the result (Rubin 1987) to derive an estimate of the treatment effect, including a p-value.*

Across the 500,000 simulations, the power achieved, with the N patients per arm was calculated by dividing the number of times the p-value (in above Step 4) was below 5% by 500,000. The above procedure was repeated by only changing the N until the calculated power was close to 80%.

It was estimated that 220 patients per arm will provide approximately 80% power, at a two-sided $\alpha = 0.05$ level, to detect a 40% slowing of clinical decline for RO7234292 as compared with placebo at 101 weeks. This treatment effect translates into an expected average decline of ~0.82 points at 101 weeks for the RO7234292 arms. The minimal detectable difference with these assumptions is ~0.38 points.

6.3 *TESTING STRATEGY AND MULTIPLICITY ADJUSTMENT*

A hierarchical approach will be used for multiple adjustments that accounts for comparisons of two active dosing regimens (RO7234292 Q8W and RO7234292 Q16W) versus placebo, as well as multiple endpoints (the primary and secondary endpoints).

The primary endpoint will be tested for RO7234292 Q8W against placebo at alpha level 5% and, if significant, then RO7234292 Q16W against placebo.

Secondary endpoints will be tested for each active treatment versus placebo. Within each testing chain (RO7234292 Q8W and RO7234292 Q16W), the endpoint will be tested only if the preceding endpoint is significant at the divided alpha level. Details of the order for secondary endpoints and the split of alpha will be detailed in the SAP.

6.4 SUMMARIES OF CONDUCT OF STUDY

The numbers 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. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.5 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, CAG repeat length, CAP, HD stage, education) 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.

6.6 EFFICACY ANALYSES

To ensure the treatment groups under comparison are concurrent and that treatment regimens are comparable across the entire dosing period of the 25-month study, for all efficacy analyses, patients enrolled prior to implementation of Protocol Version 4 will not be included and will be offered the option to enroll into Study BN40955 before reaching the primary endpoint assessment in the current study.

6.6.1 Estimands

Following the very recent estimand framework outlined in the ICH-E9 draft addendum (FDA 2017), the attributes of the estimand for the primary endpoint are defined as follows:

- Population: ITT population (see Section 6.1)
- Variable: Change from baseline in cUHDRS score at Week 101
  - Note: cUHDRS scale will be replaced by TFC scale for the FDA.
- Intercurrent events (ICEs):
  - Treatment discontinued for study drug–related reasons (e.g., treatment-related adverse event or lack of efficacy):

    After treatment discontinuation, the actual off-treatment values will be used in the analysis.

- Treatment discontinued for NSDR reasons (e.g., lost to follow-up):

  After treatment discontinuation, imputed hypothetical values as if patients had continued receiving study drug will be used in the analysis. In this instance, any data collected after treatment discontinuation will not be included in the analysis.

- Population level summary: Difference in mean change from baseline at Week 101 between each active arm and the placebo arm

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE.

The Sponsor will emphasize to investigators the importance of collecting data for the primary endpoint through Week 101, even if patients discontinue study drug but do not withdraw study consent, as well as the importance of providing detailed reasons for treatment discontinuation. The primary estimator, described by the statistical model in Section 6.6.2, will be applied on the dataset produced after multiple imputation of *any missing value. In principle,*

- *missing data as well as off-treatment data from patients who discontinued treatment for NSDR reasons will be imputed from patients with available data from the same treatment arm collected while on treatment*
- *missing data from patients who discontinued treatment for SDR reasons will be imputed from:*
  - *patients with available data from the placebo arm collected either while on treatment or off treatment and*
  - *patients with available data from the same treatment arm collected while off treatment*

Multiple imputation of missing data values will be performed as follows:

1. ***Imputation step:*** *Missing data values will be imputed "m" times leading to "m" complete datasets.*
2. ***Analysis step:*** *Each of the resulting "m" datasets will be analyzed using the statistical model described in Section 6.6.2, which will provide an estimate of treatment difference.*
3. ***Pooling step:*** *The results from the "m" datasets will be combined (Rubin 1987) leading to an overall estimate of the treatment effect and associated 95% confidence intervals and p-values.*

Full details of the algorithm for multiple imputation (e.g., *which reference population to use for each missing data pattern*, number of imputed datasets, method for imputation, *etc.*) will be provided in the SAP.

A supplementary estimand may be considered (and will be defined in the SAP).

6.6.2 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in cUHDRS score at Week 101. This is defined as the attribute "variable" of the primary estimand in Section 6.6.1.

Note: The primary efficacy endpoint for the U.S. FDA will be change from baseline in the TFC score at Week 101. TFC will be analyzed the same way as the cUHDRS.

The primary efficacy analysis for this study will compare each active treatment arm, RO7234292 $Q8W$ and RO7234292 $Q16W$, against the placebo arm.

To account for the multiple comparison, an appropriate procedure will be used to maintain the overall two-sided type I error at 5% (details will be given in the SAP).

The analysis of the primary endpoint will be performed by means of analysis of covariance (ANCOVA). The model will include the corresponding endpoint baseline score, CAG repeat length, baseline CAP score (defined in Section 4.1.1), and treatment as covariates. On the basis of this analysis, least squares mean for the treatment differences at Week 101 and corresponding 95% CIs will be derived.

The robustness of the primary method of estimation described above may be explored by alternative sensitivity estimators based on varying assumptions underlying the multiple imputation strategy. These sensitivity analyses will be described in the SAP.

6.6.3 Secondary Efficacy Analyses

The secondary efficacy endpoints are identified in Section 2.1.2.

Similar hypotheses as for the primary efficacy endpoint will be tested for the secondary continuous efficacy endpoints.

Categorical endpoints, such as CGI-C and the proportion of progressors, will be analyzed by means of logistic regression and will include treatment (categorical), CAG repeat length, and CAP score as covariates.

Methods for controlling type I error in the testing of the secondary endpoints will be described in the SAP.

6.6.4 Subgroup Analyses

The results of selected efficacy variables will be summarized within subgroups using descriptive statistics. The following variables will be used to define subgroups:

- Sex (male vs. female)
- Age at baseline (< 45 vs. ≥ 45 years)
- CAG repeat length (< 43 vs. ≥ 43)
- Stage at baseline (I, II, III)
  - Stage III will be considered only if there are enough patients.

Additional exploratory analyses of efficacy results may be performed using an ANCOVA model, similar to the primary analysis, based on change from baseline for the variable of interest, with baseline score (not for analysis by baseline stage), CAP score, CAG repeat length (not for analysis by CAG repeat length), treatment, subgroup, and treatment-by-subgroup interaction as covariates.

6.6.5 Exploratory Efficacy Analysis

The exploratory efficacy endpoints are identified in Section 2.1.3.

The exploratory endpoints will be summarized using tables, listings, and graphs, as appropriate. Additional statistical modeling may be considered (e.g., ANCOVA, logistic regression).

6.6.6 Historical Controls

Should the treatment discontinuation rate in the placebo arm be significantly higher than expected, the Sponsor may consider the use of historical controls for efficacy analysis. In this scenario, the use of historical controls will be deemed supportive analyses.

Prior to database lock, the Sponsor may select historical controls from ENROLL-HD. These historical controls may be selected to match patients with regard to important baseline characteristics (e.g., gender, CAG, age, IS, International Standard Classification of Education). The objective for use and exact algorithm for selecting historical controls will be specified in the SAP. If implemented, the actual selection will be made before database lock and *unblinding of treatment allocation and will be* documented and stored in the Sponsor's database.

Whether the Sponsor will decide to use those the historical controls, the exact algorithm for borrowing and for deriving an overall treatment effect will be described in the SAP before unblinding.

Additionally, given that some of the patients who will be enrolled in this study may have been part of ENROLL-HD, the Sponsor may explore a within-patient comparison for the

rate of decline in cUHDRS or TFC score, before treatment with RO7234292 (prior to randomization, using ENROLL-HD registry data) and after treatment with RO7234292 (after randomization, using study data), for patients who were randomized to the active arm and had follow-up in ENROLL-HD of at least 1 year's duration prior to randomization into this study.

6.7 SAFETY ANALYSES

The *safety* population (see Section 6.1) will be the primary population for all analyses of safety data. Incorrect treatment assignments (patients who received a treatment different than their planned randomized treatment) will be summarized and the impact on the safety assessment will be discussed.

For all safety analyses, patients enrolled prior to implementation of the Version 4 of the protocol will be summarized separately.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms. The adverse event severity grading scale indicated in Table 4 will be used for assessing adverse event severity. Laboratory values determined as an adverse event should be graded as per Appendix 5, which is based on the NCI CTCAE (v5.0).

All safety data, including adverse events, laboratory tests, CSSR-S, 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 adverse events will be summarized on the basis of body systems and dictionary preferred terms. The incidence of adverse events by severity and relationship to study drug or study procedure and incidence of marked abnormal laboratory test results will be provided.

The iDMC will review safety data throughout the study. Analyses required for the iDMC data review will be performed as described in the iDMC Charter.

6.8 PHARMACOKINETIC ANALYSES

For all patients in the PK population (Section 6.1), 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., area under the plasma

concentration–time curve, average trough plasma concentration) will be computed and used to explore exposure-response relationship on primary and key secondary 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.

6.9 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 or, if no treatment is received prior to study discontinuation, according to treatment assigned.

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 for patients on active treatment only. 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).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported via descriptive statistics.

6.10 BIOMARKER ANALYSES

The biomarker endpoints are described in Section 2.5.

A mixed-effects model repeat measurement model will be used to model the change in each primary and secondary biomarker endpoint, adjusting for the baseline endpoint, CAG repeat length, CAP score, treatment, visit, and treatment-by-visit interaction (the final list of covariates and details of the model will be specified in the SAP).

6.11 HEALTH STATUS UTILITY ANALYSIS

The health status utility endpoints are described in Section 2.6.

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

6.12 OPTIONAL INTERIM ANALYSES

The Sponsor may choose to conduct one or more interim analyses for efficacy. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct an interim analysis, along with the rationale, specification of the endpoint (e.g., clinical and/or biomarker endpoint), number of patients, and statistical details for each analysis, will be *introduced via a future protocol amendment*, which will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of an interim analysis, and the iDMC Charter will be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of an interim analysis of efficacy data, the type I error rate will be controlled to ensure statistical validity is maintained. Additional criteria for recommending that the study be stopped for positive efficacy will be added *to a future protocol amendment*.

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.

eCRFs 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.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs 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. eCRFs 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. eCRFs 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-, CLINICIAN-, AND OBSERVER-REPORTED OUTCOME DATA

Electronic devices will be used to capture PRO, ClinRO, ObsRO, and PerfO data. The devices are 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 MONITORING PLATFORM

During "active tests" and "passive monitoring," the smartphone and wrist-worn wearable record 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 Wi-Fi. 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 health authorities.

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 health

authority 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, ClinRO, ObsRO (if applicable), and PerfO data (if applicable), Informed Consent Forms, 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 health authorities, 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 health authorities, 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 United States 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 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 Informed Consent Form (and ancillary sample Informed Consent Forms) 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 Informed Consent Forms 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 health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form 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 before his or her participation in the study. If a study companion will participate, he/she must also sign and date a consent form prior to 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.

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 health authority 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 patient should lose capacity to consent during the study (i.e., after enrollment), as judged by the investigator, a legally authorized representative may sign on behalf of the patient.

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 United States, 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 Informed Consent Forms, 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 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority 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 health authority 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 Informed Consent Form (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 on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, 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, 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. 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 health authorities. 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, Informed Consent Forms, 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 health authorities. 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 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 health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 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 *90* sites globally will participate to enroll approximately 660 patients *after implementation of Version 4 of the protocol*. 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.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.5 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 web site:

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.

9.6 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).

10. REFERENCES

Andrzejewski KL, Dowling AV, Stamler D, et al. Wearable sensors in Huntington disease: a pilot study. J Huntington's Dis 2016;5.2:199–206.

Adams JL, Dinesh K, Xiong M,et al. Multiple wearable sensors in parkinson and Huntington disease individuals: a pilot study in clinic and at home. Digit Biomark 2017:1:52–63

Baig SS, Strong M, Quarrell OW. The global prevalence of Huntington's disease: a systematic review and discussion. Neurodegener Dis Manag 2016;6:331–43.

Beglinger LJ, Prest L, Mills JA, et al. Clinical predictors of driving status in Huntington's disease. Mov Disord 2012;27:1146–52.

Bohanna I, Georgiou-Karistianis N, Sritharan A, et al. Diffusion tensor imaging in Huntington's disease reveals distinct patterns of white matter degeneration associated with motor cognitive deficits. Brain Imaging Behav 2011;5:171–80.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Cerritelli SM, Crouch RJ. Ribonuclease H: the enzymes in eukaryotes. FEBS J 2009;276:1494–505.

Crooke ST, Bennett CF. Progress in antisense oligonucleotide therapeutics. Annu Rev Pharmacol Toxicol 1996;36:107–29.

Dogan I, Eickhoff CR, Fox PT, et al. Functional connectivity modeling of consistent cortico-striatal degeneration in Huntington's disease. Neuroimage Clin 2015;7:640–52.

Douaud G, Gaura V, Ribeiro MJ, et al. Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study. Neuroimage 2006;32:1562–75.

Duyao M, Ambrose C, Myers R, et al. Trinucleotide repeat length instability and age of onset in Huntington's disease. Nat Genet 1993;4:387–92.

Espinoza FA, Turner JA, Vergara VM, et al. Whole-brain connectivity in a large study of Huntington's disease gene mutation carriers and healthy controls. Brain Connect 2018;8:166–78.

EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

[FDA] Food and Drug Administration. Guidance for industry: suicidal ideation and behavior: prospective assessment of occurrence in clinical trials [resource on the Internet] 2012 [cited 28 February 2018]. Available from: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm315156.htm.

[FDA] Food and Drug Administration. E9(R1) statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials. [resource on the Internet] 2017 [cited 1 August 2018]. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582738.pdf.

Feeny D, Furlong W, Boyle M, et al. Multi-attribute health status classification systems. Health utilities index. Pharmacoeconomics 1995;7:490–502.

Genetic Modifiers of Huntington's Disease Consortium. Identification of genetic factors that modify clinical onset of Huntington's disease. Cell 2015;162:516–26.

Harrington DL, Long JD, Durgerian S, et al. Cross-sectional and longitudinal multimodal structural imaging in prodromal Huntington's disease. Mov Disord 2016;31:1664–75.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Hogarth P, Kayson E, Kieburtz K, et al. Interrater agreement in the assessment of motor manifestations of Huntington's disease. Mov Disord 2005;20:293–7.

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

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Johnson EB, Byrne LM, Gregory S, et al. Neurofilament light protein in blood predicts regional atrophy in Huntington disease. Neurology 2018;90:e717–23.

Kordasiewicz HB, Stanek LM, Wancewicz EV, et al. Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron 2012;74:1031–44.

Lipsmeier F, Taylor KI, Kilchenmann T, et al. Evaluation of smartphone-based tsting to generate exploratory outcome measures in a phase 1 Parkinson's disease clinical trial. Mov Disord 2018. doi : 10.1002/mds.27376. Epub ahead of print.

Liu JP, Zeitlin SO. Is huntingtin dispensable in the adult brain? J Huntingtons Dis 2017;6:1–17.

Liu W, Yang J, Chen K, et al. Resting-state fMRI reveals potential neural correlates of impaired cognition in Huntington's disease. Parkinsonism Relat Disord 2016;27:41–6.

Maetzler W, Domingos J, Srulijes K, et al. Quantitative wearable sensors for objective assessment of Parkinson's disease. Mov Disord 2013;28:1628–37.

McCarrier KP, Deal LS, Abraham L, et al. Patient-centered research to support the development of the Symptoms of Major Depressive Disorder Scale (SMDDS): initial qualitative research. Patient 2016;9:117–34.

Moumné L, Betuing S, Caboche J. Multiple aspects of gene dysregulation in Huntington's disease. Front Neurol 2013;4:127.

Nance M, Paulsen JS, Rosenblatt A, et al. A physician's guide to the management of Huntington's disease, 3rd edition. Huntington's Disease Society of America, 2011.

Novak MJ, Seunarine KK, Gibbard CR, et al. Basal ganglia-cortical structural connectivity in Huntington's disease. Hum Brain Mapp 2015;36:1728–40.

Paulsen JS, Long JD, Ross CA, et al. Prediction of manifest Huntington's disease with clinical and imaging measures: a prospective observational study. Lancet Neurol 2014;13:1193–201.

Paulson HL, Albin RL. Huntington's disease: clinical features and routes to therapy. In: Lo DC, Hughes RE, editors. Neurobiology of Huntington's disease: applications to drug discovery. Boca Raton (FL): CRC Press/Taylor & Francis; 2011: Chapter 1.

Peinemann A, Schuller S, Pohl C, et al. Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study. J Neurol Sci 2005;239:11–9.

Penney JB, Young AB, Shoulson I, et al. Huntington's disease in Venezuela: 7 years of follow-up on symptomatic and asymptomatic individuals. Movement Disorders 1990;5:93–9.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266–77.

Ross CA, Pantelyat A, Kogan J, et al. Determinants of functional disability in Huntington's disease: role of cognitive and motor dysfunction. Mov Disord 2014;29:1351–8.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons. 1987.

Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. Neurology 2017;89:2495–2502.

Schoch KM, Miller TM. Antisense oligonucleotides: translation from mouse models to human neurodegenerative diseases. Neuron 2017;94:1056–70.

Shoulson I, Fahn S. Huntington disease: clinical care and evaluation. Neurology 1979;29:1–3.

Smith, A. Symbol Digit Modalities Test (SDMT). Manual (rev.). Los Angeles: Western Psychological Services, 1982.

Sorensen SA, Fenger K. Causes of death in patients with Huntington's disease and in unaffected first degree relatives. J Med Genet 1992;29:911–4.

Stanek LM, Yang W, Angus S, et al. Antisense oligonucleotide-mediated correction of transcriptional dysregulation is correlated with behavioral benefits in the YAC128 mouse model of Huntington's disease. J Huntingtons Dis 2013;2:217–28.

Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol 2012;11:42–53.

Van Raamsdonk JM, Pearson J, Rogers DA, et al. Loss of wild-type huntingtin influences motor dysfunction and survival in the YAC128 mouse model of Huntington disease. Hum Mol Genet 2005;14:1379–92.

Walker FO. Huntington's disease. Semin Neurol 2007;27:143–50.

Werner CJ, Dogan I, Saß C, et al. Altered resting-state connectivity in Huntington's disease. Hum Brain Mapp 2014;35:2582–93.

Wexler NS, Young AB, Tanzi RE, et al. Homozygotes for Huntington's disease. Nature 1987;326:194–7.

Wild EJ, Boggio R, Langbehn D, et al. Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. J Clin Invest 2015;125:1979–86.

Wild EJ, Tabrizi SJ. Therapies targeting DNA and RNA in Huntington's disease. Lancet Neurol 2017;16:837–47.

Zhang Y, Long JD, Mills JA, et al. Indexing disease progression at study entry with individuals at-risk for Huntington disease. Am J Med Genet B Neuropsychiatr Genet 2011;156:751–63.

Appendix 1
Schedule of Activities *for Patients Enrolled after Implementation of Protocol Version 4*

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT	*Safety Follow-Up Calls* [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	–4 to –1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	–28 to –2	–1	1	(±3)	(±7) [dd]												(±7)		(±7)	
Signed informed consent [c]	x																			
Review of inclusion and exclusion criteria	x																			
Demographic data	x																			
Medical history and baseline conditions [d]	x	x[e]																		
Blood sample for CAG repeat length	x																			
Viral serology [f]	x																			
Thyroid panel [g]	x																			
Vital signs [h]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Complete physical examination [i]	x	x[e]			x			x				x				x			x	x
Neurologic examination [j]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
ECG [k]	x	x[e]			x			x				x				x	x		x	x
Hematology [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x			x	x

Appendix 1:Schedule of Activities *for Patients Enrolled after Implementation of Protocol Version 4 (cont.)*

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT	*Safety Follow-Up Calls* [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	–4 to –1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	–28 to –2	–1	1	(±3)	(±7) [dd]												(±7)		(±7)	
Chemistry [m]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Pregnancy test [n]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Local INR *and/or PT*, aPTT, platelet count [x]		x		x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Urinalysis [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x			x	x
Plasma sample for PK			x		x	x		x[p]		x		x		x		x			x	
Plasma sample for immunogenicity testing			x		x	x		x		x		x		x		x			x	x
Plasma sample for biomarkers			x		x	x		x		x		x		x		x			x	x
Blood sample for clinical genotyping			x[e]																	
CSF sample for PK/safety/biomarkers			x	x	x	x	x	x	x	x	x	x	x	x	x	x[y]			x	
MRI [q]	x				x			x				x				x	x			
HD-DAS	x				x		x		x		x		x		x					
Independence Scale	x		x	x		x		x		x		x		x		x	x		x	
MoCA	x		x	x		x		x		x		x		x		x	x		x	
C-SSRS [r]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	

Appendix 1:Schedule of Activities *for Patients Enrolled after Implementation of Protocol Version 4 (cont.)*

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT	*Safety Follow-Up Calls* [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	–4 to –1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	–28 to –2	–1	1	(±3)	(±7) [dd]												(±7)		(±7)	
UHDRS FA			x	x		x		x		x		x		x		x	x		x	
TFC [s]			x	x		x		x		x		x		x		x	x		x	
TMS [s, cc]	x		x	x		x		x		x		x		x		x	x		x	
CGI-S			x	x		x		x		x		x		x		x	x		x	
CGI-C				x		x		x		x		x		x		x	x		x	
SDMT [s]			x	x		x		x		x		x		x		x	x		x	
SWR [s]			x	x		x		x		x		x		x		x	x		x	
AES			x		x		x		x		x		x		x	x	x			
SMDDS			x		x		x		x		x		x		x	x	x			
NeuroQoL			x	x		x		x		x		x		x		x	x		x	
EQ-5D-5L (in-clinic)			x	x		x		x		x		x		x		x	x		x	
PGI-S			x	x		x		x		x		x		x		x	x		x	
PGI-C				x		x		x		x		x		x		x	x		x	
Roche HD mobile app in-clinic assessments	x		x	*x*						x						x	x		x	
Roche HD mobile app remote data collection		Continuous remote data collection [t]																		
Optional exit interview [u]																x	x			

Appendix 1:Schedule of Activities *for Patients Enrolled after Implementation of Protocol Version 4 (cont.)*

	Screening [a]	BL		Treatment Period												EoT [b]	EoT for ETT	*Safety Follow-Up Calls* [ee]	ETT [b]	SFU
Month				1	3	5	7	9	11	13	15	17	19	21	23	25	25			29
Week	–4 to –1	1		5	13	21	29	37	45	53	61	69	77	85	93	101	101			117
Day (Window)	–28 to –2	–1	1	(±3)	(±7) [dd]												(±7)		(±7)	
CRQ: EQ-5D-5L, HUI-self, HUI-proxy, CrGI-S			*x*	*x*		*x*		*x*		*x*		*x*		*x*		*x*	*x*		*x*	
CRQ: AES			*x*		*x*		*x*		*x*		*x*		*x*		*x*	*x*	*x*			
CRQ: CrGI-C				*x*		*x*		*x*		*x*		*x*		*x*		*x*	*x*		*x*	
Remote data collection of CRQ (EQ-5D-5L, HUI-self, HUI-proxy, HD-CIAOS, WPAI)		*Remote data collection (see Appendix 4)*																		
Blood sample for RBR DNA (optional) [v]			x																	
Blood sample for RBR RNA (optional) [v]			x					x				x				x			x	
Serum sample for RBR (optional) [v]			x					x				x				x			x	
Change in medical information since previous visit [w]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*	x	x
Lumbar puncture [x]			x	x	x	x	x	x	x	x	x	x	x	x	x	x [y]			x [y]	
Study drug administration			x	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]					
Concomitant medications [aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*	x	x
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	*x*	x	x

ADA=anti-drug antibody; AES=Apathy Evaluation Scale; BL=baseline; CGI-C = Clinical Global Impression, Change; CGI-S = Clinical Global Impression, Severity; *CrGI-C=Companion-Reported Global Impression, Change; CrGI-S=Companion-Reported Global Impression, Severity; CRQ=Companion-reported questionnaire;* 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; ETT=early treatment termination; FA=Functional Assessment; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HD=Huntington disease; HD-*CIAOS=Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale; HD-*DAS=HD Daily Activities Scale; HUI=Health Utilities Index; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; Neuro-Qol = Quality of Life in Neurological Disorders; PGI-C = Patient Global Impression, Change; PGI-S = Patient Global Impression, Severity; PK=pharmacokinetic; Q8W=every 8 weeks; RBR = Research Biosample Repository; SDMT=Symbol Digit Modalities Test; SFU = safety follow-up; SMDDS = Symptoms of Major Depressive Disorder Scale; SWR = Stroop Word Reading; TFC = Total Functional Capacity Scale; TMS = Total Motor Score; UHDRS=Unified Huntington's Disease Rating Scale.

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] A maximum of one 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). If re-screening is required, CAG repeat length testing does not need to be repeated and the screening MRI and viral serology from the initial screening*, including for other Roche studies,* may be acceptable as part of the re-screening assessments, if performed within 12 weeks of the baseline visit.

[b] Patients who complete the treatment period will return to the clinic for a treatment completion visit at Week 101 (i.e., the EoT visit). All patients *enrolled in Study BN40423* who *choose to* discontinue study treatment prematurely but do not withdraw consent for continued participation in the study will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) and at Week 101 (i.e., the EoT for ETT visit) for collection of at least the data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). If the ETT visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only ETT will be considered. The ETT visit should be performed 28 days (±7 days) after the last dose. Patients will also attend the scheduled EoT for ETT visit at Week 101 for limited assessments including the collection of the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2 *and 2.5.2).* Study visits should be planned as per the study schedule, however under exceptional circumstances, time window of ±7 days can be utilized.
Patients enrolled prior to implementation of-Version 4 of the protocol: all patients will be prematurely discontinued from the Study BN40423 and will complete their EoT visit for early treatment termination prior to entry into Study BN40955.

[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, HD history (including past hospitalizations [i.e., number, duration, and reason]), over the last 2 years, reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline.

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

[f] Viral serology: HBsAg and HCV antibody

[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. *All data should be recorded on the appropriate eCRF.*

[i] A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems (including fundoscopy); 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. 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 measured at baseline only.

[j] A neurologic examination, performed at screening 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. 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. Weight should also be measured at each visit. Any abnormality identified at baseline *(Week 1)* 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.

[k] Triplicate ECG are to be performed *within approximately 5 minutes of each other,* after the patient has been in a supine position for approximately 10 minutes. ECGs for each patient should be obtained from the same machine whenever possible. At screening, baseline (Day −1 or Day 1) and other visits, pre-dose ECG should be performed prior to any blood draws and where applicable before the lumbar puncture.

[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] At the Week 37 visit, PK samples will be collected prior to dosing and at 1, 2, and 4 hours post-dose. All patients will remain in clinic at least 4 hours after lumbar puncture.

[q] *MRI 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 QC and the results must be available before the patient can be enrolled in the study.* At Weeks 13, 37, 69*, 101* and at the EoT *for ETT* visit the MRI should be scheduled to occur before the lumbar puncture.

The MRI scan should be performed 7–14 days prior to the lumbar puncture to allow time for re-scanning if the quality of the initial MRI is inadequate.

[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).

[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] Optional exit interviews will be conducted *for patients who consent from the selected sites* within approximately 1 week after the EoT visit; these interviews can be conducted by telephone.

[v] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[w] At the time of each study drug administration *and safety follow-up telephone calls*, an interval medical history should be obtained and any changes in medications, any major procedures or hospitalizations, and any physician visits for HD or general medical care should be recorded.

[x] Prior to performing each scheduled lumbar puncture, 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 lumbar puncture. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, 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 manual,* 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 lumbar puncture procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. Patients will be discouraged from resting supine after the lumbar puncture 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 72 hours postdose (e.g., air travel, scuba diving, or hot air balloons).*

[y] The last CSF sample will be obtained at the Week 101 EoT visit, but no study drug will be administered.

[z] Patients in *Q16W* arm will receive placebo at these visits.

[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 screening to the study completion/discontinuation visit.

[bb] 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, 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] 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.

[dd] Excluding MRIs, which have a visit window of –14 *to –7* days.

[ee] *Telephone safety follow-up calls will assess any changes to ongoing adverse events or occurrence of new adverse events and changes to concomitant medication. Unscheduled visits can occur based on the outcome of this safety follow-up call.*

Appendix 2 Clinician-Reported Outcomes *for Patients Enrolled after Implementation of Protocol Version 4*

Assessment	Name	Items	Concepts	Approx. Duration	Timing
FA	UHDRS Functional Assessment	25	Daily function	15 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
IS	Independence Scale	1	Functional disability	3 min	Screening, baseline, and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TFC	Total Functional Capacity Scale	5	Overall function	10 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TMS	Total Motor Score	31	Motor function	15 min	DCL only: Screening TMS without DCL: Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
C-SSRS	Columbia-Suicide Severity Scale	5	Suicidal ideation and behavior	20 min full version; 5 min follow-up version	Full version at screening in clinic; follow-up version at baseline and all post-baseline clinic visits
CGI-S	Clinical Global Impression, Severity	1	Overall severity of patient status	2 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
CGI-C	Clinical Global Impression, Change	1	Overall change in patient status	2 min	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
HD-DAS	Huntington's Disease Daily Activities Scale	25	Daily function	25 min	Screening and Weeks 13, 29, 45, 61, 77, and 93

DCL = diagnostic confidence level.

Appendix 3 Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application *for Patients Enrolled after Implementation of Protocol Version 4*

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
AES	Apathy Evaluation Scale	18	Apathy	10	PRO+ObsRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
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	5	Sensor data, PRO, PerfO	Daily+at clinic visits (Screening, baseline and Weeks *5, 53*, and 101 and ETT visits)	Roche HD mobile app
CrGI-C	Companion-Reported Global Impression, Change	1	Overall change in patient status	2	ObsRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
CrGI-S	Companion-Reported Global Impression, Severity	1	Overall severity of patient status	2	ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire	6	Health utilities	5	PRO+ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						Weekly	Roche HD mobile app; electronic device

Appendix 3:Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application ***for Patients Enrolled after Implementation of Protocol Version 4 (cont.)***

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
HD-SDI	Huntington's Disease Speaking Difficulty Item	1	Speech	1	PRO	Weekly	Roche HD mobile app
HD-CIAOS	Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale	3	Irritability and angry outbursts	2	ObsRO	Weekly	Electronic device
HUI®	Health Utilities Index	15	Health-related quality of life	10	ObsRO	Baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
						Weekly	Electronic device
MoCA	Montreal Cognitive Assessment	11	Overall cognitive status	10	PerfO	Screening, baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
Neuro-QoI Cog Func	Neuro-QoI Cognitive Function Short Form	8	Cognition	5	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101	In-clinic
PGI-C	Patient Global Impression, Change	1	Overall change in patient status	2	PRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
PGI-S	Patient Global Impression, Severity	1	Overall severity of patient status	2	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic

Appendix 3:Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application ***for Patients Enrolled after Implementation of Protocol Version 4 (cont.)***

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
SDMT/ eSDMT	Symbol Digit Modalities Test	Max number in 90 seconds	Cognitive	5	PerfO	SDMT at baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						eSDMT *monthly* + at *clinic visits (*screening, baseline, *Weeks 5, 53,101,* and *ETT)*	Roche HD mobile app (eSDMT)
SMDDS	Symptoms of Major Depressive Disorder Scale	16	Depression, anxiety, irritability, sleep	10	PRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
SWR/eSWR	Stroop Word Reading Test	Max numbers in 45 seconds	Cognitive	5	PerfO	SWR at baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						eSWR *monthly* + at *clinic visits (*screening, baseline, *Weeks 5, 53, and* 101 *and ETT)*	Roche HD mobile app (eSWR)
WPAI	Work Productivity and Activity Impairment	6	Work productivity	5	PRO + ObsRO	*Baseline and then monthly*	Roche HD mobile app and electronic device

app = application; ETT = early treatment termination; HD = Huntington disease; ObsRO = observer-reported outcome; PerfO = performance outcome; PRO = patient-reported outcome.

Appendix 4 Clinical Assessments Order and Duration *for Patients Enrolled after Implementation of Protocol Version 4*

Table 1 Screening Visit Clinical Assessments

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Diagnostic Confidence Level Huntington's Disease Daily Activities Scale Independence Scale MoCA C-SSRS	~60	Qualified study physician
Break (if needed)		~20-30	
2	Roche HD mobile application	~20	Qualified study personnel

C-SSR = Columbia-Suicide Severity Rating Scale; HD = Huntington disease; MoCA = Montreal Cognitive Assessment.

Table 2 Baseline and Week 101 Clinical Assessments (for Primary Analysis)

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change (post-baseline visits only)	~60	Qualified study physician
Break (if needed)		~20–30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10–20	
4 [a]	Neuro-Qol Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change (post-baseline visits only)	~20	Qualified study personnel
Break (if needed)		~10–20	
5 [a]	Roche HD mobile application	~20	Qualified study personnel

HD = Huntington disease; MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale.

[a] At the baseline visit and at week 101, Blocks 3, 4, and 5 can be completed on the same day after Blocks 1 and 2, or on the following day, but must be completed predose at the baseline visit.

Table 3 Follow-Up Clinical Assessments at Weeks 5, 21, 37, 53, 69, and 85

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change	~60	Qualified study physician
Break (if needed)		~20-30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3	Neuro-Qol Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change	~30	Qualified study personnel
4	*Roche HD mobile application* [a]	*~20*	*Qualified study personnel*

MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale

[a] *These assessments will take place only at Weeks 5 and 53.*

Table 4 Follow-Up Clinical Assessments at Weeks 13, 29, 45, 61, 77, and 93

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10	
2	Huntington's Disease-Daily Activities Scale	~25	Qualified study physician

[a] To be completed prior to safety assessments.

Appendix 5 Grading Scale for Adverse Events Relating to Laboratory Abnormalities *for All Patients*

The following grading recommendations for adverse events relating to lab 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

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

Appendix 5: Grading Scale for Adverse Events Relating to Laboratory Abnormalities *for All Patients (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

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

Appendix 5: Grading Scale for Adverse Events Relating to Laboratory Abnormalities *for All Patients (cont.)*

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)

Appendix 6 Roche HD Mobile Application *for Patients Enrolled after Implementation of Protocol Version 4*: Active Test

The following tasks are part of the "active tests" conducted on the Roche Huntington's Disease (HD) mobile application by the patient.

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 (eSDMT)
The Cognitive Test asks participants to match symbols with numbers according to a key as quickly and accurately as possible. The key, symbols, numbers are all displayed on a smartphone screen. The test assesses visuo-motor integration, and measures visual attention and motor speed. It is modelled on the pen and paper Symbol Digit Modalities Test (SDMT) (Smith, 1968). The SDMT has been shown to be sensitive to symptom changes in early HD patients (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 modelled on the Stroop Word Reading (SWR) (Ridley 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 modelled 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 early HD patients. It is modelled 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 two points that are at least four steps apart, while wearing the smartphone and wrist-worn wearable. They need to make at least five turns. The test is designed to assess gait and lower-body bradykinesia, which are also assessed by the UHDRS. It is modelled 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 done in 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).

Tasks are automatically scheduled as shown below in Figure 1 and take no more than 5 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., EuroQol 5-Dimension, 5 Level Questionnaire, Work Productivity and Activity Impairment, Huntington's Disease Speaking Difficulty Item, 2-Minute Walk Test) are rolled over to the next time the active test is completed.

References

Bechtel N, Scahill RI, Rosas HD, et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. Neurology 2010;75:2150–60.

Berg KO, Wood-Dauphinee SL, Williams JI, et al. Measuring balance in the elderly: validation of an instrument. Can J Public Health 1992;83(Suppl 2):S7–11.

Busse ME, Wiles CM, Rosser AE. Mobility and falls in people with Huntington's disease. J Neurol Neurosurg Psychiatry 2009;80:88–90.

Dalton A, Khalil H, Busse M, et al. Analysis of gait and balance through a single triaxial accelerometer in presymptomatic and symptomatic Huntington's disease. Gait Posture 2013;37:49–54.

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136–42.Kegelmeyer et al. 2017

Rao AK, Muratori L, Louis ED, et al. Clinical measurement of mobility and balance impairments in Huntington's disease: validity and responsiveness. Gait Posture 2009;29:433–6.

Reilmann R, Bohlen S, Kirsten F, et al. Assessment of involuntary choreatic movements in Huntington's disease—toward objective and quantitative measures. Mov Disord 2011;26:2267–73.

Reilmann R, Bohlen S, Klopstock T, et al. Grasping premanifest Huntington's disease - shaping new endpoints for new trials. Mov Disord 2010;25:2858–62.

Say MJ, Jones R, Scahill R, et al. Visuomotor integration deficits precede clinical onset in Huntington's disease. Neuropsychologia 2011;49:264–70.

Smith A. The symbol-digit modalites test: a neuropsychologic test of learning and other cerebral disorders. In: Helmuth J, editor. Learning disorders. Seattle: Special Child Publications; 1968:83–91.

Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.

Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. The Lancet Neurology 2012;11.1:42–53.

Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12:637–49.

Appendix 6: Roche HD Mobile Application *for Patients Enrolled after Implementation of Protocol Version 4*: **Active Test (cont.)**

Figure 1 Timing of Assessments

	Screening, Baseline, Week 5, 53, 101, ETT	Timing of assessments in 4-week rotation (day)																											
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
PROs																													
2 Daily Questions (Physical, Mood)	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
EQ-5D-5L		o							o							o							o						
WPAI					o																								
HD-SDI							o							o							o							o	
Cognitive Tests																													
eSDMT	o																	o											
Word reading test	o																	o											
Motor tests																													
Speeded tapping Test (L+R)	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Draw shape Test (L+R)	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Chorea Test (L+R)	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Balance Test	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
U-Turn Test	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Walking																													
2 Minute Walk Test	o	o							o							o							o						

EQ-5D-5L = EuroQol 5-Dimension, 5 Level Questionnaire; eSDMT = electronic Symbol Digit Modalities Test; HD-SDI = Huntington's Disease Speaking Difficulty Item; L = left; PRO = patient-reported outcome; R = right; WPAI = *Work Productivity and Activity Impairment Questionnaire.*

Appendix 7 Diagnostic Confidence Level *for All Patients*

The Diagnostic Confidence Level is calculated as shown below (from UHDRS Total Motor Score 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 8 Guidance for Neurological Examination for All Patients

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 Vision 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.

Appendix 9 Schedule of Activities for Patients Enrolled before Implementation of Protocol Version 4

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	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	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
Signed informed consent [c]	x																														
Review of inclusion and exclusion criteria	x																														
Demographic data	x																														
Medical history and baseline conditions [d]	x	x[e]																													
Blood sample for CAG repeat length	x																														
Viral serology [f]	x																														
Thyroid panel [g]	x																														
Vital signs [h]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Complete physical examination [i]	x	x[e]				x						x								x								x		x	x
Neurologic examination [j]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 9: Schedule of Assessments for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	–4 to –1	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	101	101		117
Day (Window)	–28 to –2	–1	1	(±3) [dd]																											
ECG [k]	x	x [e]				x						x								x								x	x	x	x
Hematology [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Chemistry [m]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Pregnancy test [n]	x	x [e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Local INR, aPTT, PT platelet count [x]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Urinalysis [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Plasma sample for PK			x			x		x				x [p]				x				x				x				x		x	
Plasma sample for immunogenicity testing			x			x		x				x				x				x				x				x		x	x
Plasma sample for biomarkers			x			x		x				x				x				x				x				x		x	x
Blood sample for clinical genotyping		x [e]																													
CSF sample for PK/safety/biomarkers			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [y]		x	
MRI [q]	x					x						x								x								x	x		
HD-DAS	x					x				x				x				x				x				x					
Independence Scale	x		x	x				x				x				x				x				x				x	x	x	
MoCA	x		x	x				x				x				x				x				x				x	x	x	

Appendix 9: Schedule of Assessments for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	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	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
C-SSRS [r]	x	x [e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
UHDRS FA			x	x				x				x				x				x				x				x	x	x	
TFC [s]			x	x				x				x				x				x				x				x	x	x	
TMS [s, cc]	x		x	x				x				x				x				x				x				x	x	x	
CGI-S			x	x				x				x				x				x				x				x	x	x	
CGI-C				x				x				x				x				x				x				x	x	x	
SDMT [s]			x	x				x				x				x				x				x				x	x	x	
SWR [s]			x	x				x				x				x				x				x				x	x	x	
AES			x			x				x				x				x				x				x		x	x		
SMDDS			x			x				x				x				x				x				x		x	x		
NeuroQoL			x	x				x				x				x				x				x				x	x	x	
EQ-5D-5L (in-clinic)			x	x				x				x				x				x				x				x	x	x	
HUI® (in-clinic)			x	x				x				x				x				x				x				x	x	x	
PGI-S			x	x				x				x				x				x				x				x	x	x	
PGI-C				x				x				x				x				x				x				x	x	x	
Roche HD mobile app in-clinic assessments	x		x						x						x						x							x	x	x	
Roche HD mobile app remote data collection	Continuous remote data collection [t]																														

Appendix 9: Schedule of Assessments for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	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	101	101		117
Day (Window)	−28 to −2	−1	1	(±3) [dd]																											
Optional exit interview [u]																												x	x		
Blood sample for RBR DNA (optional) [v]			x																												
Blood sample for RBR RNA (optional) [v]			x									x								x								x		x	
Serum sample for RBR (optional) [v]			x									x								x								x		x	
Change in medical information since previous visit [w]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lumbar puncture [x]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [y]		x [y]	
Study drug administration			x	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]				
Concomitant medications [aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; AES = Apathy Evaluation Scale; BL = baseline; 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; ETT = early treatment termination; FA = Functional Assessment; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HD = Huntington disease; HD-DAS = HD Daily Activities Scale; HUI = Health Utilities Index; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; Neuro-Qol = Quality of Life in Neurological Disorders; PGI-C = Patient Global Impression,

Change; PGI-S = Patient Global Impression, Severity; PK = pharmacokinetic; Q8W = every 8 weeks; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up; SMDDS = Symptoms of Major Depressive Disorder Scale; SWR = Stroop Word Reading; TFC = Total Functional Capacity Scale; TMS = Total Motor Score; UHDRS = Unified Huntington's Disease Rating Scale.

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] A maximum of one 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). If re-screening is required, CAG repeat length testing does not need to be repeated and 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 baseline visit.

[b] Patients who complete the treatment period will return to the clinic for a treatment completion visit at Week 101 (i.e., the EoT visit). All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) and at Week 101 (i.e., the EoT for ETT visit) for collection of at least the data for the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). If the ETT visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only ETT will be considered. The ETT visit should be performed 28 days (±3 days) after the last dose. Patients will also attend the scheduled EoT for ETT visit at Week 101 for limited assessments including the collection of the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2). Study visits should be planned as per the study schedule, however under exceptional circumstances, time window of ±3 days can be utilized.

[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, HD history (including past hospitalizations [i.e., number, duration, and reason]), over the last 2 years, reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline.

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

[f] Viral serology: HBsAg and HCV antibody

[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 baseline (Day -1 or Day 1) 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, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems (including fundoscopy); 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. 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 measured at baseline only.

[j] A neurologic examination, performed at screening and at every clinical visit, should include assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, 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. Weight should also be measured at each visit. Any abnormality identified at baseline 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.

[k] Triplicate ECG are to be performed after the patient has been in a supine position for approximately 10 minutes. ECGs for each patient should be obtained from the same machine whenever possible. At screening, baseline (Day −1 or Day 1) and other visits, pre-dose ECG should be performed prior to any blood draws and where applicable before the lumbar puncture.

[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 (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[p] At the Week 37 visit, PK samples will be collected prior to dosing and at 1, 2, and 4 hours post-dose. All patients will remain in clinic at least 4 hours after lumbar puncture.

[q] At Weeks 13, 37, and 69 and at the EoT visit, the MRI should be scheduled to occur before the lumbar puncture. It can be scheduled in the days prior to the lumbar puncture (provided it occurs within the visit window). After patient enrollment, the MRI scan should be performed 7−14 days prior to the lumbar puncture to allow time for re-scanning if the quality of the initial MRI is inadequate. MRI should take place as early as possible within the screening window but may take place at any time during screening. Results must be available before the patient can be enrolled in the study.

[r] The C-SSRS will be used to assess eligibility for the study (full version at baseline, 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).

[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] Optional exit interviews will be conducted within approximately 1 week after the EoT visit; these interviews can be conducted by telephone.

[v] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[w] At the time of each study drug administration, an interval medical history should be obtained and any changes in medications, any major procedures or hospitalizations, and any physician visits for HD or general medical care should be recorded.

[x] Prior to performing each scheduled lumbar puncture, local laboratory analysis of coagulation factors (INR, aPTT, PT) 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 lumbar puncture. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 5 mL should be collected over a maximum of 60 minutes. 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 Whitacre (atraumatic) needle 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 lumbar puncture procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. Patients will be discouraged from resting supine after the lumbar puncture procedure and will be encouraged to mobilize immediately by walking around at a minimum and, if feasible, walking briskly.

[y] The last CSF sample will be obtained at the Week 101 EoT visit, but no study drug will be administered.

[z] Patients in Q8W arm will receive placebo at these visits.

[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 screening to the study completion/discontinuation visit.

[bb] 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, 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] 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.

[dd] Excluding MRIs, which have a visit window of −14 days.

Appendix 10 Clinician-Reported Outcomes for Patients Enrolled before Implementation of Protocol Version 4

Assessment	Name	Items	Concepts	Approx. Duration	Timing
FA	UHDRS Functional Assessment	25	Daily function	15 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
IS	Independence Scale	1	Functional disability	3 min	Screening, baseline, and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TFC	Total Functional Capacity Scale	5	Overall function	10 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
TMS	Total Motor Score	31	Motor function	15 min	DCL only: Screening TMS without DCL: Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
C-SSRS	Columbia-Suicide Severity Scale	5	Suicidal ideation and behavior	20 min full version; 5 min follow-up version	Full version at screening in clinic; follow-up version at baseline and all post-baseline clinic visits
CGI-S	Clinical Global Impression, Severity	1	Overall severity of patient status	2 min	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
CGI-C	Clinical Global Impression, Change	1	Overall change in patient status	2 min	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits
HD-DAS	Huntington's Disease Daily Activities Scale	25	Daily function	25 min	Screening and Weeks 13, 29, 45, 61, 77, and 93

DCL = diagnostic confidence level.

Appendix 11 Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
AES	Apathy Evaluation Scale	18	Apathy	10	PRO + ObsRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
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	5	Sensor data, PRO, PerfO	Daily + at clinic visits (Screening, baseline and Weeks 25, 49, 73, and 101 and ETT visits)	Roche HD mobile app
CrGI-C	Companion-Reported Global Impression, Change	1	Overall change in patient status	2	ObsRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
CrGI-S	Companion-Reported Global Impression, Severity	1	Overall severity of patient status	2	ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic on electronic device
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire	6	Health utilities	5	PRO + ObsRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
						Weekly	Roche HD mobile app; electronic device

Appendix 11: Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
HD-SDI	Huntington's Disease—Speaking Difficulty Item	1	Speech	1	PRO	Weekly	Roche HD mobile app
HD-CIAOS	Huntington's Disease—Companion-Reported Irritability and Angry Outbursts Scale	3	Irritability and angry outbursts	2	ObsRO	Weekly	Electronic device
HUI®	Health Utilities Index	15	Health-related quality of life	10	ObsRO	Baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
						Weekly	Electronic device
MoCA	Montreal Cognitive Assessment	11	Overall cognitive status	10	PerfO	Screening, baseline, Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic
Neuro-Qol Cog Func	Neuro-Qol Cognitive Function Short Form	8	Cognition	5	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101	In-clinic
PGI-C	Patient Global Impression, Change	1	Overall change in patient status	2	PRO	Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT visits	In-clinic
PGI-S	Patient Global Impression, Severity	1	Overall severity of patient status	2	PRO	Baseline and Weeks 5, 21, 37, 53, 69, 85, and 101 and ETT	In-clinic

Appendix 11: Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4 (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing	Location
SDMT/ eSDMT	Symbol Digit Modalities Test	Max number in 90 seconds	Cognitive	5	PerfO	SDMT at baseline and Weeks 5, 21, 37, 53, 61 69, 85, and 101 and ETT visits	In-clinic
						eSDMT at screening, baseline, and Week 101 in last block post-SDMT assessment	Roche HD mobile app (eSDMT)
SMDDS	Symptoms of Major Depressive Disorder Scale	16	Depression, anxiety, irritability, sleep	10	PRO	Baseline and Weeks 13, 29, 45, 61, 77, 93, and 101	In-clinic
SWR/eSWR	Stroop Word Reading Test	Max numbers in 45 seconds	Cognitive	5	PerfO	SWR at baseline and Weeks 5, 21, 37, 53, 61 69, 85, and 101 and ETT visits	In-clinic
						eSWR at screening, baseline, and Week 101 in last block post-SWR assessment	Roche HD mobile app (eSWR)
WPAI	Work Productivity and Activity Impairment	6	Work productivity	5	PRO + ObsRO	Monthly	Roche HD mobile app and electronic device

app = application; ETT = early treatment termination; HD = Huntington disease; ObsRO = observer-reported outcome; PerfO = performance outcome; PRO = patient-reported outcome.

Appendix 12 Clinical Assessments Order and Duration for Patients Enrolled before Implementation of Protocol Version 4

Table 1 Screening Visit Clinical Assessments

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Diagnostic Confidence Level Huntington's Disease Daily Activities Scale Independence Scale MoCA C-SSRS	~60	Qualified study physician
Break (if needed)		~20-30	
2	Roche HD mobile application	~20	Qualified study personnel

C-SSR = Columbia-Suicide Severity Rating Scale; HD = Huntington disease; MoCA = Montreal Cognitive Assessment.

Table 2 Baseline and Week 101 Clinical Assessments (for Primary Analysis)

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change (post-baseline visits only)	~60	Qualified study physician
Break (if needed)		~20–30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10–20	
4 [a]	Neuro-QoI Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change (post-baseline visits only)	~20	Qualified study personnel
Break (if needed)		~10–20	
5 [a]	Roche HD mobile application	~20	Qualified study personnel

HD = Huntington disease; MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale.

[a] At the baseline visit and at week 101, Blocks 3, 4, and 5 can be completed on the same day after Blocks 1 and 2, or on the following day, but must be completed predose at the baseline visit.

Table 3 Follow-Up Clinical Assessments at Weeks 5, 21, 37, 53, 69, and 85

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	UHDRS Functional Assessment Independence Scale Total Functional Capacity Scale Total Motor Score (without Diagnostic Confidence Level) Columbia-Suicide Severity Rating Scale Clinical Global Impression–Severity Clinical Global Impression–Change	~60	Qualified study physician
Break (if needed)		~20-30	
2	Symbol Digit Modalities Test Stroop Word Reading Test MoCA	~20	Qualified study personnel
Break (if needed)		~10	
3	Neuro-Qol Cognition Function Short Form EuroQol 5-Dimension, 5-Level Questionnaire (patient and companion) Health Utilities Index (companion: self and proxy) Patient/Companion-reported Global Impression–Severity Patient/Companion-reported Global Impression–Change	~30	Qualified study personnel

MoCA = Montreal Cognitive Assessment; Neuro-QoL = Quality of Life in Neurological Disorders; UHDRS = Unified Huntington's Disease Rating Scale

Table 4 Follow-Up Clinical Assessments at Weeks 13, 29, 45, 61, 77, and 93

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1 [a]	Apathy Evaluation Scale (patient and companion) Symptoms of Major Depressive Disorder Scale	~20	Qualified study personnel
Break (if needed)		~10	
2	Huntington's Disease-Daily Activities Scale	~25	Qualified study physician

[a] To be completed prior to safety assessments.

Table 5 Digital Monitoring Platform Assessment Supervised by Study Staff in Clinic at Weeks 25, 49, 73

Block	Assessments	Total Duration (minutes)	Site Staff Responsible
1	Roche HD mobile application	~20	Qualified study personnel

HD = Huntington disease.

Appendix 13 Roche HD Mobile Application for Patients Enrolled before Implementation of Protocol Version 4: Active Test

The following tasks are part of the "active tests" conducted on the Roche Huntington's Disease (HD) mobile application by the patient.

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 (eSDMT)
The Cognitive Test asks participants to match symbols with numbers according to a key as quickly and accurately as possible. The key, symbols, numbers are all displayed on a smartphone screen. The test assesses visuo-motor integration, and measures visual attention and motor speed. It is modelled on the pen and paper Symbol Digit Modalities Test (SDMT) (Smith, 1968). The SDMT has been shown to be sensitive to symptom changes in early HD patients (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 modelled on the Stroop Word Reading (SWR) (Ridley 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 modelled 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 early HD patients. It is modelled 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 two points that are at least four steps apart, while wearing the smartphone and wrist-worn wearable. They need to make at least five turns. The test is designed to assess gait and lower-body bradykinesia, which are also assessed by the UHDRS. It is modelled 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 done in 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).

Tasks are automatically scheduled as shown below in Figure 1 and take no more than 5 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., EuroQol 5-Dimension, 5 Level Questionnaire, Work Productivity and Activity Impairment, Huntington's Disease Speaking Difficulty Item, 2-Minute Walk Test) are rolled over to the next time the active test is completed.

References

Bechtel N, Scahill RI, Rosas HD, et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. Neurology 2010;75:2150–60.

Berg KO, Wood-Dauphinee SL, Williams JI, et al. Measuring balance in the elderly: validation of an instrument. Can J Public Health 1992;83(Suppl 2):S7–11.

Busse ME, Wiles CM, Rosser AE. Mobility and falls in people with Huntington's disease. J Neurol Neurosurg Psychiatry 2009;80:88–90.

Dalton A, Khalil H, Busse M, et al. Analysis of gait and balance through a single triaxial accelerometer in presymptomatic and symptomatic Huntington's disease. Gait Posture 2013;37:49–54.

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136–42.Kegelmeyer et al. 2017

Rao AK, Muratori L, Louis ED, et al. Clinical measurement of mobility and balance impairments in Huntington's disease: validity and responsiveness. Gait Posture 2009;29:433–6.

Reilmann R, Bohlen S, Kirsten F, et al. Assessment of involuntary choreatic movements in Huntington's disease—toward objective and quantitative measures. Mov Disord 2011;26:2267–73.

Reilmann R, Bohlen S, Klopstock T, et al. Grasping premanifest Huntington's disease - shaping new endpoints for new trials. Mov Disord 2010;25:2858–62.

Say MJ, Jones R, Scahill R, et al. Visuomotor integration deficits precede clinical onset in Huntington's disease. Neuropsychologia 2011;49:264–70.

Smith A. The symbol-digit modalites test: a neuropsychologic test of learning and other cerebral disorders. In: Helmuth J, editor. Learning disorders. Seattle: Special Child Publications; 1968:83–91.

Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–62.

Tabrizi SJ, Reilmann R, Roos RAC, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. The Lancet Neurology 2012;11.1:42–53.

Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. Lancet Neurol 2013;12:637–49.

Figure 1 Timing of Assessments

	Baseline, Month 25	Screening, Month 6, 12, 18	Timing of assessments in 4-week rotation (day)																										
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
PROs																														
2 Daily Questions (Physical, Mood)			o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
EQ-5D-5L			o							o							o							o					
WPAI						o																							
HD-SDI								o							o							o						o	
Cognitive Tests																														
eSDMT	o																													
Word reading test	o																													
Motor tests																														
Speeded tapping Test (L+R)	o	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Draw shape Test (L+R)	o	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o	
Chorea Test (L+R)	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Balance Test	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
U-Turn Test	o	o		o		o		o		o		o		o		o		o		o		o		o		o		o		o
Walking																														
2 Minute Walk Test									o							o							o							o

EQ-5D-5L = EuroQol 5-Dimension, 5 Level Questionnaire; eSDMT = electronic Symbol Digit Modalities Test; HD-SDI = Huntington's Disease Speaking Difficulty Item; L = left; PRO = patient-reported outcome; R = right; WPAI.