PROTOCOL

TITLE:	**AN OPEN-LABEL, ADAPTIVE MULTIPLE-DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS AND PHARMACODYNAMICS OF RO7234292 IN CSF AND PLASMA, AND SAFETY AND TOLERABILITY FOLLOWING INTRATHECAL ADMINISTRATION IN PATIENTS WITH HUNTINGTON'S DISEASE**
PROTOCOL NUMBER:	BP40410
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-003010-40
NCT NUMBER:	*NCT04000594*
TEST PRODUCT:	RO7234292
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 11 December 2018
DATES AMENDED:	Version 2: 30 January 2019 Version 3: 27 May 2019 Version 4: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
24-Feb-2020 14:34:23	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol BP40410 has been amended for the following reasons:

- To address the reporting of two serious adverse events of lumbar abscess after removal of intrathecal (IT) catheter, an Urgent Safety Measure Dear Investigator Letter was submitted on 8 and 11 February 2020 in the United Kingdom and the Netherlands, respectively, requesting immediate suspension of RO7234292 administration via IT catheter. Consequently, enhanced antiseptic measures prior to IT catheter insertion, additional monitoring for infection while the catheter is indwelling and after catheter removal, improved guidance for monitoring in the event of back pain, and reduction of the catheter implantation duration have been incorporated in this amendment and will be implement upon approval of protocol Version 4.
- Magnetic resonance imaging (MRI) has been added as an assessment during the screening period and at the follow-up visit 6 months after the last study drug administration (or at early termination visit, if applicable). MRI is a non-invasive method to assess structure and function of the human brain and can provide insights into the pathophysiological mechanisms of neurologic and neuropsychiatric diseases. Standard safety sequences will be acquired; structural MRI will be used to assess brain volume. If clinically indicated, optional diffusion-weighted and resting state functional MRI sequences will be acquired. MRI assessments will primarily serve as a safety measure to exclude any contraindication to IT catheter insertion and lumbar puncture and any overall contraindication to participation in Study BP40410. In addition, both screening and 6-month follow-up MRI assessments will serve as a baseline assessment to enable ongoing safety monitoring for those patients who enroll in the open-label extension study (OLE) Study BN40955 upon completion of Study BP40410.
- The dose level used for enrolled patients in the third dose group has been modified from 90 mg to 30 mg. This change will potentially enable a reduction in the total number of patients to be recruited and to undergo IT catheter insertion, as relevant data will be collected from the first 12 patients (as originally planned). Data generated in recently completed Phase I/IIa Study (ISIS 443139-CS1) and ongoing OLE Study BN40697 have enabled refinement of model-based simulations, leading to the indication that 30 mg doses of RO723429 may be more informative than 90 mg doses to enable characterization of the pharmacokinetics, pharmacodynamics, and pharmacokinetic/pharmacodynamic relationships of RO723429, i.e. addressing the primary study objectives.
- Safety Section 5.1 has been updated with recent data from the 15-month data analysis of the ongoing OLE Study BN40697.

Changes to the protocol are summarized below:

- Because duration of the catheter presence is believed to be one of the risk factors for infection, the indwelling IT–catheter duration has been reduced from 96 hours to 48 hours by eliminating the insertion 24 hours predose and the final day of sampling postdose. Thus, the catheter will be inserted prior to dosing on Day 1 and will be removed 48 hours after dosing. Applicable changes have been made to Section 1.3, Figure 1 and the schedules of activities (Appendix 1 and Appendix 2).
- The 90 mg dose level has been replaced with 30 mg in Sections 3.1 and 4.3.2, and data supporting the change of dose level have been added in Section 3.3.1.
- A subsection to the Rationale for Biomarker Assessments (Section 3.3.3.5) has been added to summarize the use of different MRI techniques to assess structure and function of the human brain and provide insights into the pathophysiological mechanisms of neurologic and neuropsychiatric diseases.
- An inclusion criterion for the ability to undergo and tolerate MRI scans has been added to Section 4.1.1. An exclusion criterion for preexisting intra-axial or extra-axial lesions has been added to Section 4.1.2.
- Language on the prohibition of the use of anti-anxiety medication during scheduled MRI scans has been added to Section 4.4.2.
- Language has been added to Section 4.5.1 detailing instructions for a separate optional procedure consent and to include MRI among the assessments not required at re-screening.
- Additional safety measures pre- and post-insertion of the IT catheter have been added in Section 4.5.5 and Section 4.5.6 as preventive and monitoring measures to limit the risk of infection. Known risks associated with an indwelling catheter have been added in a new subsection 5.1.1.4, to reflect updated safety data. Additional safety assessments, including skin and nasal swabs for methicillin-resistant *Staphylococcus aureus* (MRSA) screening, blood tests (CRP, ESR and hematology), CSF sample culture, and culture of the catheter tip upon removal of the catheter have been added. The schedules of activities (Appendix 1 and Appendix 2) have been updated accordingly. Table 1 has been updated to provide guidance for management of a persistent back pain event.
- Language regarding MRI assessments during the screening period and at the follow-up visit has been added to Section 4.5 (new subsection 4.5.9) and the schedule of activities (Appendix 1).

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.

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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

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TEST PRODUCT:	RO7234292
PHASE:	I
INDICATION:	Huntington's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of RO7234292 in patients with Huntington's disease (HD). Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objectives and Endpoints	
The primary objectives for this study are as follows: • To characterize the PK of RO7234292 in CSF and plasma following administration of multiple (2) IT doses of RO7234292 • To characterize mHTT CSF protein time course following administration of multiple (2) IT doses of RO7234292 in patients with HD • To investigate the PK/PD relationship of multiple (2) IT doses of RO7234292 on mHTT in CSF	The corresponding primary endpoints are as follows: • CSF and plasma concentrations of RO7234292 • Change from baseline of mHTT concentrations in CSF • Relationship between plasma and/or CSF concentration or PK parameters and biomarker measures (mHTT in CSF)

Secondary Objectives and Endpoints	
The secondary objectives for this study are as follows: • To assess the safety and tolerability of multiple (2) IT doses of RO7234292 in patients with HD • To evaluate the immunogenicity of RO7234292 • To characterize the PK of RO7234292 in urine following administration of an IT dose of RO7234292	The corresponding secondary endpoints are as follows: • Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale • Changes in vital signs, ECGs, and clinical laboratory results • Proportion of patients with suicidal ideation or behavior, as assessed by C-SSRS score at visits indicated in the schedule of assessments, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct • Incidence of ADAs at specified timelines relative to the prevalence of ADAs at baseline • Titer and antibody subtype, determined if ADAs are identified • Urine concentrations of RO7234292
Exploratory Objectives and Endpoints	
The exploratory objectives for this study would be to evaluate the effects of RO7234292 compared on the basis of the exploratory endpoints.	The corresponding exploratory endpoints are as follows: • Change from baseline in exploratory biomarkers in CSF (e.g. NfL) • Relationship between exploratory fluid biomarkers in CSF and blood (e.g. CSF and plasma NfL) • Relationship between biomarkers, safety (including Holter monitoring), PK, and immunogenicity • Relationship of biomarkers to clinical severity at baseline using the Unified Huntington's Disease Rating Scale and Clinical Global Impression

ADA=anti-drug antibodies; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; HD=Huntington's disease; IT=intrathecal; mHTT=mutant Huntingtin; NfL=neurofilament light chain; PD=pharmacodynamics; PK=pharmacokinetic.

Study Design

Description of the Study

Study BP40410 is an open-label, adaptive multiple-dose clinical study designed to generate more granular time course data on PK, PD, and the PK/PD relationship after intrathecal (IT) administration of RO7234292 to patients with manifest HD.

Up to a maximum of 20 patients will be enrolled in the study. Prospective patients will undergo screening assessments during a 4-week screening period. A maximum of one re-screening will be allowed within 4 weeks of the initial screening failure for patients who fail the initial screening.

Patients will undergo safety and tolerability evaluations that include physical and neurological examinations, vital signs, electrocardiograms (ECGs), *magnetic resonance imaging (MRI) scans,* clinical laboratory safety tests, Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event monitoring including related concomitant medications, as detailed in Appendix 1.

The following tentative dose levels are planned for the study:

- Dose level 1: 120 mg RO7234292 (n=4 patients)
- Dose level 2: 60 mg RO7234292 (n=4 patients)
- Dose level 3: *30* mg RO7234292 (n=4 patients)

Patients will be assigned to a dose level in the order in which they are enrolled into the study. The final number of dose levels and total number of patients assigned to a given dose level will be defined during the study. Up to a maximum of 20 patients may be enrolled in the study, in order to enable investigation of additional dose levels other than those planned, or to repeat a dose level if required to fully characterize the PK, PD, safety and tolerability, or other pharmacological responses.

The highest tested RO7234292 dose in this study will not exceed 120 mg, which is the highest test dose in the previous Phase I/IIa clinical study (ISIS 443139-CS1).

After ongoing review of all available medical data (including adverse events, ECGs, vital signs, laboratory safety data, PK, and biomarker data) of the initial three dose groups of 120 mg, 60 mg, and *30* mg, the decision will be made if any should be repeated, adjusted downwards, or if intermediate doses should be investigated.

Patients who complete the treatment period will return to the clinic for the follow-up visit, at 6 months $\pm$ 2 weeks after the last study drug administration. Patients will then be given the option, on an individual basis, of receiving RO7234292 in an open-label extension (OLE) study (Study BN40955) upon completion of Study BP40410, provided they meet eligibility criteria, the data from the ongoing RO7234292 program support continued development, and approval of the OLE study is granted by the relevant competent authority and Ethics Committee.

Number of Patients

Approximately 20

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form.
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form.
- Manifest HD diagnosis, defined as a diagnostic confidence level (DCL) score of 4 (see Appendix 3 and Appendix 5).
- Independence Scale score of $\geq$ 70.
- Genetically confirmed disease by direct deoxyribonucleic acid testing with a cytosine, adenine, and guanine base sequence found in DNA which is translated into glutamine (CAG) age product (CAP) score > 400 (Zhang et al. 2011), calculated as follows:

  CAP = Age × (CAG repeat length $-$ 33.66).
- Ability to read the words “red,” “blue,” and “green” in the patient’s native language.

- Ability to walk unassisted without a cane or walker and move about without a wheelchair on a daily basis as reviewed at screening and baseline visit.

  Long distance use of wheelchairs for convenience (e.g., greater than 50 meters) for transfer is permitted.
- Body mass index $\geq$ 16 and $\leq$ 32 kg/m^2; total body weight $>$ 40 kg.
- Ability to tolerate blood draws and lumbar punctures.
- Estimated glomerular filtration rate $\geq$ 60 mL/min/1.73 m^2 (Cockcroft-Gault formula).
- Ability and willingness, in the Investigator's judgment, to comply with all aspects of the protocol including completion of interviews and assessments for the duration of the study.
- 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 and fulfills the following criteria:

– Age $\geq$ 18 years.

– Reliable and competent, in the Investigator's judgement.

– Sufficiently knowledgeable of the patient's condition to complete study companion assessments of the patient, and likely to remain sufficiently knowledgeable throughout the study, in the Investigator's judgment.

– Able to comment on the study participant's symptoms and functioning experience, as required per Appendix 1.

  Note: Companions with genetic confirmation of the mutant gene can only participate if they do not have confirmation of motor symptoms onset and, in the opinion of the Investigator, do not display any disease symptoms (i.e., the companion must have a DCL of < 4, as well as no cognitive or behavioral change that would question the validity of the acquired observer-reported data).

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

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods, and agreement to refrain from donating eggs, as defined below:

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

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

  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.

  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 study 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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 5 months after the last 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 study 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.
- *Ability to undergo and tolerate MRI scans (e.g., no claustrophobia; no severe chorea or other condition that precludes MRI scans or renders scanning intolerable for the patient; no MRI incompatible intrauterine devices, metallic dental braces, or other metal implants).*

Exclusion Criteria

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 appropriately qualified mental health professional.
- Current active psychosis, confusional state, or violent behavior.
- Any serious medical condition or clinically significant laboratory, vital signs, or ECG abnormalities at screening that, in the Investigator's judgment, precludes the patient's safe participation in and completion of the study.
- Increased QTc interval (QT interval corrected through use of Fridericia's formula > 470 ms), baseline resting bradycardia < 45 bpm, or baseline resting tachycardia > 100 bpm.
- Family history of long QT syndrome or other risk factors for torsades de pointes.
- 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 or history of low pressure headache after lumbar puncture requiring hospitalization or blood patch.
- Pregnant or breastfeeding, or intending to become pregnant during the study or until the follow-up visit (6 months $\pm$ 2 weeks after the last dose of study drug).

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Presence of implanted shunt for the drainage of cerebrospinal fluid (CSF) or an implanted central nervous system catheter.
- Positive for hepatitis C virus antibody or hepatitis B surface antigen at screening.
- Positive for human immunodeficiency virus (HIV)-1 or HIV-2 at screening.
- Current or previous use of an antisense oligonucleotide (ASO) (including small interfering ribonucleic acid).

- Current or previous use of antipsychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks of enrollment.
- Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation.
- Current use of tetrabenazine, valbenazine, or deutetrabenazine within 2 weeks prior to screening or within 6 $\times$ the elimination half-life of the medication prior to screening (whichever is longer) or anticipated use during the study.
- 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 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 prior to screening or 5 drug elimination half-lives of investigational therapy, whichever is longer.
- Antiplatelet or anticoagulant therapy within the 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 or cell transplantation or any other experimental brain surgery.
- Concurrent or planned concurrent participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions. Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
- 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.
- Unable or unsafe to perform lumbar puncture on the patient.
- Previous lumbar surgery that is likely, in the opinion of the Investigator or surgical team, to make IT catheter insertion or IT injection unduly difficult or hazardous.
- Poor peripheral venous access.
- Scoliosis or spinal deformity making IT injection not feasible in the outpatient setting.
- Serious infection requiring oral or intravenous antibiotics within 14 days prior to screening.
- Antiretroviral medications.
- 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 6 months (±2 weeks) after the last study drug administration has occurred.

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 2 years.

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

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is RO7234292.

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

RO7234292 drug product is provided as 6.0 mg/mL RO7234292 for IT injection. The drug product is supplied as sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL of 6.0 mg/mL RO7234292 drug product having a pH of approximately 7.2. In addition to the active drug substance, the liquid is also composed of sodium dihydrogen phosphate dihydrate, sodium phosphate dibasic anhydrous, sodium chloride, potassium chloride, calcium chloride dihydrate, and magnesium chloride hexahydrate.

Statistical Methods

All patients who have received at least 1 dose of the study drug, whether prematurely withdrawn from the study or not, will be included in the safety analyses.

Patients will be excluded from the PK analysis population if they did not receive treatment or otherwise significantly deviated from the protocol, violated inclusion or exclusion criteria, or if data are unavailable or incomplete which may influence the PK analysis.

Patients will be excluded from the PD analysis population if they did not receive treatment or otherwise significantly deviated from the protocol, violated inclusion or exclusion criteria, or if data are unavailable or incomplete which may influence the PD analysis.

Safety Analyses

All safety analyses will be based on the safety analysis population. The safety data, including adverse events, reasons for withdrawal from study, laboratory data, ECG, concomitant medications, vital signs, physical and neurological examinations, and C-SSRS, will be reported in individual listings and summarized by treatment for each assessment time using descriptive statistics.

The incidence of adverse events will be summarized on the basis of body systems and Medical Dictionary for Regulatory Affairs 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.

Pharmacokinetic Analyses

All PK analyses will be based on the PK analysis population.

Individual and mean PK concentration data at each sampling timepoint of RO7234292 (and its metabolite[s] as appropriate) in plasma, CSF, and urine, and calculated PK parameters thereof, will be presented by listings and descriptive summary statistics including arithmetic means, geometric means, ranges, standard deviations, and coefficients of variation. Individual and mean concentration versus time of RO7234292 (and its metabolite[s] as appropriate) will be plotted on linear or semi-logarithmic scales as appropriate.

All PK parameters will be presented by individual listings and summary statistics including arithmetic means, geometric means, medians, ranges, standard deviations, and coefficients of variation.

Immunogenicity Analyses

The immunogenicity analysis population will consist of all patients with at least 1 anti-drug antibody (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.

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be explored.

Biomarker Analyses

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

Determination of Sample Size

Up to 20 patients with HD may be enrolled in this study. Due to the exploratory nature of this study, the actual number of patients will be determined during the study.

While there is no formal statistical basis for the sample size of 20 patients (at maximum), it has been selected based on prior experience with second generation 2 ASOs given by IT injection to ensure that the PK and PD will be adequately assessed while minimizing patient exposure. However, the number of patients may be adapted during the study to sufficiently characterize the PK/PD relationship in CSF of RO7234292, while not exceeding 20.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
CAG	cytosine, adenine, guanine base sequence found in DNA which is translated into glutamine
CAP	CAG age product
CGI-C	Clinical Global Impression – Change
CGI-S	Clinical Global Impression – Severity
ClinRO	clinician-reported outcome
CNS	central nervous system
CRP	*C-reactive protein*
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DCL	diagnostic confidence level
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
HD	Huntington's disease
HD-DAS	Huntington's Disease -Daily Activities Scale
HIV	human immunodeficiency virus
HTT	Huntingtin gene
ICH	International Council for Harmonisation
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IT	intrathecal
MAD	multiple ascending dose
mHTT	mutant Huntingtin
MoCA	Montreal Cognitive Assessment

MOE	methoxyethyl
MRI	*magnetic resonance imaging*
mRNA	messenger ribonucleic acid
MRSA	*methicillin-resistant Staphylococcus aureus*
NfL	neurofilament light chain
OLE	open-label extension
PD	pharmacodynamics(s)
PerfO	performance outcome
PK	pharmacokinetic(s)
PT	prothrombin time
QTc	corrected QT interval
QTcF	QT interval corrected through use of Fridericia's formula
Q4W	every-4-weeks
Q8W	every-8-weeks
RBC	red blood cell
RBR	Research Biosample Repository
RNA	ribonucleic acid
SDMT	Symbol Digit Modalities Test
SI	Système International d'Unités
SWRT	Stroop Word Reading Test
TFC	Total Functional Capacity
TMS	Total Motor Scale
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of normal
WBC	white blood cell
WES	whole exome sequencing
WGS	whole genome sequencing
wtHTT	wild-type huntingtin

1. BACKGROUND

1.1 BACKGROUND ON HUNTINGTON'S DISEASE

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by the expansion of cytosine, adenine, guanine base sequence found in deoxyribonucleic acid (DNA) which is translated into glutamine (CAG) repeats in exon 1 of the Huntingtin gene (HTT) on chromosome 4, which encodes for a mutant Huntingtin (mHTT) protein. Based upon non-clinical and clinical evidence, mHTT protein 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 to 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, and rigidity) or "motor onset" (Huntington Study Group 1996; Hogarth et al. 2005). Motor onset is typically confirmed through the 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 5 stages based on functional capacity (Ross et al. 2014). Stage 1 represents the highest level of capacity and is characterized by mild or no incapacity in terms of independence in daily activities. Stage 5 represents severe disability and dependence on full-time care (Shoulson and Fahn 1979). The 5 clinical stages are defined by the score on the UHDRS Total Functional Capacity (TFC) Scale, with Stage 1 corresponding to TFC scores of 11 to 13, Stage 2 to scores of 7 to 10, Stage 3 to scores of 3 to 6, Stage 4 to scores of 1 to 2, and Stage 5 to a score of 0 (Shoulson et al. 1979).

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

Currently approved treatments aim to reduce the burden of symptoms, maximize function, and improve the patient's quality of life (Nance et al. 2011). Tetrabenazine and deutetrabenazine target abnormal involuntary movements (i.e., chorea) associated with HD, and these symptomatic therapies have a challenging benefit-risk profile. These drugs have been linked to many significant adverse events, including parkinsonism, akathisia, sedation, depression, and suicidal thoughts. They are contraindicated in patients who are actively suicidal and in patients with untreated or inadequately treated depression. Additionally, they may prolong the corrected QT interval (QTc), and caution is advised when used in combination with other drugs or medical conditions that potentially prolong the QTc.

Other medications are utilized in HD to address particular symptoms, such as antidepressants (for depression, agitation, and irritability), anticonvulsants (for irritability and impulsive behavior), anxiolytics (for anxiety), cognitive-enhancing agents (for cognitive disturbances), and neuroleptics (for chorea) (Paulson and Albin 2011).

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 a single 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) was developed to reduce the synthesis of all forms of the HTT protein by targeting the HTT messenger ribonucleic acid (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 central nervous system (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 mHTT 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).

Non-clinical proof-of-concept studies with ASOs targeting mHTT have been conducted in 3 models of HD, including YAC128 mice expressing the full-length mutant human HTT transgene with a 128 CAG repeat expansion, BACHD mice expressing the full-length human mHTT genomic sequence with 97 CAG/CAA repeats, and R6/2 mice expressing exon 1 of the human mHTT gene with 110 to 135 CAG repeats. These studies demonstrate that ASOs targeting human HTT mRNA improve motor function and protect against human HTT transgene expression in YAC128 mice; improve motor function, hypoactivity, and stress response in BACHD mice; and preserve striatal volume and increase survival in R6/2 mice.

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

In a first-in-human, Phase I/IIa double-blind, placebo-controlled, dose-escalation study (Clinicaltrials.gov Identifier NCT02519036) (ISIS 443139-CS1) four doses of RO7234292 (ranging from 10 to 120 mg) were well tolerated and achieved significant dose-dependent lowering of cerebrospinal fluid (CSF) mHTT protein when administered IT every 4 weeks 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. This on-going open-label study is evaluating the longer-term safety and tolerability of RO7234292 and the sustained effect of the drug on lowering CSF mHTT protein of both a monthly and bimonthly (i.e., every other month) regimen.

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-weeks (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-weeks (Q4W) dosing regimen achieves 66% median lowering at trough. Both results exceed the 20% to 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 non-clinical 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, non-clinical and clinical data have been generated to support further investigation of RO7234292 in patients with early manifest HD.

Building on the completed Phase I/IIa study and the ongoing OLE Study BN40697, this Phase I study (BP40410) will collect clinical PK and pharmacodynamics (PD) data to characterize the magnitude and duration of CSF mHTT reduction after short-term IT bolus dosing with RO7234292. This study will also further inform the semi-mechanistic population PK/PD model that has been developed on the basis of the currently available clinical and non-clinical data. Ultimately, this will guide clinical decision-making about optimal treatment regimens by providing information about the relationship between RO7234292 dosing and the time course of mHTT reduction, which could not be obtained any other way.

This study is open-label and will be conducted in an early manifest HD population over 8 months including an approximately 4-week screening period and an approximately 28-week study period.

Patients will be admitted to the site in the afternoon/evening of Day -2 or in the morning of Day -1 to begin the first in-house period of the study. After completing the safety assessments *including Holter ECG*, an IT catheter will be inserted *on the morning of Day 1* to facilitate frequent CSF sampling and IT bolus dosing of RO7234292. After

baseline CSF sampling, a single dose of RO7234292 will be given, after which sampling will continue for a further *48* hours before the catheter is removed. The patients will be discharged on Day *4* after all assessments have been completed.

Patients will return to the site for the second in-house period in the afternoon/evening of Day 28 or in the morning on Day 29 and will be discharged on Day 29 after all assessments have been completed. The second dose of RO7234292 will occur via a lumbar puncture on Day 29.

Patients will return to the site for daily visits on Days 30, 43, 71, 127, and the follow-up visit (6 months after the last study drug administration).

After study completion, participants will be eligible to enroll in an OLE study (Study BN40955) with active RO7234292 compound, provided the data from the ongoing RO7234292 program support continued development, the patient meets the inclusion and exclusion criteria for the OLE, and the OLE is approved by the relevant competent authorities and Ethics Committees (ECs).

The known potential risks associated with RO7234292, as well as additional study associated risks related to lumbar IT study drug administration, are elaborated in the Guidance to Investigator section of the Investigator's Brochure and Section 5.1 of this protocol.

The patients participating in this study are not expected to benefit given only two doses will be administered; appropriate measures have been taken to minimize risks. The study will provide critical data for RO7234292 to potentially enable patients with HD to benefit from treatment in the future.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the PK, PD, and safety of RO7234292 in patients with HD. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PRIMARY OBJECTIVES

The primary objectives for this study are as follows:

- To characterize the PK of RO7234292 in CSF and plasma following administration of multiple (2) IT doses of RO7234292
- To characterize mHTT CSF protein time course following administration of multiple (2) IT doses of RO7234292 in patients with HD
- To investigate the PK/PD relationship of multiple (2) IT doses of RO7234292 on mHTT in CSF

2.1.1 Primary Endpoints

The corresponding primary endpoints are as follows:

- CSF and plasma concentrations of RO7234292
- Change from baseline of mHTT concentrations in CSF
- Relationship between plasma and/or CSF concentration or PK parameters and biomarker measures (mHTT in CSF)

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To assess the safety and tolerability of multiple (2) IT doses of RO7234292 in patients with HD
- To evaluate the immunogenicity of RO7234292
- To characterize the PK of RO7234292 in urine following administration of an IT dose of RO7234292

2.2.1 Secondary Endpoints

The corresponding secondary endpoints are as follows:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale (see Section 5.3.3)
- Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory results
- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at visits indicated in the schedule of activities, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct
- Incidence of anti-drug antibodies (ADAs) at specified timelines relative to the prevalence of ADAs at baseline
- Titer and antibody subtype, determined if ADAs are identified
- Urine concentrations of RO7234292

2.3 EXPLORATORY OBJECTIVES/ENDPOINTS

The exploratory objectives for this study would be to evaluate the effects of RO7234292 compared on the basis of the following endpoints:

- Change from baseline in exploratory biomarkers in CSF (e.g. neurofilament light chain [NfL])
- Relationship between exploratory fluid biomarkers in CSF and blood (e.g. CSF and plasma NfL)
- Relationship between biomarkers, safety (including Holter monitoring), PK, and immunogenicity
- Relationship of biomarkers to clinical severity at baseline using the UHDRS and Clinical Global Impression

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study BP40410 is an open-label, adaptive multiple-dose clinical study designed to generate more granular time course data on PK, PD, and the PK/PD relationship after IT administration of RO7234292 to patients with manifest HD.

Up to a maximum of 20 patients will be enrolled in the study. Prospective patients will undergo screening assessments during a 4-week screening period. A maximum of one re-screening will be allowed within 4 weeks of the initial screening failure for patients who fail the initial screening (see Section 4.5).

Patients will undergo safety and tolerability evaluations that include physical and neurological examinations, vital signs, ECGs, *magnetic resonance imaging (MRI) scans,* clinical laboratory safety tests, C-SSRS, and adverse event monitoring including related concomitant medications, as detailed in Appendix 1.

The following tentative dose levels are planned for the study:

- Dose level 1: 120 mg RO7234292 (n=4 patients)
- Dose level 2: 60 mg RO7234292 (n=4 patients)
- Dose level 3: *30* mg RO7234292 (n=4 patients)

Patients will be assigned to a dose level in the order in which they are enrolled into the study. The final number of dose levels and total number of patients assigned to a given dose level will be defined during the study. Up to a maximum of 20 patients may be enrolled in the study, in order to enable investigation of additional dose levels other than those planned, or to repeat a dose level if required to fully characterize the PK, PD, safety and tolerability, or other pharmacological responses.

The highest tested RO7234292 dose in this study will not exceed 120 mg, which is the highest test dose in the previous Phase I/IIa clinical study (ISIS 443139-CS1).

After ongoing review of all available medical data (including adverse events, ECGs, vital signs, laboratory safety data, PK, and biomarker data) of the initial three dose groups of 120 mg, 60 mg, and *30* mg, the decision will be made if any should be repeated, adjusted downwards, or if intermediate doses should be investigated.

Patients who complete the treatment period will return to the clinic for the follow-up visit, at 6 months ± 2 weeks after last study drug administration. Patients will then be given the option, on an individual basis, of receiving RO7234292 in an OLE study (Study BN40955) upon completion of Study BP40410, provided they meet eligibility criteria, the data from the ongoing RO7234292 program support continued development, and approval of the OLE study is granted by the relevant competent authority and EC (see Section 4.3.4).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Overview of Study Design

<table>
<tr><td>Screening</td><td colspan="6">Treatment Period</td><td>Follow-up</td></tr>
<tr><td></td><td colspan="2">In-House Periods</td><td colspan="4">Out-Patient Visits</td><td></td></tr>
<tr><td>Day -28 to Day -3</td><td>Day -2 to Day 4*</td><td>Day 28 to Day 29*</td><td>Day 30</td><td>Day 43</td><td>Day 71</td><td>Day 127</td><td>6 months (± 2 weeks) after last study drug administration</td></tr>
<tr><td></td><td>• 1st dose of study drug on Day 1
• CSF sampling from predose to 48 hours postdose</td><td>• 2nd dose of study drug on Day 29
• Single predose CSF sample on Day 29</td><td colspan="4">• Single (equivalent to predose) CSF sample on Day 43, Day 71, Day 127, and FU</td><td></td></tr>
</table>

* Note: Patients will be admitted to the site in the afternoon/evening of Day -2 or in the morning of Day-1 to begin the first in-house period of the study; patients will be discharged on Day 4 after all assessments have been completed. Patients will return to the site for the second in-house period in the afternoon/evening of Day 28 or in the morning on Day 29 and will be discharged on Day 29 after all assessments have been completed.

CSF=cerebrospinal fluid; FU=follow-up.

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 6 months (± 2 weeks) after the last study drug administration has occurred.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately *2* 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

In order to characterize the concentration time profile of RO7234292 and mHTT in plasma and CSF and the influence of dose on the magnitude and duration of mHTT lowering in CSF, initially, two IT bolus doses ranging from *30* mg up to 120 mg given 28 days apart will be investigated in the present study. Data from the completed Phase I/IIa multiple ascending dose (MAD) study (ISIS 443139-CS1) showed doses up to 120 mg IT RO7234292 over four doses administered every 28 days were safe and well tolerated. Dose-dependent reductions of CSF mHTT from baseline at the end of the dosing interval after IT administration of doses ranging from 10 mg to 120 mg were observed.

In the chronic toxicology study in monkeys, the No Observed Adverse Effect Level was determined to be 35 mg dose. Conservatively correcting for differences in CSF volume between 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 maximum dose of 120 mg, to be evaluated in the present study.

Further details on non-clinical and clinical studies can be found in the Roche Investigator's Brochure.

The target reduction for clinical efficacy based on a non-clinical PK/PD model is at least 30% reduction in CSF mHTT. The administration of two IT doses of RO7234292 lead to trough percentage change of CSF mHTT of -25%, -28%, and -30% on average for 60 mg, 90 mg, and 120 mg of RO7234292 in the Phase I/IIa MAD study (ISIS 443139-CS1).

Using a model developed based on data from the completed Phase I/IIa study *and the ongoing OLE Study BN40697,* non-linear mixed-effects simulations predict *two* IT doses of *30 mg,* 60 mg, 90 mg, and 120 mg of RO7234292 are to result in *median* percentage change from baseline of CSF mHTT of -*24%, -27%, -29*%, and -*30*%, respectively, *at the end of the dosing interval (29 days) after the second IT administration.* Therefore, in order to characterize a mHTT concentration-time curve in the relevant range of mHTT reduction (~30% reduction), two IT doses administered every 4 weeks will be studied in this study.

Once a clear concentration effect has been established (peak effect and time course of effect) the information may inform a different dose regimen, including the potential for less frequent dosing.

3.3.2 Rationale for Patient Population

Adult patients (age 25 to 65 years) with manifest HD (DCL 4) who are ambulatory without assistance, verbal, possess a CAG age product (CAP) score of > 400, and an Independence Scale score of 70 or greater will be included in this study. This population represents an early stage of manifest disease where disability might be more plausibly reversed or slowed in response to a therapeutic intervention versus more advanced patients at baseline (Penney et al. 1990). This definition also corresponds to the stage of participants most commonly recruited at present for clinical studies aiming to slow clinical progression. Such cohorts are known to have longitudinal decline of clinical measures (Paulsen et al. 2014) over a timeframe appropriate for clinical studies.

3.3.3 Rationale for Biomarker Assessments

3.3.3.1 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 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 markers of neuronal damage, including CSF NfL and CSF tau levels (Wild et al. 2015). NfL levels in CSF predict progressive magnetic resonance imaging measures of brain atrophy, as well as progressive clinical decline in patients (Wild and Tabrizi 2017). Longitudinal analysis of CSF mHTT, NfL, and other biomarkers related to HD, neurodegeneration, and inflammation 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.

3.3.3.2 Blood-Derived 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 will facilitate the understanding of HD pathophysiology and progression.

3.3.3.3 Genetic Testing to Determine CAG Repeat Length

HD is caused by mutation in the first exon of the HTT gene located on 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). The CAG repeat length will be determined by direct DNA testing. The results of the CAG repeat length testing will be used to confirm eligibility for enrollment into this study.

3.3.3.4 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, severity, or response to treatment.

3.3.3.5 *Magnetic Resonance Imaging*

MRI is a non-invasive method to assess structure and function of the human brain and can provide insights into the pathophysiological mechanisms of neurologic and neuropsychiatric diseases. Several MRI techniques have shown sensitivity to detect abnormal structure and function within brains of individuals suffering from HD. Structural MRI (mandatory) will be used to assess brain volume. As clinically indicated (and if patient gives specific consent), optional diffusion-weighted MRI may also be employed to examine structural brain connectivity, and optional resting-state functional MRI may be employed to identify functional connectivity. All of the measures will be assessed at the whole-brain and regional levels. These MRI assessments performed at screening and follow-up visits will serve as a safety measure to exclude any contraindication to IT catheter insertion and lumbar puncture and any overall contraindication to participation in the study. In addition, MRI assessments will serve as a baseline assessment to enable ongoing safety monitoring for those patients who enroll in the OLE study (Study BN40955) upon completion of Study BP40410.

The acquisition parameters of the 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 (Optional)

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 Total Motor Scale (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 (Optional)

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

Up to 20 patients with manifest HD, aged 25 to 65 years (inclusive) may be enrolled in this study. Due to the exploratory nature of this study, the actual number of patients will be determined during the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form.
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form.
- Manifest HD diagnosis, defined as a DCL score of 4 (see Appendix 3 and Appendix 5).
- Independence Scale score of ≥ 70.
- Genetically confirmed disease by direct DNA testing with a CAP score > 400 (Zhang et al. 2011), calculated as follows:

  CAP = Age × (CAG repeat length − 33.66).
- Ability to read the words “red,” “blue,” and “green” in the patient’s native language.

- Ability to walk unassisted without a cane or walker and move about without a wheelchair on a daily basis as reviewed at screening and baseline visit.

  Long distance use of wheelchairs for convenience (e.g., greater than 50 meters) for transfer is permitted.
- Body mass index $\geq$ 16 and $\leq$ 32 kg/m^2; total body weight $>$ 40 kg.
- Ability to tolerate blood draws and lumbar punctures.
- Estimated glomerular filtration rate $\geq$ 60 mL/min/1.73 m^2 (Cockcroft-Gault formula).
- Ability and willingness, in the Investigator's judgment, to comply with all aspects of the protocol including completion of interviews and assessments for the duration of the study.
- 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 and fulfills the following criteria:
  - Age $\geq$ 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 the study participant's symptoms and functioning experience, as required per Appendix 1.

    Note: Companions with genetic confirmation of the mutant gene can only participate if they do not have confirmation of motor symptoms onset and, in the opinion of the Investigator, do not display any disease symptoms (i.e., the companion must have a DCL of < 4, as well as no cognitive or behavioral change that would question the validity of the acquired observer-reported data).

    All effort should be made to retain the study companion; however, should this not be possible, a study companion can be replaced and new consent obtained.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods, and agreement to refrain from donating eggs, as defined below:

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

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

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.

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 study 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 female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 5 months after the last 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 study 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.

- *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).*

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 appropriately qualified mental health professional.

- Current active psychosis, confusional state, or violent behavior.

- Any serious medical condition or clinically significant laboratory, vital signs, or ECG abnormalities at screening that, in the Investigator's judgment, precludes the patient's safe participation in and completion of the study.

- Increased QTc interval (QT interval corrected through use of Fridericia's formula [QTcF] > 470 ms), baseline resting bradycardia < 45 bpm, or baseline resting tachycardia > 100 bpm.
- Family history of long QT syndrome or other risk factors for torsades de pointes.
- 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 or history of low pressure headache after lumbar puncture requiring hospitalization or blood patch.
- Pregnant or breastfeeding, or intending to become pregnant during the study or until the follow-up visit (6 months $\pm$ 2 weeks after the last dose of study drug).

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Presence of implanted shunt for the drainage of CSF or an implanted CNS catheter.
- Positive for hepatitis C virus antibody or hepatitis B surface antigen at screening.
- Positive for human immunodeficiency virus (HIV)-1 or HIV-2 at screening.
- Current or previous use of an ASO (including small interfering ribonucleic acid [RNA]).
- Current or previous use of antipsychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks of enrollment.
- Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation.
- Current use of tetrabenazine, valbenazine, or deutetrabenazine within 2 weeks prior to screening or within 6 $\times$ the elimination half-life of the medication prior to screening (whichever is longer) or anticipated use during the study.
- 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 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 prior to screening or 5 drug elimination half-lives of investigational therapy, whichever is longer.

- Antiplatelet or anticoagulant therapy within the 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 or cell transplantation or any other experimental brain surgery.
- Concurrent or planned concurrent participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions. Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
- 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.
- Unable or unsafe to perform lumbar puncture on the patient.
- Previous lumbar surgery that is likely, in the opinion of the Investigator or surgical team, to make IT catheter insertion or IT injection unduly difficult or hazardous.
- Poor peripheral venous access.
- Scoliosis or spinal deformity making IT injection not feasible in the outpatient setting.
- Serious infection requiring oral or intravenous antibiotics within 14 days prior to screening.
- Antiretroviral medications.
- 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

This is an open-label study, therefore no blinding will be used.

Patients will be assigned to a dose level in the order in which they are enrolled into the study. Treatment assignment across clinical sites will be managed manually.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

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

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 RO7234292

RO7234292 drug product is provided as 6.0 mg/mL RO7234292 for IT injection. The drug product is supplied as sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL of 6.0 mg/mL RO7234292 drug product having a pH of approximately 7.2. In addition to the active drug substance, the liquid is also composed of sodium dihydrogen phosphate dihydrate, sodium phosphate dibasic anhydrous, sodium chloride, potassium chloride, calcium chloride dihydrate, and magnesium chloride hexahydrate.

RO7234292 should be prepared by a pharmacist using aseptic technique. RO7234292 vials do not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. All transfer procedures require strict adherence to aseptic techniques. Do not use RO7234292 beyond the use by date stamped on the carton.

The study drug must be stored according to the details on the product label. The recommended storage conditions for RO7234292 drug product is between 2°C to 8°C (36°F to 46°F), protected from light.

RO7234292 will be provided by Roche to investigational centers on a regular basis. Investigational product packaging will be overseen by the Roche Global Clinical Trial Supplies department. The supply will be packed bearing labels with the identification required by local regulations and in accordance with Roche standards and local regulations.

Upon arrival of investigational products at the site, site personnel should check the investigational product for damage and verify proper identity, quantity, integrity of seals, and temperate conditions, and report any deviations or product complaints to the monitor upon discovery.

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

4.3.1.2 Diluent

RO7234292 diluent for IT injection is provided as a sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL of RO7234292 diluent having a pH of approximately 7.2. The liquid is also composed of sodium dihydrogen phosphate dihydrate, sodium phosphate dibasic anhydrous, sodium chloride, potassium chloride, calcium chloride dihydrate, and magnesium chloride hexahydrate.

RO7234292 diluent must be stored according to the details on the product label. The recommended storage conditions for RO7234292 drug product is between 2°C to 8°C (36°F to 46°F), protected from light.

RO7234292 diluent will be provided by Roche to investigational centers on a regular basis. Investigational product packaging will be overseen by the Roche Global Clinical Trial Supplies department. The supply will be packed bearing labels with the identification required by local regulations and in accordance with Roche standards and local regulations.

Upon arrival of RO7234292 diluent at the site, site personnel should check the investigational product for damage and verify proper identity, quantity, integrity of seals, and temperate conditions, and report any deviations or product complaints to the monitor upon discovery.

For information on the formulation, study drug preparation, and handling of RO7234292 diluent, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Each dose of RO7234292 will be administered as a single IT bolus injection of 20 mL.

Administration of the first dose will occur via an IT catheter inserted at baseline and also used for CSF sampling. Administration of the second dose 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.

For details on the lumbar puncture and IT bolus dosing procedure, please refer to the lumbar puncture manual and instructional video. Of note, Investigators will perform a predose neurological examination, including fundoscopy, to rule out increased intracranial pressure prior to performing the lumbar puncture, which is a contraindication to the procedure.

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.

Patients may receive doses, which have previously been investigated in the Phase I/IIa MAD study (ISIS 443139-CS1) or OLE study (ISIS 443139-CS2), ranging from 30 to

120 mg of RO7234292. The decision to determine which doses will be explored after the initial three dose levels of 120 mg, 60 mg, and *30* mg will be made following review of all relevant safety, tolerability, PK, and biomarker data collected from all previous patients.

The patient's bladder must be completely emptied at the time of study drug administration.

No dosage adjustment from planned treatment is permitted in this study. If a patient misses a dose visit, the Investigator should contact the Medical Monitor to determine appropriate continuation of the patient in the study.

Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

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) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor 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

It is intended that patients will be eligible to receive RO7234292 as part of an OLE study (Study BN40955) as described in Section 3.1.

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 IMP, 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 IMP is available at the following website:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, and nutritional supplements) used by a patient in addition to protocol-mandated treatment from screening to the study completion/discontinuation visit. All such medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF) at each clinical visit.

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 mood stabilization (i.e., irritability or aggressive behavior) if the does 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 treatment initiation.

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

- Antidepressants or benzodiazepines 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 starting or stopping can occur as per Investigator judgment during the course of the study.

- Anti-epileptics if given for mood stabilization and/or pain.
- 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:

- Current use of tetrabenazine, valbenazine, or deutetrabenazine.
- 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/or riluzole.
- Antiplatelet or anticoagulation 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.
- *Use of anti-anxiety medication is prohibited during scheduled MRI scans. 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 exclusion criterion.*

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 2. 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.

If applicable, the Informed Consent Form will contain a separate consent for 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 for optional procedures at any time and 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 in optional procedures will not be required to provide a separate signature.

All screening evaluations must be completed and reviewed to confirm that patients meet all 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 4 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); *MRI* and viral serology from the initial screening may be acceptable as part of the re-screening assessments, if performed within 4 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, and nutritional supplements) used by the patient from screening to study completion/discontinuation will be recorded. At the time of each study drug administration, an interval medical history should be obtained and any changes in medication, smoking, or allergies 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. Race/ethnicity will be recorded because of the potential contribution of this variable to differences in observed PK, PD, toxicity, and/or response to treatment.

4.5.3 Physical 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 neurological systems (including fundoscopy); genitourinary examinations may be performed as 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 screening only.

A neurologic examination should be performed at screening and other specified visits (see Appendix 1), and includes assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. 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 neurologic examination.

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 should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will be collected at screening and other specified visits (see Appendix 1). Vital signs will include measurements of respiratory rate, pulse, systolic and diastolic blood pressure, and temperature while the patient is in a seated position after resting for approximately 5 minutes.

Abnormalities observed at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

4.5.5 Collection of Cerebrospinal Fluid (Lumbar Puncture Procedure)

Skin (groin area) and nose swabs will be taken during screening to test for Methicillin-resistant Staphylococcus aureus (MRSA). If the MRSA screening result is positive, treatment for decolonization (as per local standard procedure) should be administered for 5 days prior to catheter insertion.

In preparation for the catheter insertion, patients will be required to remove all body piercings, make up, and nail polish and to cleanse the entire body (including hair) with antibacterial soap on Day -2 or Day -1.

Within 72 hours prior to performing each scheduled lumbar puncture or IT catheter insertion, local laboratory analysis of coagulation factors (international normalized ratio [INR], activated partial thromboplastin time [aPTT], prothrombin time [PT]) and platelets must be conducted and the results reviewed. Each 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. *A 20 mL sample will be taken at predose after the IT catheter has been inserted. Subsequently,* during the CSF sampling period until *48* hours postdose, a maximum 5 mL of CSF fluid will be collected (via the IT catheter) at each timepoint indicated in Appendix 2. *In addition, up to 2 mL CSF sample will be collected for daily CSF safety testing, including culture, during the indwelling-catheter period at the timepoints indicated in Appendix 1 and Appendix 2. Upon removal, the catheter tip should be sent for culture.*

For all other lumbar punctures, CSF fluid (20 mL) will be collected by needle 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. The operator must confirm CSF flow is present prior to any injection of study drug. A 24G (atraumatic) needle 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 lumbar puncture manual and instructional video.

Lumbar punctures will be performed as specified in Appendix 1 and Appendix 2.

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, aPTT, and PT.
- Platelet count.
- Pregnancy test.

  All women of childbearing potential will have a serum pregnancy test at screening (central laboratory). Urine pregnancy tests (local laboratory) will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (analyzed at a central laboratory).
- CSF safety sample: cell count (red blood cell [RBC] and white blood cell [WBC]), glucose, protein*, and culture*.
- *Blood for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)*
- *Hematology: WBC count, RBC count, platelet count, hemoglobin, hematocrit, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).*
- *Skin and nasal swab for MRSA screening.*

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

- Serum chemistry panel: bicarbonate, sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid, gamma-glutamyl transferase, and creatine phosphokinase.
- Hormone panel (female subjects only): follicle-stimulating hormone and Estradiol.
- Thyroid panel: thyroid-stimulating hormone and free thyroxine (also known as T4) levels.
- Viral serology: hepatitis B virus surface antigen, hepatitis C virus antibody, HIV-1 antibody, HIV-2 antibody.
- Serum pregnancy test.

  Serum pregnancy tests will be performed on women of childbearing potential at screening and subsequent visits to confirm a positive urine pregnancy test (if applicable).
- Urinalysis including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).
- CSF, urine, and plasma samples for PK analyses and metabolite identification.
- Blood samples for immunogenicity analysis.
- Blood sample for determination of CAG repeat length in HTT for patient eligibility.

- Blood sample for clinical genotyping for DNA extraction to enable exploratory analysis and assay development with respect to genes related to HTT function and severity of the disease.
- CSF samples to perform biomarker analysis, including mHTT and NfL, and other exploratory biomarkers related to HD, neurodegeneration, inflammation, and drug response.
- Plasma samples, which may be used to evaluate biomarkers such as NfL and tau, as well as other exploratory blood-based biomarkers related to HD, neurodegeneration, inflammation, and drug response.
- Blood, plasma, and CSF samples for exploratory research on biomarkers may also be used to support the development of additional biomarker assays.

Exploratory biomarker research may include, but will not be limited to, total HTT, tau, and other substances 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 in the Research Biosample Repository (RBR) (see Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:

- Blood, plasma, and CSF samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- CSF, plasma, and urine samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation and 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 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 Electrocardiograms

Single 12-lead ECGs will be obtained at specific timepoints, as outlined in the schedule of activities (see Appendix 1 and Appendix 2), 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. Electrocardiograms for each patient should be obtained from the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings 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 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, and conversation), should be avoided during the pre-ECG resting period and during ECG recording. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site.

ECG characteristics, including heart rate, QRS duration, and PR and QT intervals, will be recorded on the eCRF. QTcF and RR will be calculated. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal. U-wave information will be captured in two categories: absent/normal or abnormal.

4.5.7.1 Holter ECG Monitoring

From Day -1 to Day *3,* patients will wear a digital Holter monitoring device for continuous recordings of 12-lead ECG traces over 72 hours (starting 24 hours before first study drug administration until 48 hours postdose), as specified in the schedules of activities. On Day 29, patients will again wear a digital Holter ECG device for recordings of data over 4 hours, starting at predose until 4 hours postdose. See Appendix 1 and Appendix 2.

Holter recordings will be sent to a central ECG analysis laboratory for ECG extraction and retrospective expert review with estimation of ECG intervals. Triplicate ECG tracings will be extracted from the continuous recording at the period of verified stability of the heart rate for 1 minute as close as possible to the scheduled PK (plasma)

sampling timepoint. Triplicate estimates of uncorrected QT intervals, QTcF, individual-specific QTc will be derived from the ECG traces at each nominal PK (plasma) sampling timepoint, along with other intervals (PR, RR, QRS) and information on T-wave and U-wave morphology, as appropriate.

Triplicate ECG tracings from the continuous recordings will be extracted within 10 minutes of the nominal timepoints for PK (plasma) sampling as specified in the schedules of activities (see Appendix 1 and Appendix 2). At these specific timepoints, the patient should be at rest and in a supine position for at least 10 minutes prior to and remain in the supine position for at least 5 more minutes after the specified PK (plasma) sampling timepoint.

4.5.7.1.1 Holter monitoring conditions

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.

In order for the Holter recordings to be conducted under the same conditions, food consumption/intake must occur at the same time on Day -1, Day 1, and Day 29. Food consumption/intake should be avoided (to the extent possible) when the Holter ECG data is collected.

4.5.8 Performance Outcome and Clinician-Reported Outcomes

Performance outcome (PerfO) and clinician-reported outcome (ClinRO) data will be collected via assessments to document the treatment effect of RO7234292. The assessments, 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, assessments will be self-administered or interviewer-administered (as appropriate) before the patient or clinician receives any information on disease status, prior to the performance of non-PerfO/ClinRO assessments, and prior to the administration of study treatment, unless otherwise specified.

Patients and clinicians may use paper forms or electronic devices to capture PerfO and ClinRO data. The paper forms, electronic devices, and/or instructions for completing the assessments will be provided by site staff. The data will be entered into the eCRF. The data will be available for access by appropriate study personnel.

The intent of the clinical measures (Huntington's disease-Daily Activities Scale [HD-DAS], TFC, Total Motor Scale [TMS], Independence Scale, Clinical Global Impression – Severity [CGI-S], Clinical Global Impression – Change [CGI-C], Montreal Cognitive Assessment [MoCA], Symbol Digit Modalities Test [SDMT], Stroop Word Reading Test [SWRT], and C-SSRS) is to assess the relationship of baseline clinical variables to biomarkers, i.e., to explore the cross-sectional relationship of clinical severity to

biomarker abnormalities, and secondly, to collect baseline clinical data prior to study drug administration and prior to enrollment in the OLE study for longer treatment, such that the clinical status and change in clinical status can be known in these individuals over time; no efficacy analyses are planned to be performed on clinical measure data collected for this study.

4.5.8.1 Total Functional Capacity Scale

The TFC Scale 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. The TFC takes approximately 10 minutes to administer and will be completed at clinic visits as indicated in Appendix 1.

4.5.8.2 Independence Scale

A patient's Independence Scale score is a measure of disease progression in functional disability. The Independence Scale evaluates a patient's degree of independence, as assessed by the Investigator, and 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 patient is fed by tube and requires total bed care.

4.5.8.3 Huntington's Disease 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 to perform daily tasks such as eating or using a telephone will be recorded. Each item is scored on a 4-point Likert-type scale, where 0 indicates no impact and 3 indicates severe impact. The HD-DAS can be completed in approximately 25 minutes.

4.5.8.4 Total Motor Scale

The TMS is a holistic measure of motor function in HD that is linked to 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.

4.5.8.5 Clinical Global Impression – Severity

The CGI-S is a single-item measure of current global severity and is completed by the clinician at clinic visits (as indicated in Appendix 1). The CGI-S is assessed using an 11-point numeric rating scale, where higher scores indicate greater severity. The CGI-S can be completed in approximately 2 minutes.

4.5.8.6 Clinical Global Impression – Change

The CGI-C is a single-item measure of change in global status (since starting the study) and is completed by the clinician at the follow-up visit (as indicated in Appendix 1). 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.

4.5.8.7 Montreal Cognitive Assessment

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

4.5.8.8 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 (as indicated in Appendix 1) and can be completed in less than 5 minutes. It will also be administered at specified timepoints on the Roche HD mobile app (via electronic SDMT).

4.5.8.9 Stroop Word Reading Test

The SWRT 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 clinic visits (as indicated in Appendix 1).

4.5.8.10 Columbia-Suicide Severity Rating Scale

The C-SSRS is a structured tool to assess suicidal ideation and behavior.

Four constructs are measured: severity of ideation, intensity of ideation, behavior, and lethality of actual suicide attempts. Binary (yes/no) data are collected for 10 categories,

and composite endpoints based on the categories are followed over time to monitor patient safety (Posner et al. 2011). It maps to the Columbia-Classification Algorithm for Suicide Assessment and meets the criteria listed in the U.S. Food and Drug Administration (FDA) draft guidance for assessment of suicidality in clinical studies (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 (as indicated in Appendix 1) (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 *Magnetic Resonance Imaging*

MRI images of the brain will be acquired (standard safety sequences, as well as structural MRI) at screening and at the follow-up visit (or at early termination visit, if applicable). Structural MRI is mandatory and must be performed at screening and at the follow-up visit (or at early termination visit, if applicable). As clinically indicated (and if patient gives specific consent), optional diffusion-weighted MRI may also be employed to examine structural brain connectivity and resting-state functional MRI may be employed to identify functional connectivity. All of the measures will be assessed at the whole-brain and regional levels.

MRI should be performed using a 3-Tesla (3T) magnet. The acquisition parameters of the 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. During central review, the Sponsor and/or site staff will be notified of any unexpected findings requiring clinical follow up. Local neuroradiologists will be responsible for assessing MRI-related ongoing safety monitoring.

MRI should take place as early as possible within the screening window but may take place at any time during screening. The screening MRI scan should be performed at least 7 days prior to the IT catheter insertion to allow time for re-scanning if the quality of the initial MRI is inadequate. The screening MRI scan must pass central laboratory image quality control review and results must be available before the patient can be enrolled in the study.

The follow-up (or early termination, if applicable) MRI should take place within the 14-day window allowed for the follow-up visit (or early termination visit, if applicable)and prior to the lumbar puncture scheduled at the follow-up visit. If patient

who enrolled under protocol Version 3 cannot undergo and tolerate MRI scans, no MRI scans will be performed at the follow-up visit (or early termination visit, if applicable).

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

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The 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 Institutional Review Board (IRB) or 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:

- Leftover blood, CSF, and plasma biomarker samples, and any derivatives thereof (e.g., proteins, peptides)
- Blood (for RBR DNA and RBR RNA) at Day 1 and RBR serum samples collected at Days 1, 28, 43, 71, and 127

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 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. 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, 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

An excessive rate of withdrawals (either study treatment discontinuation or withdraw from the study) can render the study 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 study.

Investigators should explore all possible options to reach 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
- Any event that meets stopping criteria defined in Section 5.1.3

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 withdraw or discontinue from study treatment early will be asked to return to the clinic for the early termination visit within 28 days ± 14 days after the last dose of study drug.

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 anticipated important safety risks for RO7234292 are outlined below. 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. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. Specific procedures for sterile preparation and microbiologcal testing are required to lower the risk of catheter infection and provide more rapid recognition of catheter associated infection, as described in Section 4.5.5. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Known Risks Associated with Lumbar Puncture

In the completed Phase I/IIa study, 46 patients were randomized to receive RO7234292 (n=34) or placebo (n=12). The most commonly reported adverse events across all treatment groups included procedural pain (54%) and post-lumbar puncture syndrome (37%). One patient who received placebo reported a serious adverse event of post-dural-puncture headache.

In the ongoing Phase II OLE Study BN40967 (*15*-month data cut), potential post-lumbar puncture adverse events (including procedural pain, post-lumbar puncture syndrome, post-procedural discomfort, *puncture site pain,* headache, migraine*, nausea, dyspepsia, backpain, malaise, and paraesthesia*) occurring within 72 hours of drug administration were summarized per cohort. For the Q4W cohort (n= 23), *35* events were reported in *14 (60.9*%) patients; for the Q8W cohort (n=23), *36* events were reported in 12 (*65*.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 and post the lumbar puncture procedure. Lumbar puncture should be avoided when 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 will be provided prior to initiation of lumbar puncture in the study, 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 the 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, that is likely, in the opinion of the Investigator or surgical team, to make IT catheter insertion or IT injection unduly difficult or hazardous, 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, and/or 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 (*15*-month data cut), *13* events of *potential* post-lumbar puncture syndrome *events (post-lumbar puncture syndrome, headache and nausea)* were reported in the Q4W cohort and *12 events* in the Q8W cohort.

Patients should walk post-lumbar procedure to assist drug distribution (see Section 4.5.5); 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 magnetic resonance imaging 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 this study (see Section 4.1.2). Management of spinal hematomas should be in 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 the management of patients with suspected meningitis are provided in Table 1.

5.1.1.4 *Known Risks Associated with an Indwelling Catheter*

Insertion of an intrathecal catheter carries the same risks as a lumbar puncture, with additional risks of catheter blockage, disconnection or retraction.

Of note, in the current study, 2 out of 6 patients developed a lumbar abscess after having had the catheter implanted for 4 days.

5.1.2 Potential Risks Associated with RO7234292

The potential risks identified below have been considered in relation to clinical data available as of *18 July* 2019, including the completed Phase I/IIa study and ongoing Phase II OLE study (*15*-month data cut).

5.1.2.1 Neurological 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.

In the ongoing Phase II OLE Study BN40697, 2 cases of asymptomatic lumbar radiculopathy that were characterized by loss of ankle reflexes, without changes in motor or sensory function, have been observed in the Q4W cohort. In the same cohort, central nervous system effects have been reported, including 2 suspected unexpected serious adverse reaction (SUSAR) cases (hemiparesis, hyporeflexia, myelitis, neuritis, and radiculopathy in 1 patient and hydrocephalus following chemical meningitis in another patient who also experienced speech and coordination difficulties), which the investigator considered to be unrelated to the study drug (for details see the RO7234292 Investigator's Brochure).

Full neurological examinations will be conducted as indicated in Appendix 1. *In addition, patients should be observed in clinic for any complications or complaints post-LP and IT administration 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/μL 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 an MRI of the spine, with no other clinical sequelae noted and follow-up ongoing.

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'-methoxyethyl (MOE) chimeric ASOs to clinical study subjects. However, no clinically significant reduction in platelet counts has 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 adverse events of thrombocytopenia have been reported to date.

Platelet counts will be monitored as indicated in Appendix 1. Guidelines for the management of patients who develop reductions in platelet counts are provided in Table 1.

5.1.2.4 Kidney Effects

Reductions in renal function have been observed after administration of some 2'-MOE containing chimeric ASOs to clinical study subjects. In a 13-week and 9-month IT toxicity study of RO7234292 in the cynomolgus monkey, 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, 1 case of moderate proteinuria considered related to the study drug has been reported in the Q4W cohort (resolved without any intervention *and continued study drug administration*); no other clinically significant kidney abnormality has been observed.

Kidney function will be monitored as indicated in Appendix 1. Guidelines for the management of patients who develop decreased renal function are provided in Table 1.

5.1.2.5 Liver Effects

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

In a 13-week and 9-month IT toxicity study of RO7234292 in the cynomolgus monkey, there were no test article-related histologic findings in the visceral organs including the liver or effects on clinical chemistries. 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, *no drug-related* clinically significant hepatic abnormality has been observed *to date*.

Liver enzymes will be monitored as indicated in Appendix 1. Guidelines for the management of patients who develop decreased hepatic function are provided in Table 1.

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). *A single case of hydrocephalus following chemical meningitis has been observed in the Q4W cohort of* the ongoing Phase II OLE Study BN40697 to date. *For details please see the RO7234292 Investigator's Brochure; for management guidelines, see Section* 5.1.3.3.

5.1.2.7 Neuropsychiatric Changes

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.

In consideration that RO7234292 is being administered directly to the CNS, and that there is limited clinical experience with RO7234292, patients should be closely monitored for signs and symptoms of neuropsychiatric changes in addition to routine monitoring with the C-SSRS.

5.1.2.8 Potential Risk due to Reduction of Target Protein HTT

By specifically targeting mRNA from both HTT alleles, RO7234292 can lower levels of both mHTT and normal "wild-type" huntingtin (wtHTT) protein in all patients, regardless of other 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 in non-clinical studies or in 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 2 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 expression ameliorate disease and increases in mHTT exacerbate disease in animal models of HD, regardless of concomitant changes in wtHTT levels.

No clinically significant new neurologic events were observed in the completed Phase I/IIa study.

As a precaution a full neurological examination will be conducted as indicated in Appendix 1.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Dose Modifications

No dose adjustment from the planned treatment is 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 at the prespecified dose level).

5.1.3.2 Treatment Interruption

RO7234292 treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If RO7234292 has been withheld for $>$3 days because of toxicity, the patient should be discontinued from RO7234292, unless

resumption of treatment is approved following Investigator discussion with the Medical Monitor. RO7234292 treatment 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 1. 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 1 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 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, and 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 to 50/µL WBC count) elevations in CSF WBC count without clinical symptoms do not meet criteria for diagnosis of suspected meningitis. • *In the event of persistent back pain or fever, promptly consider imaging investigation to exclude spinal abscess and discuss with Medical Monitor.* • The Medical Monitor should be consulted in all cases of WBC count CSF elevations, 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 a diagnosis of suspected meningitis, radiculitis, arachnoiditis, *hydrocephalus* or 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.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; CSF=cerebrospinal fluid; eGFR=estimated glomerular filtration rate; INR=international normalized ratio; ULN=upper limit of normal; WBC=white blood cell.

Table 1 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Event	Action to Be Taken
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. Monitor platelet counts daily until two successive values show improvement. Then monitor every 2 to 3 days until platelet count is stable, and at least weekly until platelet count returns to normal. Administration of steroids may 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 of eGFR or CrCl or increase in creatinine, as defined below: 1. eGFR or CrCl $<$ 60 mL/min/1.73 m^2. 2. Creatinine level increase of 2.0 $\times$ above baseline. • Study Drug may be resumed when follow-up test results show that the patient no longer meets the dose interruption criteria.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; CSF=cerebrospinal fluid; eGFR=estimated glomerular filtration rate; INR=international normalized ratio; ULN=upper limit of normal; WBC=white blood cell.

Table 1 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Elevated liver enzymes	• ALT or AST is $>3\times$ULN: Monitor weekly until ALT and AST return to $\leq 1.2\times$ ULN. Further investigation into the liver enzyme elevations may include hepatitis serologies and other diagnostic tests at the discretion of the Investigator in consultation with the Medical Monitor. • Withhold study drug in the event of liver enzymes that meet the following criteria without an alternative explanation (as discussed with the Medical Monitor): ALT or AST $>5\times$ULN. ALT or AST $>3\times$ULN, combined with total bilirubin $>2\times$ULN or INR >1.5. 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. Discontinue study drug permanently if levels do not return to baseline after 30 days.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CrCl=creatinine clearance; CSF=cerebrospinal fluid; eGFR=estimated glomerular filtration rate; INR=international normalized ratio; ULN=upper limit of normal; WBC=white blood cell.

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 Section 5.3.5.9 and Section 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; 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 Section 5.4 to Section 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, all adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as catheter insertion, biopsies, discontinuation of medications) should be reported. If the adverse event meets the criteria for serious adverse event, it should be reported immediately (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until the follow-up visit or until the patient receives his or her first dose of study drug in the OLE study (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 2 will be used for assessing adverse event severity. Laboratory values determined as an adverse event should be graded as per Appendix 7, which is based on National Cancer Institute Common Terminology Criteria for Adverse Events (v5.0).

Table 2 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

Regardless of severity, some events may also meet seriousness criteria. Refer to the 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 (Table 3):

- 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 3 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

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 [see Section 4.5.5]).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.4) 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 3 events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All 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., alkaline phosphatase and bilirubin 5 × upper limit of normal [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 5.3.5.5) 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 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 HD

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 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 study. 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)
- Accidental overdoses or medication errors (see Section 5.4.4 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 EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted] (Primary)

Telephone No.: [redacted] Ext. [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 Medical

Responsible (listed above and/or on the Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days a week. Toll-free numbers for the Help Desk, as well as the 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, any serious adverse events caused by a protocol-mandated intervention should be reported. 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.

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 the follow-up visit. 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 after the follow-up visit 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 until the follow-up visit. 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 until the follow-up visit. 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).

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication errors (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, 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, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded 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 the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

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 study-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 until the follow-up visit), 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 information in this protocol and the following reference document:

- RO7234292 Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

Up to 20 patients with HD may be enrolled in this study. Due to the exploratory nature of this study, the actual number of patients will be determined during the study.

While there is no formal statistical basis for the sample size of 20 patients (at maximum), it has been selected based on prior experience with second generation 2 ASOs given by IT injection to ensure that the PK and PD will be adequately assessed while minimizing patient exposure. However, the number of patients may be adapted during the study to sufficiently characterize the PK/PD relationship in CSF of RO7234292, while not exceeding 20.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. 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.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All patients who have received at least 1 dose of the study drug, whether prematurely withdrawn from the study or not, will be included in the safety analyses.

6.3.2 Pharmacokinetic Analysis Population

Patients will be excluded from the PK analysis population if they did not receive treatment or otherwise significantly deviated from the protocol, violated inclusion or exclusion criteria, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

6.3.3 Pharmacodynamic Analysis Population

Patients will be excluded from the PD analysis population if they did not receive treatment or otherwise significantly deviated from the protocol, violated inclusion or exclusion criteria, or if data are unavailable or incomplete which may influence the PD analysis. Excluded cases will be documented together with the reason for exclusion.

6.4 SAFETY ANALYSES

All safety analyses will be based on the safety analysis population. The safety data, including adverse events, reasons for withdrawal from study, laboratory data, ECG, concomitant medications, vital signs, physical and neurological examinations, and C-SSRS, will be reported in individual listings and summarized by treatment for each assessment time using descriptive statistics.

The incidence of adverse events will be summarized on the basis of body systems and Medical Dictionary for Regulatory Affairs 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.

6.4.1 Adverse Events

All safety analyses will be based on the safety analysis population.

The original terms recorded on the eCRF by the Investigator for adverse events will be standardized by the Sponsor. Adverse events will be listed and summarized by body system and preferred term using the most recent Medical Dictionary for Regulatory Affairs version available.

6.4.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory test values will be presented by individual listings with flagging of values outside the normal ranges.

6.4.2.1 Standard Reference Ranges and Transformation of Data

Roche standard reference ranges, rather than the reference ranges of the Investigator, will be used for all parameters. For most parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, alkaline phosphatase, and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

6.4.2.2 Definition of Laboratory Abnormalities

A Roche predefined standard reference range exists for all laboratory parameters included. Laboratory values falling outside of this standard reference range will be labeled "H" for high or "L" for low in patient listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for each laboratory parameter. The marked reference range is broader than the standard reference range. Values falling outside of the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a patient, the midpoint of the standard reference range will be used as the patient's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the patient listings as "HH" for very high or "LL" for very low.

6.4.3 Vital Signs

Vital signs data will be presented by individual listings and tabular summaries, as appropriate.

6.4.4 12-lead ECG

ECG data will be presented by individual listings with both values outside the normal ranges and marked abnormalities flagged. In addition, tabular summaries will be used, as appropriate.

12-lead Holter ECG recordings may be used for concentration-QT modeling using linear or non-linear mixed-effects models that relate individual PK concentrations to the QT interval or its change from baseline. Results of this will be provided in a separate report.

6.4.5 Concomitant Medications

The original terms recorded on the patients' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms.

Concomitant medications will be presented in summary tables and listings.

6.5 PHARMACOKINETIC ANALYSES

All PK analyses will be based on the PK analysis population.

PK parameters will be read directly from the (plasma and CSF) concentration-time profiles, or calculated using standard non-compartmental methods. The following PK parameters will be computed for RO7234292 and its metabolite(s), as appropriate. However, other PK parameters might be computed in addition as appropriate:

- Time to maximum (or peak) serum concentration, maximum (or peak) serum concentration
- Area under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration, AUC from time zero to a timepoint, AUC from time zero to infinity, extrapolated AUC, AUC for a dosing interval
- Lambda(z), half-life; apparent total clearance
- Cumulative amount of unchanged drug excreted in urine, fraction of IT administered drug excreted in urine, renal clearance of the drug from plasma

Individual and mean PK concentration data at each sampling timepoint of RO7234292 (and its metabolite[s] as appropriate) in plasma, CSF, and urine, and calculated PK parameters thereof, will be presented by listings and descriptive summary statistics including arithmetic means, geometric means, ranges, standard deviations, and coefficients of variation. Individual and mean concentration versus time of RO7234292 (and its metabolite[s] as appropriate) will be plotted on linear or semi-logarithmic scales as appropriate.

All PK parameters will be presented by individual listings and summary statistics including arithmetic means, geometric means, medians, ranges, standard deviations, and coefficients of variation.

In addition, data from the present study may be pooled with data from other studies to analyze the concentration-time data for RO7234292 in CSF and plasma following IT administration using non-linear mixed-effects modeling. A covariate analysis may also 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., AUC and average trough

plasma concentration) will be computed and used to describe the relationship between plasma and/or CSF exposure and biomarker measures (mHTT in CSF) as well as safety measures. The data from this study may be pooled with data from other studies conducted with RO7234292 to support 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.

6.6 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least 1 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 1 or more post-baseline samples 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 may be explored.

6.7 BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

Individual and mean exploratory biomarker data and parameters will be presented by listings and descriptive summary statistics including means, geometric means, medians, ranges, standard deviations, and coefficients of variation, as appropriate.

The data from this study may be pooled with data from other studies conducted with RO7234292 to support the biomarker analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data 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.

PerfO and ClinRO data will be collected on paper forms or electronic devices. The data from the assessments will be entered into the EDC system by site staff.

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 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, PerfOs, 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 study.

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 7.5.

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

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PerfO and ClinRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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 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).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) 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 EC submission. The final 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 or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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 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 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.

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.

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 EC by the Principal Investigator and reviewed and approved by the EC before the study is initiated. In addition, any patient recruitment materials must be approved by the EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. Investigators are also responsible for promptly informing the 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 EC. Investigators may receive written Investigational New Drug 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 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 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. 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 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 EC in accordance with established 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 study will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, safety, and biostatistical management.

A contract research organization will be contracted to manage the study site(s) and perform monitoring activities.

A minimum of 1 site globally will participate to enroll approximately 20 patients. However, additional clinical sites may participate in order to facilitate patient enrollment.

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. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, at scientific congresses, in clinical study registries of the U.S. National Institutes of Health and the European Medicines Agency, 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, and redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical studies 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 study results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical studies 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 studies 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 EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the 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

Baig SS, Strong M, Quarrel OW. The global prevalence of Huntington's disease: a systemic review and discussion. Neurodegener Dis Manage 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 and cognitive deficits. Brain Imaging Behav 2011;5:171–80.

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

Crooke ST and 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.

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

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

Hogarth P, Kayson E, Kieburtz K, et al; and the United States-Venezuela Huntington's Disease Collaborative Research Group, and the Huntington Study Group. 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(2):136–42.

Investigator's Brochure for RO7234292. Version 4. July 2018.

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.

Liu JP and Zeitlin SO. Is Huntingtin dispensable in the adult brain? J Huntingtons Dis 2017;6(1):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.

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, Wheelock V. 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, Johnson HJ, et al. Clinical and biomarker changes in premanifest huntington disease show study feasibility: a decade of the PREDICT-HD study. Front Aging Neurosci 2014;6:78.

Paulson HL and 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 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. Mov Disord 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, Aylward EH, Wild EJ, et al. Huntington's disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol 2014;10(4):204–16.

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.

Shoulson I and 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 and 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;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(10):1379–92.

Walker FO. Huntington's disease. Lancet 2007;369:218–28.

Werner CJ, Dogan I, Saß C, et al. Altered resting-state connectivity in Huntington's disease. Hum Brain Mapp 2014;35(6):2582–93.

Wexler NS, Young AB, Tanzi RE, et al. Homozygote for huntington's disease. Nature1987;326:194–7.

Wild EJ and 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

Assessment	Screening[a)]	Treatment Period												Follow-up[b)]	Early Termination[c)]
Visits	**-28 to -3 days before 1st study drug admin**	**Day -2**	**Day -1[d)]**	**Day 1[d)]**	**Day 2**	**Day 3**	**Day 4**	**Day 28**	**Day 29[d)]**	**Day 30**	**Day 43**	**Day 71**	**Day 127**	**6 months after last study drug admin**	**up to 28 days after last study drug admin**
Window	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**
Month	**-1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**3-4**	**5-6**	**7-8**	**NA**
Week	**-4 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**5**	**5**	**5**	**6-7**	**8-12**	**16-20**	*27-31*	**NA**
Hour	**NA**	**NA**	**-24**	**0**	**24**	**48**	**72**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Signed informed consent[e)]	x														
Review of inclusion and exclusion criteria	x														
Demographic data	x														
Medical history and baseline conditions[f)]	x		x												
Blood sample for CAG repeat length	x														
Skin and nose swab for MRSA[g)]	*x*														
Viral serology[h)]	x														
Thyroid panel[i)]	x														
MRI[i)]	*x*													*x*	*x*
Vital signs[k)]	x		x	x	x	x	x	x	x		x	x	x	x	x
Complete physical examination[l)]	x	x						x			x	x	x	x	x
Neurological examination[m)]	x	x		x			x		x		x	x	x	x	x
12-lead (single) ECG[n)]	x		x	x	x	x	x	x	x		x	x	x	x	x
12-lead Holter ECG[d), o)]			x	x	x	x			x						
Hematology *(local)*[p)]	x		x	*x*	x	*x*	x	x	*x*		x	x	x	x	x
Chemistry[q)]	x		x		x		x	x			x	x	x	x	x
Pregnancy test[r)]	x	x						x			x	x	x	x	x
Hormone panel[s)]	x	x													
Local PT, INR, aPTT, platelet count	x	x						x			x	x	x	x	x
Urinalysis[t)]	x		x		x		x	x			x	x	x	x	x

Appendix 1: Schedule of Activities

Assessment	Screening[a)]	Treatment Period												Follow-up[b)]	Early Termination[c)]
Visits	**-28 to -3 days before 1st study drug admin**	**Day -2**	**Day -1[d)]**	**Day 1[d)]**	**Day 2**	**Day 3**	**Day 4**	**Day 28**	**Day 29[d)]**	**Day 30**	**Day 43**	**Day 71**	**Day 127**	**6 months after last study drug admin**	**up to 28 days after last study drug admin**
Window	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**
Month	**-1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**3-4**	**5-6**	**7-8**	**NA**
Week	**-4 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**5**	**5**	**5**	**6-7**	**8-12**	**16-20**	*27-31*	**NA**
Hour	**NA**	**NA**	**-24**	**0**	**24**	**48**	**72**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
RO7234292 PK sampling (plasma)[u)]				x	x	x	x	x	x	x	x	x	x	x	x
RO7234292 PK sampling (urine)[v)]				x	x	x	x								
RO7234292 PK sampling (CSF)[w)]				x	x	x			x		x	x	x	x	x
Plasma sampling for immunogenicity testing				x				x						x	x
CSF sample for safety[w)]				*x*	*x*	*x*			x		x	x	x	x	x
CSF sample for biomarkers[w)]				x	x	x			x		x	x	x	x	x
Blood sample for CRP and ESR (local)			*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	x
Treatment assignment		*x*													
Admission to site[y)]		x						x		x	x	x	x	x	x
Overnight stay at site		x	x	x	x	x		x							
Discharge from site							x		x	x	x	x	x	x	x
Insertion of IT catheter[z)]				x											
Removal of IT catheter						x									
Catheter tip for culture						*x*									
Study drug administration				x					x						

Appendix 1: Schedule of Activities

Assessment	Screening[a)]	Treatment Period												Follow-up[b)]	Early Termination[c)]
Visits	**-28 to -3 days before 1st study drug admin**	**Day -2**	**Day -1[d)]**	**Day 1[d)]**	**Day 2**	**Day 3**	**Day 4**	**Day 28**	**Day 29[d)]**	**Day 30**	**Day 43**	**Day 71**	**Day 127**	**6 months after last study drug admin**	**up to 28 days after last study drug admin**
Window	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**± 2 days**	**± 2 days**	**± 2 days**	**± 7 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**
Month	**-1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**3-4**	**5-6**	**7-8**	**NA**
Week	**-4 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**5**	**5**	**5**	**6-7**	**8-12**	**16-20**	*27-31*	**NA**
Hour	**NA**	**NA**	**-24**	**0**	**24**	**48**	**72**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
Lumbar puncture[aa)]				CSF sampling from *predose* until (and including) *48* hours postdose					x		x	x	x	x	x
C-SSRS[bb)]	x		x					x				x	x	x	x
Independence Scale	x													x	x
HD-DAS	x													x	
MoCA	x													x	
TMS	x													x	
CGI-S	x													x	
CGI-C														x	
SDMT	x													x	
SWRT	x													x	
TFC	x													x	x
Blood sample for RBR DNA (optional)[cc)]				x											
Blood sample for RBR RNA (optional)[cc)]				x											
Serum sample for RBR (optional)[cc)]				x				x			x	x	x		
Clinical genotyping				x											
Adverse events[dd)]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Change in medical information since previous visits[ee)]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications[ff)]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: At timepoints where more than one assessment is required, the sequence noted in Appendix 6 should be followed as applicable.

a) A maximum of one re-screening will be allowed within 4 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 viral serology from the initial screening may be acceptable as part of the re-screening assessments, if performed within 4 weeks of the baseline visit.

b) Patients who complete the treatment period will return to the clinic for the follow-up visit 6 months (± 2 weeks) after last study drug administration. Study visits should be planned as per the study schedule; however, under exceptional circumstances, time windows as indicated in the schedule of activities can be utilized.

c) All patients who withdraw or discontinue from study treatment early will be asked to return to the clinic for the early termination visit within 28 days ± 14 days after the last dose of study drug.

d) In order for the Holter recordings to be conducted in the same conditions, food consumption/intake must occur at the same time on Day -1, Day 1, and Day 29. Food consumption/intake should be avoided (to the extent possible) when the Holter ECG data is collected.

e) 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.

f) 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.

g) *Skin (groin area) and nose swabs will be taken during screening to test for Methicillin-resistant Staphylococcus aureus (MRSA). If the MRSA screening result is positive, treatment for decolonization (as per local standard procedure) should be administered for 5 days prior to catheter insertion.*

h) Viral serology: HbsAg, HCV antibody, HIV-1 antibody, and HIV-2 antibody.

i) Thyroid panel: thyroid-stimulating hormone and free thyroxine (also known as T4).

j) *Structural MRI is mandatory; diffusion-weighted and resting-state functional MRIs are optional, as clinically indicated (and if patient gives specific consent). MRIs should take place as early as possible within the screening window but may take place at any time during screening. The screening MRI scan should be performed at least 7 days prior to the IT catheter insertion to allow time for re-scanning if the quality of the initial MRI is inadequate. The screening MRI scan must pass central laboratory image quality control review and results must be available before the patient can be enrolled in the study. The follow-up (or early termination, if applicable) MRI should take place within the 14-day window allowed for the follow-up visit (or early termination visit, if applicable) and prior to the lumbar puncture scheduled at follow-up (or early termination, if applicable). If patient who enrolled under protocol Version 3 cannot undergo and tolerate MRI scans, no MRI scans will be performed at the follow-up visit (or early termination visit, if applicable).*

k) Includes respiratory rate, pulse, temperature, and systolic and diastolic blood pressure while the patient is in a seated position for approximately 5 minutes. Record abnormalities observed at baseline (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.

l) A complete physical examination, performed at screening and at other visits as specified in the schedule of activities, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurological 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. 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. Height will be measured at screening only.

m) A neurologic examination, performed at screening and at other visits as specified in the schedule of activities, should include assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. 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 neurologic examination. 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.

n) Single 12-lead ECGs are to be recorded 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), and other visits, pre-dose ECGs are to be recorded prior to any blood draws and before the lumbar puncture.

o) *From Day -1 to Day 3,* patients will wear a digital Holter monitoring device for continuous recordings of 12-lead ECG traces over 72 hours (starting 24 hours before first study drug administration until 48 hours postdose). On Day 29, patients will again wear a digital Holter device for recordings of data over 4 hours, starting from predose until 4 hours postdose. Collection of 12-lead ECG traces from Holter recordings will be done at pre-defined timepoints (See Appendix 2). Extraction times on Day -1 must match the times of extraction on Day 1 and Day 29. The Day 29 Holter ECG recording data will be extracted at predose (~0 hour), 1, 2, and 4 hours postdose. Triplicate ECG tracings from the continuous recordings will be extracted within 10 minutes of the nominal timepoints for PK (plasma) sampling. At these specific timepoints the patient should be at rest and in a supine position for at least 10 minutes prior to and remain in the supine position for at least 5 more minutes after the specified PK (plasma) sampling timepoint.

p) Hematology includes WBC count, RBC count, platelet count, hemoglobin, hematocrit, differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes).

q) Serum chemistry panel: bicarbonate, sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, gamma-glutamyl transferase, and creatine phosphokinase.

r) 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.

s) Females only to confirm post-menopausal status. Includes measurement of follicle-stimulating hormone and Estradiol.

t) Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria).

u) Plasma PK sampling will be collected as follows: at Day 1 (0 [predose], 1, 2, 4, 6, 8, 12, and 16 hours postdose), Day 2 (24 and 36 hours postdose), Day 3 (48 and 60 hours postdose), Day 4 (72 hours postdose), Day 28 (at a timepoint equivalent to Day 1 predose sample), Day 29 (0 [predose], 1, 2, and 4 hours postdose), Day 30, 43, 71, and 127 (at a timepoint equivalent to Day 29 predose sample), and the follow-up visit (early termination visit if applicable).

v) Bladder must be completely emptied at the time of study drug administration. Quantitative urine will be collected in the following intervals: 0 to 24 hours, 24 to 48 hours, and 48 to 72 hours following first study drug administration.

w) Cerebrospinal fluid sampling will be performed from *predose* to (and including) *48* hours postdose via the IT catheter, at all other visits CSF sampling will be done by single lumbar puncture. Pharmacokinetic CSF sampling will be collected as follows: at Day 1 (0 [predose], 2, 4, 8, 12, and 16 hours postdose), Day 2 (24 and 36 hours postdose), Day 3 (48 *hours*), Day 29 (predose), Day 43, 71, and 127, and the follow-up visit (early termination visit if applicable). Sampling for CSF biomarkers will be collected as follows: Day 1 (0 [predose], 4, 8, 12, and 16 hours postdose), Day 2 (24 and 36 hours postdose), Day 3 (48 *hours postdose*), Day 29 (predose), Day 43, 71, and 127, and the follow-up visit (early termination visit if applicable). *In addition, up to 2 mL CSF sample will be collected for daily CSF safety testing, including culture, during the indwelling-catheter period.*

x) Sampling for plasma biomarkers will be collected as follows: at Day -1 (-24, -20, -16, -12, and -8 hours), Day 1 (0 [predose], 1, 2, 4, 6, 8, 12, and 16 hours postdose), Day 2 (24 and 36 hours postdose), Day 3 (48 and 60 hours postdose), Day 4 (72 hours postdose), Day 29 (predose), Day 43, 71, and 127, and the follow-up visit (early termination visit if applicable).

y) Admission to the clinical unit may occur either on the evening/afternoon of Day -2 or the morning of Day -1. *Assessments for Day -2 should be conducted on Day -2, but it is not mandatory for the patient to remain at the clinic overnight on Day -2 if it is more convenient to stay at a hotel or return home.*

z) In preparation for the catheter insertion, patients will be required to remove all body piercings, make up, and nail polish and to cleanse the entire body (including hair) with antibacterial soap on Day -2 or Day -1.

aa) 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 of these local laboratory tests may occur at any time in the 72 hours prior to the lumbar puncture (with the exception of CSF collection during the CSF sampling period from *predose* prior to first study drug administration until *48* hours postdose). The lumbar puncture (with the exception of the CSF sampling around the first dose) 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. *A 20 mL CSF sample will be collected at predose after the IT catheter has been inserted and before the study drug administration. Subsequently,* during the CSF sampling period from *predose* until *48* hours postdose approximately 5 mL of CSF fluid will be collected (via the IT catheter) at the timepoints indicated in Appendix 2. *In addition, up to 2 mL CSF sample will be collected for daily CSF safety testing, including culture, during the indwelling-catheter period.* For all other lumbar punctures, 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. The operator must confirm CSF flow is present prior to injecting study drug. A 24G (atraumatic) needle 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. Spinal 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.

bb) 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).

cc) Performed only for patients at participating sites who have provided written informed consent to participate.

dd) After informed consent has been obtained but prior to initiation of study drug, any serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 6 months after the last 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.

ee) 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.

ff) 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 follow-up visit.

Admin=administration; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; CAG=cytosine, adenine, guanine base sequence found in DNA which is translated into glutamine; CGI-C=Clinical Global Impression–Change; CGI-S=Clinical Global Impression–Severity; CRP=C-reactive protein; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; DNA=deoxyribonucleic acid; ECG=electrocardiogram; eCRF=electronic Case Report Form; ESR=erythrocyte sedimentation rate; HbsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; HD=Huntington's disease; HD-DAS=Huntington's Disease Daily Activity Scale; HIV=human immunodeficiency virus; INR=international normalized ratio; IT=intrathecal; MoCA=Montreal Cognitive Assessment; *MRSA=Methicillin-resistant Staphylococcus aureus; MRI magnetic resonance imaging;* NA=not applicable; PK=pharmacokinetic; PT=prothrombin time; RBC=red blood cell; RBR=Research Biosample Repository; RNA=ribonucleic acid; SDMT=Symbol Digit Modalities Test; SWRT=Stroop Word Reading Test; TFC=Total Functional Capacity; TMS=Total Motor Score; WBC=white blood cell.

Appendix 2
Schedule of Detailed Assessments During the In-house Periods

Assessment	Treatment Period																						
Day	**-1**	**-1**	**-1**	**-1**	**-1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**28**	**29**	**29**	**29**	**29**
Month	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**2**
Week	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**5**	**5**	**5**	**5**	**5**
Hour	**-24**	**-20**	**-16**	**-12**	**-8**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**60**	**72**	**0**	**0**	**1**	**2**	**4**
Medical history and baseline conditions[f)]	x																						
Vital signs[k)]	x					x			x		x			x		x		x	x	x			
Complete physical examination[l)]																			x				
Neurological examination[m)]						x												*x*		x			
12-lead (single) ECG[n)]	x					x			x		x			x		x		x	x	x			
12-lead Holter ECG[d), o)]	-24 hours to 48 hours postdose																			0 to 4 hours postdose			
Holter ECG timepoints for extraction[o)]	x					x	x	x	x	x	x	x	x	x	x	x				x	x	x	x
Hematology *(local)*[p)]	x					*x*								x		*x*		x	x				
Chemistry[q)]	x													x				x	x				
Pregnancy test[r)]																			x				
Local PT, INR, aPTT, platelet count																			x				
Urinalysis[t)]	x													x				x	x				

Appendix 2: Schedule of Detailed Assessments During the In-House Periods

Assessment	Treatment Period																						
Day	**-1**	**-1**	**-1**	**-1**	**-1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**28**	**29**	**29**	**29**	**29**
Month	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**2**
Week	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**5**	**5**	**5**	**5**	**5**
Hour	**-24**	**-20**	**-16**	**-12**	**-8**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**60**	**72**	**0**	**0**	**1**	**2**	**4**
RO7234292 PK sampling (plasma)[u)]						x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RO7234292 PK sampling (urine)[v)]						0 to 24 hours								24 to 48 hrs		48 to 72 hrs							
RO7234292 PK sampling (CSF)[w)]						x		x	x		x	x	x	x	x	x				x			
Plasma sampling for immunogenicity testing						x													x				
CSF sample for safety[w)]						x								x		x				x			
CSF sample for biomarkers[w)]						x			x		x	x	x	x	x	x				x			
Blood for CRP and ESR (local)	*x*					*x*								*x*		*x*		*x*		*x*			
Plasma sample for biomarkers[x)]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x			
Insertion of IT catheter[z)]						*x*																	
Removal of IT catheter																x							
Catheter tip for culture																*x*							

Appendix 2: Schedule of Detailed Assessments During the In-House Periods

Assessment	Treatment Period																						
Day	**-1**	**-1**	**-1**	**-1**	**-1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**28**	**29**	**29**	**29**	**29**
Month	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**2**
Week	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**5**	**5**	**5**	**5**	**5**
Hour	**-24**	**-20**	**-16**	**-12**	**-8**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**24**	**36**	**48**	**60**	**72**	**0**	**0**	**1**	**2**	**4**
Study drug administration						x														x			
Lumbar puncture[aa)]						CSF sampling from *predose* until (and including) *48* hours postdose														x			
C-SSRS[bb)]			x																x				
Blood sample for RBR DNA (optional)[cc)]						x																	
Blood sample for RBR RNA (optional)[cc)]						x																	
Serum sample for RBR (optional)[cc)]						x													x				
Clinical genotyping						x																	
Adverse events[dd)]	x →																						
Change in medical information since previous visits[ee)]	x →																						
Concomitant medications[ff)]	x →																						

Note: Patients will be admitted to the site in the afternoon/evening of Day -2 or the morning of Day -1 to begin the first in-house period of the study; patients will be discharged on Day *4* after all assessments have been completed. Patients will return to the site for the second in-house period in the afternoon/evening of Day 28 or in the morning on Day 29 and will be discharged on Day 29 after all assessments have been completed.

See corresponding footnotes in Appendix 1.

Appendix 3 Clinician-Reported Outcomes

Assessment	Name	Items	Concepts	Approx. Duration	Timing
MoCA	Montreal Cognitive Assessment	11	Overall cognitive status	10 min	Screening and Follow-up visits
HD-DAS	Huntington's Disease Daily Activities Scale	25	Daily function	25 min	Screening and Follow-up visits
IS	Independence Scale	1	Functional disability/independence	3 min	Screening and Follow-up visits
TFC	Total Functional Capacity Scale	5	Overall function	10 min	Screening and Follow-up visits
TMS	Total Motor Score	31	Motor function	15 min	Screening and Follow-up 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 and follow-up version at Follow-up visit
CGI-S	Clinical Global Impression–Severity	1	Overall severity of patient status	2 min	Screening and Follow-up visits
CGI-C	Clinical Global Impression–Change	1	Overall change in patient status	2 min	Follow-up visit

Approx.=approximately.

Appendix 4 Performance Outcomes

Assessment	Name	Items	Concepts	Approx. Duration	Timing
SDMT	Symbol Digit Modalities Test	Max no. in 90 sec	Cognitive	5	Screening and Follow-up visits
SWRT	Stroop Wording Reading Test	Max no. in 45 sec	Cognitive	5	Screening and Follow-up visits

Approx.=approximately; No.=number; Max=maximum.

Appendix 5 Diagnostic Confidence Level

The diagnostic confidence level is calculated as shown below (from the Unified Huntington's Disease Rating Scale Total Motor Score Scale, Item 17):

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, or rigidity) in a subject at risk for Huntington's disease (HD)?

0=normal (no abnormalities)

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

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

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

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

Appendix 6 Order of Assessments

At timepoints where more than one assessment is required, the following sequence should be followed as applicable, and priority will be given to the CSF PK sample being taken at the scheduled time:

- Obtain resting single 12-lead ECGs and Holter ECGs collection.
- Collect resting vital signs.
- Collect CSF sample for CSF PK determination.
- Collect CSF sample for CSF PD determination and CSF biomarker determination.
- Collect CSF safety sample.
- Collect blood sample for plasma PK determination.
- Collect blood sample for plasma PD determination and blood/plasma/serum biomarker determination.
- Collect blood samples for blood chemistry, hematology, viral serology and coagulation.
- Collect urine sample for urinalysis.
- Collect urine sample for urine PK determination.
- Collect blood sample for clinical genotyping.
- Administer study drug.

Appendix 7 Grading Scale for Adverse Events Related to Laboratory Abnormalities

The following grading recommendations for adverse events related to clinical laboratory test abnormalities are based on the Common Terminology Criteria for Adverse Events, Version 5.

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

Appendix 7: Grading Scale for Adverse Events Related to Laboratory Abnormalities

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

Appendix 7: Grading Scale for Adverse Events Related to Laboratory Abnormalities

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)