Official Title: An Open-Label Extension Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO7234292 (ISIS 443139) in Huntington's Disease Patients Who Participated in Prior Investigational Studies of RO7234292 (ISIS 443139)

NCT Number: NCT03342053

Document Date: Protocol Amendment 4 (Version 5): 30-August-2018

PROTOCOL

TITLE: **AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF RO7234292 (ISIS 443139) IN HUNTINGTON'S DISEASE PATIENTS WHO PARTICIPATED IN PRIOR INVESTIGATIONAL STUDIES OF RO7234292 (ISIS 443139)**

PROTOCOL NUMBER: BN40697 (ISIS 443139-CS2)

VERSION NUMBER: Amendment 4 (Version 5)

EUDRACT NUMBER: 2017-002471-25

TEST PRODUCT: RO7234292 (ISIS 443139 or RG6042)

MEDICAL MONITOR: [redacted], *M.D., M.Sc.*

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Original (Version 1): 19 June 2017

DATES AMENDED: Amendment 1 (Version 2): 5 September 2017
Amendment 1 (Canada): 15 December 2017
Amendment 2 (Version 3): 30 January 2018
Amendment 2 (Canada): 31 January 2018
Amendment 3 (Version 4): 29 June 2018
Amendment 3 (Canada): 29 June 2018
Amendment 4 (Version 5): See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	30-Aug-2018 06:27:53

Protocol Signature Page

Protocol Number:	BN40697 (ISIS 443139-CS2)
Protocol Title:	An Open-Label Extension Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO7234292 (ISIS 443139) in Huntington's Disease Patients Who Participated in Prior Investigational Studies of RO7234292 (ISIS 443139)
Version:	Protocol Amendment 4 (Version 5)

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open-Label Extension Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO7234292 (ISIS 443139) in Huntington's Disease Patients Who Participated in Prior Investigational Studies of RO7234292 (ISIS 443139)," and agree to conduct the Study as described herein.

I agree to comply with the International Council for Harmonisation Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of F. Hoffmann-La Roche Ltd.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

PROTOCOL AMENDMENT

Protocol Number:	BN40697 (ISIS 443139-CS2)
Protocol Title:	An Open-Label Extension Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO7234292 (ISIS 443139) in Huntington's Disease Patients Who Participated in Prior Investigational Studies of RO7234292 (ISIS 443139)
Amendment Number:	Amendment 4 (Version 5)

Protocol BN40697 (previously referred to as ISIS 443139-CS2) has been amended to change the Sponsor and include a new study drug manufacturer, to make a provision for access to treatment following completion of the study, and to collect or generate a Huntington's disease identification number (HDID) number for participating patients. Changes to the protocol, along with a rationale for each change, are summarized below:

- F. Hoffmann-La Roche Ltd has taken over the future development of study drug RO7234292 (previously ISIS 443139) from Ionis Pharmaceuticals, Inc. As a consequence, the study drug name has changed from ISIS 443139 to RO7234292, and the study drug will be manufactured and packaged by F. Hoffmann-La Roche Ltd (Sections 7.1 and 7.2 and throughout the protocol). With the change in Sponsor, a new Medical Monitor will be assigned.
- The protocol has been updated to make a provision for post-trial access to treatment through an open-label extension study (Study BN40955) (Section 8.10).
- In addition, a provision has been made for the collection of patients' HDID numbers to enable data between this study and other studies and registries to be linked (Sections 6.3.2 and 11.4).
- Protocol version numbering has been changed throughout to align with the Sponsor's numbering convention.

Revisions from a previous country-specific amendment (Amendment 3, Canada) have been incorporated into Amendment 4 (Version 5) as outlined below:

- Additional clarity has been added around the platelet exclusion criteria, so patients are not unnecessarily excluded (Section 5.2).

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.

PROTOCOL SYNOPSIS

Protocol Title	An Open-Label Extension Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO7234292 (ISIS 443139) in Huntington's Disease Patients Who Participated in Prior Investigational Studies of RO7234292 (ISIS 443139)
Study Phase	2
Indication	Huntington's disease
Primary Objective	To evaluate the safety and tolerability of monthly and bimonthly (every other month) intrathecal (IT) bolus administrations of *RO7234292* to patients with Huntington's disease (HD).
Secondary Objectives	To characterize the cerebrospinal fluid (CSF) pharmacokinetics of monthly and bimonthly IT doses of *RO7234292*. To explore effects of monthly and bimonthly IT doses of *RO7234292* on key pharmacodynamic biomarkers and clinical endpoints relevant to HD, including: • Mutant Htt protein level in CSF • Structural MRI (ventricular, caudate and whole brain volumes) • Quantitative electroencephalography • Assessments of physical functioning, activities of daily living, gait, mobility and cognitive functioning
[redacted]	
Study Design	This is an open-label extension (OLE) of Study ISIS 443139-CS1. Study ISIS 443139-CS1 was a multiple-ascending dose (MAD) study in 46 patients with early manifest HD aged 25-65 years, inclusive. In the MAD study, patients received 4 doses of ISIS 443139 or placebo. Eligibility for Study *BN40697 (*ISIS 443139-CS2*)* is based on completion of the 4-dose Treatment Period of the prior MAD study and absence of deterioration in health or intervening activities that would introduce risk to the patient sufficient to preclude participation in the OLE. This is a multi-center study with study duration of up to 18 calendar months. Two (2) dosing regimens will be tested – monthly and bimonthly. Randomization between regimens (1:1) will be stratified by Study Center. • "Monthly" regimen: administrations of *RO7234292* every 28 days for 62 weeks (2-dose Loading Period followed by 14-dose Maintenance Period) • "Bimonthly" regimen: 2 administrations of *RO7234292* separated by 28 days (2-dose Loading Period) followed by administrations every 56 days for 56 weeks (7-dose Maintenance Period)

PROTOCOL SYNOPSIS *Continued*

Study Design *Continued*	The *RO7234292* doses used in these regimens will not exceed 120 mg/dose, the highest dose evaluated in the prior MAD study. A final visit will be held approximately 14 weeks after the last dose. The extent of screening procedures required for this study varies depending on the amount of time that has elapsed between participation in the MAD study and the start of the OLE (see Appendix A, Schedule of Procedures).
Number of Subjects	Up to 46 (patients who previously participated in ISIS 443139-CS1)
Study Population	**Inclusion Criteria** *Signed Written Informed Consent* 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Must be capable of giving informed consent (in the opinion of the Investigator) *Target Population* 3. Must have completed the Treatment Period of Study ISIS 443139-CS1 4. Able and willing to meet all study requirements in the opinion of the Investigator, including: a. Adequately supportive psychosocial circumstances b. Have a trial partner who is reliable, competent and at least 18 years of age, is willing to accompany the patient to select trial visits and to be available to the Study Center by phone if needed, and who (in the opinion of the Investigator) is and will remain sufficiently knowledgeable of patient's ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to HDWF and PBA-s c. Able to undergo MRI scans and able to tolerate them (e.g., no metal implants including MRI incompatible IUDs, chorea of a severity that precludes MRI scans or any condition that renders testing intolerable for the patient) d. Able to tolerate blood draws and lumbar puncture (LP) e. Stable medical, psychiatric and neurological status for at least 12 weeks prior to Screening visit

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	*Reproductive Status* 5. Females must be non-pregnant, non-lactating and either a. surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); b. post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved); c. abstinent* or, d. if engaged in sexual relations of child-bearing potential, agree to use highly effective contraception (refer to Section 6.3.1) from the time of signing the informed consent form until at least 5 months after the last dose of *RO7234292* If not surgically sterile, must have a negative HCG pregnancy test at Screening visit and prior to each dose administration Males must be surgically sterile, abstinent* or, if engaged in sexual relations with a female of child-bearing potential, must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 5 months after the last dose of *RO7234292* * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception
	Exclusion Criteria *Prohibited and Restricted Medications and Procedures* 1. Treatment with an investigational drug (other than ISIS 443139 in Study ISIS 443139-CS1), biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer. Concurrent or planned concurrent participation in any clinical study (including observational and non-interventional studies) without approval of the Sponsor Medical Monitor 2. Antiplatelet or anticoagulant therapy within the 14 days prior to first lumbar puncture in the study or anticipated use during the study, including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban 3. Prior treatment with an antisense oligonucleotide including siRNA (other than ISIS 443139 in Study ISIS 443139-CS1) 4. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter

PROTOCOL SYNOPSIS *Continued*

Study Population *Continued*	*Medical History and Concurrent Disease* 5. Clinically-relevant hematological, hepatic, cardiac or renal disease or event. Clinically-significant abnormal hepatic, renal or hematology lab tests at Screening must be discussed with the Sponsor Medical Monitor 6. Malignancy within 5 years of Screening, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated 7. Any condition that significantly increases risk of meningitis unless patient is receiving appropriate prophylactic treatment 8. History of bleeding diathesis or coagulopathy, platelet count < LLN *unless stable and assessed by the Investigator and Sponsor Medical Monitor to be not clinically significant* 9. Have any other condition which, in the opinion of the Investigator or Sponsor, would make the patient unsuitable for inclusion or could interfere with the patient participating in or completing the study
Treatment Groups	Patients will receive *RO7234292* as part of the Monthly Cohort or the Bimonthly Cohort. • Monthly Cohort: administrations of *RO7234292* every 28 days for 62 weeks (2-dose Loading Period followed by 14-dose Maintenance Period) • Bimonthly Cohort: 2 administrations of *RO7234292* separated by 28 days (2-dose Loading Period) followed by administrations every 56 days for 56 weeks (7-dose Maintenance Period)
Study Drug Dosage and Administration	The *RO7234292* doses used in this study will not exceed 120 mg/dose, the highest dose evaluated in the prior MAD study (ISIS 443139-CS1). Each dose of *RO7234292* will be administered as a single IT bolus injection. Administration will be via 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.

PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection	*RO7234292* dose levels will be selected based on safety, pharmacokinetic and pharmacodynamic data generated in the prior MAD study (Study ISIS 443139-CS1), with interpretation of the pharmacological relevance of the doses aided by comparison to expected effects based on preclinical pharmacokinetic/pharmacodynamic modeling. [redacted] Two (2) dosing regimens will be tested: the monthly regimen and the bimonthly regimen, defined above. Monthly dosing is expected to achieve steady state *RO7234292* in the brain cortex tissue by Study Day 92 (i.e., after 4 doses). Bimonthly dosing (after 2 monthly doses to serve as a load) will be investigated to determine if sufficient pharmacological effect can be achieved with a less-frequent dosing regimen.
Adjustment of Dose and/or Treatment Schedule	Dose regimen adjustments are not planned. Any observation in a patient that causes the Investigator to propose a change in dose level or frequency must be discussed with the Sponsor Medical Monitor.
Study Visit Schedule and Procedures	After informed consent is obtained, patients will undergo necessary screening procedures within a 4-week period. Patients who meet the eligibility criteria will visit the Study Center on Study Day -1 to undergo baseline clinical, blood, and electrophysiological evaluations. On Study Day 1, patients will be admitted to the Study Center, undergo pre-dose evaluations and receive an IT bolus injection of *RO7234292*. Following this IT injection, patients will be kept at the Study Center for at least 24 hours and carefully monitored for any adverse clinical symptoms or signs. Assessments during the admission period include neurological examination, vital signs, ECGs, blood sampling, urine collection and clinical laboratory analyses. At subsequent dosing visits, patients will be monitored for at least 5 hours post-dosing prior to discharge from the Study Center. *RO7234292* administration will take place every 28 days during the Loading Period and then either every 28 days or every 56 days during the Maintenance Period, according to patient randomization. The Study Center will monitor the patient's condition via telephone between clinic study visits. During the Post-Treatment Period, patients will visit the Study Center once (on Study Day 519) for in-clinic assessments.

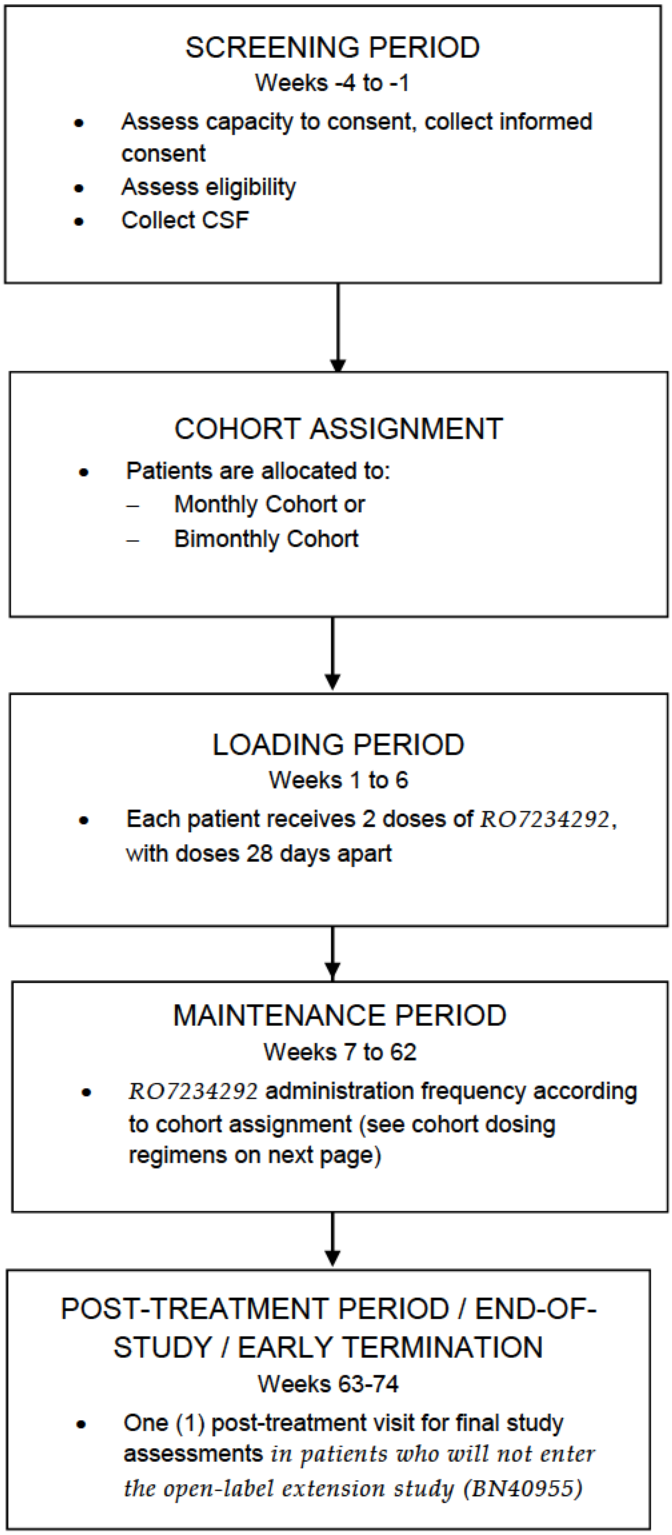
PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures *Continued*	CSF samples will be taken at the Screening visit, pre-dose on each injection day and at the Post-Treatment visit. These samples will be utilized for evaluation of pharmacokinetics, Htt protein and other biomarker and laboratory analyses. If a patient terminates early from the Loading or Maintenance Period, he/she will be encouraged to return for the Post-Treatment Period visit (Day 519) approximately 14 weeks after last administration of *RO7234292*.
Safety and Tolerability Evaluations	Safety and tolerability evaluations include: • Columbia - Suicide Severity Rating Scale (C-SSRS) • Physical examination and standard neurological assessment (including fundi) • Pregnancy testing • Vital signs (HR, BP, orthostatic changes, weight) • ECG • AEs and concomitant medications • CSF safety labs (cell counts, protein, glucose) • Plasma laboratory tests (clinical chemistry, hematology) • Urinalysis • Neuroimaging assessments (safety sequences) The safety and tolerability of *RO7234292* will be assessed by determining the incidence, severity and dose-relationships of AEs, ECG changes and changes in laboratory parameters by dose.
Pharmacokinetic Evaluations	CSF [redacted] samples will be used for evaluation of pharmacokinetic parameters. Concentration of *RO7234292* in CSF will be summarized using descriptive statistics and the *RO7234292* half-life in CSF will be calculated, if possible. [redacted] Concentration of *RO7234292* in urine following first dose will be summarized.
Pharmacodynamic and Clinical Evaluations	Pharmacodynamic and clinical evaluations include: • Mutant Htt protein level in CSF and other plausible fluid biomarkers of Huntington's disease progression • Structural MRI (ventricular, caudate and whole brain volumes), [redacted] • Quantitative electroencephalography • Assessments of physical functioning, activities of daily living, gait, mobility, cognitive functioning and neuropsychiatric condition

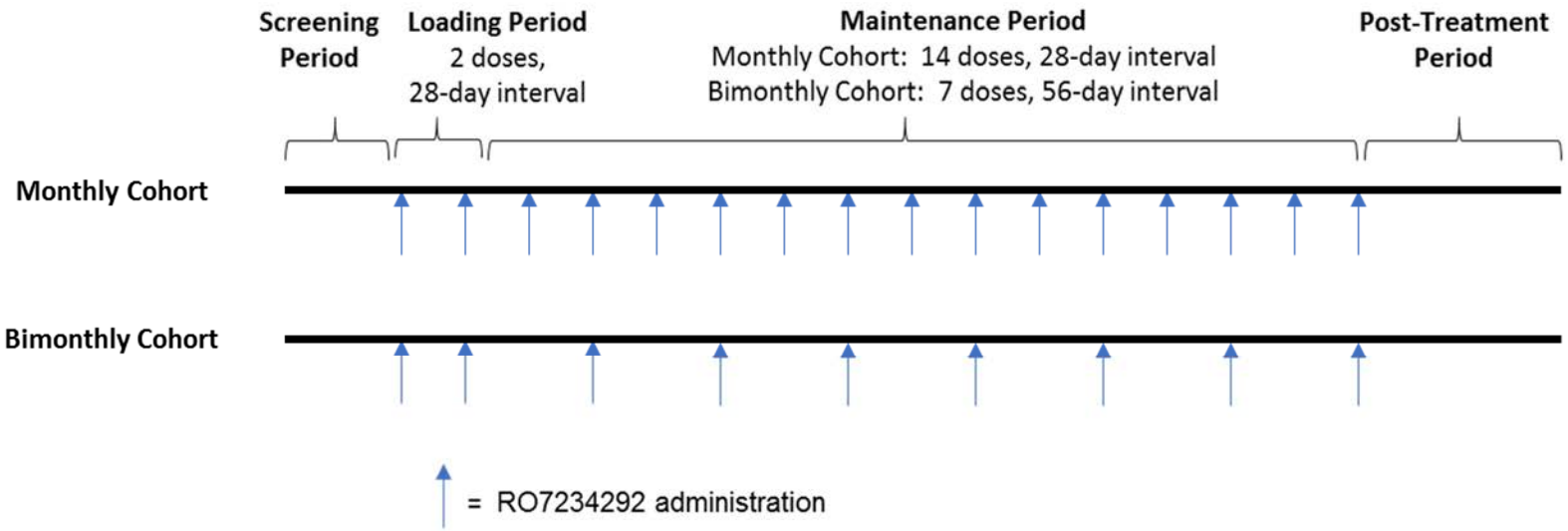
PROTOCOL SYNOPSIS *Continued*

Pharmacodynamic and Clinical Evaluations *Continued*	[redacted] Evaluations will include comparisons between Monthly and Bimonthly Cohorts, where appropriate, and correlations between pharmacokinetic and pharmacodynamic parameters.
Statistical Considerations	The sample size is dictated by the number of patients enrolled in the prior MAD study (Study ISIS 443139-CS1). Based on experience with generation 2 ASOs administered by IT injection, this number of patients (N ≈ 46) is expected to be sufficient to ensure that the safety, tolerability, pharmacokinetics and pharmacodynamics are adequately assessed.
Sponsor	*F. Hoffmann-La Roche Ltd*

STUDY DESIGN AND TREATMENT SCHEMA



COHORT DOSING REGIMENS



STUDY GLOSSARY

Abbreviation	Definition
2'-MOE	2'-*O*-(2-methoxyethyl)
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AP	Anterior-posterior
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
[redacted]	[redacted]
[redacted]	[redacted]
βhCG	Beta-subunit of human chorionic gonadotropin (pregnancy test)
Bimonthly	Every other month
BP	Blood pressure
BUN	Blood urea nitrogen
cl	clinic
[redacted]	[redacted]
CRF	Case report form
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
[redacted]	[redacted]
FSE	Fast spin echo
GCP	Good Clinical Practice
HD	Huntington's disease
HDID	*Huntington's disease identification number*
HDWF	Huntington's disease work function
Htt	Huntingtin / Htt protein
HR	Heart rate
[redacted]	[redacted]
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IL-1β	Interleukin-1 beta
[redacted]	[redacted]
IMP	*investigational medicinal product*
INR	International normalized ratio
IRB	Institutional Review Board
IT	Intrathecal(ly)
MAD	Multiple-ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
[redacted]	[redacted]
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCS	Not clinically-significant
[redacted]	[redacted]
[redacted]	[redacted]
OLE	Open-label extension
on Study	The patient is 'on Study' from signing of the informed consent until his/her last study visit
OTS	One touch stockings
pH	Measure of the acidity or basicity of a solution
ph	phone
PK	Pharmacokinetic(s)
PBA-s	Problems behavior assessment for Huntington's disease – short form
PT	Prothrombin time
qEEG	Quantitative EEG
RO7234292	Antisense inhibitor of *HTT, previously known as ISIS 443139*
[redacted]	[redacted]
RNase H1	Ribonuclease H1 (a non-specific endonuclease and catalyzes the cleavage of RNA via a hydrolytic mechanism)
[redacted]	[redacted]
SAE	Serious adverse event
siRNA	Small interfering ribonucleic acid

SAP	Statistical Analysis Plan
[redacted]	[redacted]
Study Day 1	Defined as the first day Study Drug is administered to the patient
Study Drug	*RO7234292 (previously known as ISIS 443139)*
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	Treatment-emergent adverse event
TFC	Total functional capacity
[redacted]	[redacted]
TMS	Total motor scale
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TSE	Turbo spin echo
UHDRS	Unified Huntington's disease rating scale
[redacted]	[redacted]
WBC	White blood cell
[redacted]	[redacted]

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the safety and tolerability of monthly and bimonthly (every other month) intrathecal (IT) bolus administrations of $RO7234292$ to patients with Huntington's disease (HD).

1.2 Secondary Objectives

To characterize the cerebrospinal fluid (CSF) pharmacokinetics of monthly and bimonthly IT doses of $RO7234292$.

To explore effects of monthly and bimonthly IT doses of $RO7234292$ on key pharmacodynamic biomarkers and clinical endpoints relevant to HD, including:

- Mutant huntingtin protein (mutant Htt) level in CSF
- Structural MRI (ventricular, caudate and whole brain volumes)
- Quantitative electroencephalography
- Assessments of physical functioning, activities of daily living, gait, balance, mobility, and cognitive functioning

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Overview of Disease

2.1.1 Epidemiology

Huntington's disease is an autosomal dominant neurodegenerative disease. The prevalence is approximately 5.7 per 100,000 in Europe and North America (Pringsheim et al. 2012), with the early onset/juvenile (Westphal variant or akinetic-rigid HD) form occurring in approximately 16% of all cases (Shoulson and Young 2011). Huntington's disease is caused by a CAG repeat expansion in the first exon of the *HTT* gene located on Chromosome 4 resulting in a polyglutamine expansion in the huntingtin protein (Htt). Above 35 CAG repeats, the age of HD onset is inversely correlated with the length of the expansion (Duyao et al. 1993). Variable age-dependent penetrance occurs between 36 and 39 CAG repeats, and full penetrance occurs at 40 or more repeats (Langbehn et al. 2004).

2.1.2 Huntingtin Protein

While the exact function of Htt protein has been elusive, studies suggest that it has an essential role in the earliest stages of embryogenesis (Duyao et al. 1995; Nasir et al. 1995; Zeitlin et al. 1995; White et al. 1997; Ismailoglu et al. 2014). Many pathogenic mechanisms have been hypothesized for the apparent toxic gain-of-function of this polyglutamine-expanded protein, including abnormalities in cellular proteostasis, altered gene transcription, mitochondrial dysfunction and oxidative stress, excitotoxicity, synaptic and neuronal failure, deficient axonal transport, spread of mutant Htt protein from cell-to-cell in a prion-like fashion and loss of trophic support (for reviews see Kuermmerle et al. 1999; Moumné et al. 2013; Ross et al. 2014). Mutant *HTT* messenger ribonucleic acid (mRNA) transcripts have also been shown to contribute to neuronal toxicity (Bañez-Coronel et al. 2012).

2.1.3 Clinical Features and Diagnosis of HD

Huntington's disease classically manifests with a triad of signs and symptoms, including motor, cognitive and behavioral features (Huntington 1872; Folstein 1989). Motor and cognitive symptoms, including chorea, dystonia, bradykinesia, rigidity and executive function deficits, usually progress over time (Huntington Study Group 1996; Hogarth et al. 2005; Paulsen et al. 2013; Papoutsi et al. 2014). Behavioral features, including emotional disorders and personality changes, are not universal and do not usually progress steadily over time (Ross et al. 2014).

Although genetic testing can be used to identify individuals who will develop the disease, the actual diagnosis of HD occurs when an expert clinician judges that the motor abnormalities observed are ≥ 99% likely due to HD or when the patient exhibits "the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder" (Huntington Study Group 1996; Hogarth et al. 2005). Motor onset is one of the more robust and consistently-agreed disease features among the considerable diagnostic heterogeneity of the disease. However, phenoconversion cannot be interpreted as a simple dichotomy between sick and unwell, as disease onset is really a process that occurs gradually over years or even decades. Neurodegeneration is evident in functional brain imaging studies in patients long before diagnosis, suggesting that the brain undergoes functional reorganization in response to neurodegeneration to preserve motor and cognitive performance (Papoutsi et al. 2014).

Individuals with HD can be categorized as having either premanifest disease (prior to motor symptom onset) or manifest disease (diagnosed based on motor symptom onset). The premanifest disease period can be subdivided into presymptomatic and prodromal periods. During the presymptomatic period, typically spanning 10-15 years prior to disease onset, individuals are not clinically distinguishable from controls (i.e., individuals without the HD gene mutation). During the prodromal period, subtle motor changes and variable cognitive and behavioral changes appear but are not sufficient to make the diagnosis of HD.

Manifest disease, the period of disease beginning at HD diagnosis, typically lasts for 10-20 years and is characterized by motor and cognitive changes that progress inexorably over the course of

the illness until death. The manifest disease period can be subdivided into 5 stages based on evolving changes in motor symptoms and 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, managing personal finances and ability to maintain employment; Stage 5 represents severe disability and dependence on full-time care (Shoulson and Fahn 1979). The 5 stages also correlate with score on the Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) Scale, with Stage 1 corresponding to TFC scores of 11-13, Stage 2 to scores of 7-10, Stage 3 to scores of 3-6, Stage 4 to scores of 1-2 and Stage 5 to a score of 0 (Shoulson et al. 1989). Early stage HD (Stage 1 and 2) is generally characterized by involuntary movements of the face, fingers, feet or thorax with progressive emotional, psychiatric and cognitive disturbances (Folstein 1989). Early neuropsychiatric symptoms include anxiety, apathy, disinhibited behavior, anhedonia, obsessive behaviors and irritability (Craufurd et al. 2001). The most frequent psychiatric symptom is depression, and HD patients are at an increased risk for suicidal ideation (Craufurd et al. 2001). Patients may experience weight loss, alterations in sexual behavior and disturbances in the wake-sleep cycle (Petersen et al. 2005). Less commonly, delusions and hallucinations emerge (Paulsen et al. 2001). As the disease progresses, cognitive impairments are marked by a decline in executive functioning affecting judgment, insight and the ability to organize, eventually impairing all aspects of cognition (Walker 2007; Roos 2010; Sturrock and Leavitt 2010). Motor disturbances in later stages of the disease include chorea, speech and swallowing difficulties, rigidity, bradykinesia and akinesia (Roos 2010). Oral motor dysfunction eventually leads to incoherence of speech and inability to eat (Sturrock and Leavitt 2010). Over time, relentless cognitive and physical deterioration forces patients to become dependent on full-time care. Pneumonia, followed by suicide, is the most common cause of death (Roos 2010).

2.1.4 Treatments for HD

Treatments for HD are limited. There are no therapies that can delay the onset of the disease or slow its progression, so current treatments aim to reduce the burden of symptoms, maximize function and benefit the patient's quality of life (Nance et al. 2011).

Symptomatic treatment options are tailored to the individual patient's symptoms and stage of disease progression, however patients with HD are highly vulnerable to side effects, particularly cognitive side effects, of medications.

Tetrabenazine (e.g., Xenazine®, Tetmodis®) and deutetrabenazine (Austedo™), vesicular monoamine transporter 2 inhibitors, are the only drugs currently approved for HD, with labels specific for the treatment of chorea associated with Huntington's disease. Tetrabenazine is approved in the United States, New Zealand, Australia, Canada, Israel and some European countries. Deutetrabenazine is approved in the United States. These drugs have been linked to many significant adverse events (AEs), including Parkinsonism, akathisia, sedation, depression and suicidal thoughts (Xenazine label 2011; Austedo label 2017). They are contraindicated in patients who are actively suicidal and in patients with untreated or inadequately treated

depression, a population that includes approximately > 40% of HD patients (Chen et al. 2012). Additionally, they may prolong the corrected QT interval, and caution is advised when used in combination with other drugs or medical conditions that potentially prolong the QTc.

Other medications are utilized in HD to address particular symptoms, such as antidepressants (for depression, agitation, irritability), anticonvulsants (for irritability, impulsive behavior), anxiolytics (for anxiety), cognitive enhancing agents (for cognitive disturbances) and neuroleptics (for chorea) (Paulson and Albin 2011). To date, no treatment has been shown to delay the onset of HD or to slow its progression.

2.2 Therapeutic Rationale

There are currently no treatments that cure or modify HD progression. Neuropathological abnormalities in HD appear to be the consequence of a toxic gain-of-function of the mutant huntingtin protein (mutant Htt) (Wexler et al. 1987; Walker 2007; Moumné et al. 2013). A therapy that reduces synthesis of the toxic mutant protein would directly target the primary disease mechanism. Because the genetic origin of HD is localized to just 1 gene, inhibiting *HTT* expression is a promising therapeutic option (Stanek et al. 2013).

$RO7234292$ is being developed to reduce the synthesis of Htt protein by targeting *HTT* mRNA and directing its catalytic degradation through the action of ribonuclease H1 (RNase H1), an endogenous enzyme present in most mammalian cells (Crooke and Bennett 1996; Cerritelli and Crouch 2009), including cells of interest in the CNS (e.g., neurons and glia). Reduction of mutant *HTT* gene mRNA, which limits translation of the mutant huntingtin protein, could potentially inhibit all downstream toxic effects and generate sustained reversal in HD symptoms.

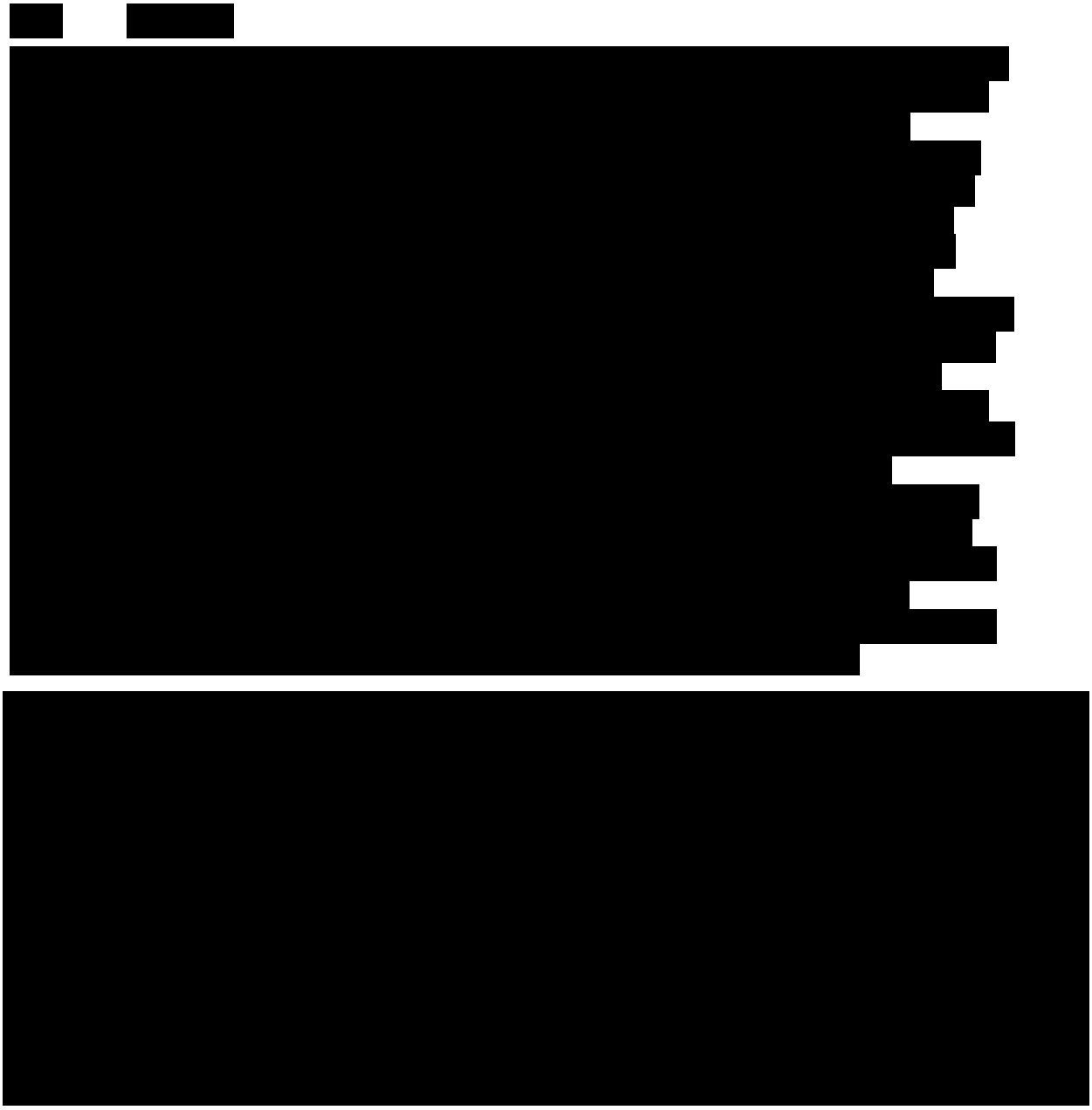
Pharmacology data support selective targeting of *HTT* mRNA transcripts as a potentially safe and effective mechanism for the treatment of HD. Using ASOs targeting human *HTT* mRNA in rodents and non-human primates, significant reduction of mutant *HTT* mRNA transcripts, wild-type *HTT* mRNA transcripts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

The known potential risks associated with $RO7234292$ are elaborated on in the Guidance to Investigator section of the Investigator's Brochure. Additional study associated risks related to the lumbar puncture (LP) procedure are also described in the Guidance to Investigator section of the Investigator's Brochure.

2.3 *RO7234292*

2.3.1 Mechanism of Action

RO7234292 is a second-generation antisense oligonucleotide drug targeted to the huntingtin gene (*HTT*). It is complementary to a nucleotide sequence in the *HTT* mRNA transcript and binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of *RO7234292* to the cognate mRNA results in the RNase H1-mediated degradation of the *HTT* mRNA, thus preventing production of the Htt protein. Both wild-type and mutant *HTT* mRNA are targeted by *RO7234292*.



[redacted]

2.3.4 Clinical Experience

A first-in-human, Phase 1 clinical study of $RO7234292$ is complete. In this study, the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple ascending doses of $RO7234292$ administered IT to patients with early manifest HD were assessed in a double-blind placebo-controlled manner. Based on data review by the Sponsor and the study's Data Safety Monitoring Board, available safety, PK and exploratory PD findings support initiation of Study $BN40697$, an open-label extension study for patients who participated in Study ISIS 443139-CS1.

2.4 Rationale for Study Design

The proposed study will test the safety, tolerability, PK and PD of multiple doses of $RO7234292$ administered as IT injections. Two (2) dose regimens will be evaluated. The dose utilized will not exceed the highest dose level found to be well-tolerated in the prior first-in-human study. The length of the Maintenance Period (56 weeks) was selected to provide sufficient duration for meaningful evaluation of imaging and clinical measures relevant to HD.

ISIS 443139 dose levels evaluated in the prior study, Study ISIS 443139-CS1, were 10, 30, 60, 90 and 120 mg/dose. These doses were selected based on preclinical toxicology and pharmacokinetic observations from monkey studies utilizing repeat dosing (for 13 weeks) IT administration and consideration of the target tissue concentration anticipated for drug pharmacology. [redacted]

The dose interval for the loading period (i.e., administration every 28 days) was selected based on the nonclinical pharmacokinetic and pharmacodynamic (*HTT* mRNA reduction) data required to achieve $RO7234292$ brain cortex tissue levels that are predicted to be at steady state by Day 92 and to achieve reduction in *HTT* mRNA levels. Monthly dosing is expected to be safe and well-tolerated by patients, and continued monthly dosing is predicted to produce prolonged suppression of *HTT* mRNA and Htt protein. Bimonthly dosing (after 2 monthly doses to serve as a load) will be investigated to determine if sufficient pharmacological effect can be achieved with a less-frequent dosing regimen.

Additional details on dose scaling and expected CSF and tissue concentrations are summarized in the Investigator's Brochure.

2.5 Risk Assessment

The known potential risks to study participants associated with IT administration of $RO7234292$ are elaborated on in the Guidance to Investigator section of the Investigator's Brochure.

In brief, there are no apparently deleterious effects associated with reduction of *HTT* mRNA in normal adult mice or adult non-human primate (McBride et al. 2008; Boudreau et al. 2009; Drouet et al. 2009; McBride et al. 2011; Kordasiewicz et al. 2012). No abnormal behavioral deficits appear to result from heterozygous *HTT* inactivation by translocation in man, i.e., a 50% reduction in expression of the normal gene product (Ambrose et al. 1994); and silencing of both mutant *HTT* and wild-type *HTT* appears to dramatically improve HD-related behavioral abnormalities in HD mice models (Kordasiewicz et al. 2012).

Intrathecal administration of $RO7234292$ requires lumbar puncture (LP), which is associated with known risk for post-LP injection syndrome (e.g., headaches, nausea, vomiting, nerve irritation pain). Headache is the most common symptom, affecting up to 5-30% of participants. Headache usually resolves spontaneously within a few days, but in a minority of patients the headache can persist for weeks if untreated (Vandam and Dripps 1956; Costigan and Sprigge 1996; Turnbull and Shepherd 2003). The very rare risk for events of infection (e.g., meningitis) and hemorrhage (e.g., spinal hematoma) following LP are mitigated by protocol inclusion/exclusion criteria and study procedures.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with $RO7234292$ are justified by the anticipated benefits that may be afforded to patients with HD.

3. EXPERIMENTAL PLAN

3.1 Study Design

This study is an OLE for patients who participated in Study ISIS 443139-CS1. Study ISIS 443139-CS1 was a multiple-ascending dose (MAD) study in 46 patients with early manifest HD aged 25-65 years, inclusive. In the MAD study, patients received 4 doses of ISIS 443139 or placebo. Eligibility for Study $BN40697$ is based on completion of the 4-dose Treatment Period of the prior MAD study and absence of deterioration in health or intervening activities that would introduce risk to the patient sufficient to preclude participation in the OLE.

The study consists of 2 cohorts: a "Monthly Cohort" and a "Bimonthly Cohort". Both cohorts receive 2 doses of $RO7234292$ during the Loading Period, with doses 28 days apart. In the Maintenance Period, the Monthly Cohort continues to receive doses at 28-day intervals (14 doses over 56 weeks) and the Bimonthly Cohort receives doses at 56-day intervals (7 doses over 56 weeks). Patients will be randomized (1:1) to either the Monthly Cohort of the Bimonthly Cohort, with randomization stratified by Study Center. The cohorts will be enrolled concurrently.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Up to 46 patients are planned to be enrolled in this study.

3.4 Overall Study Duration and Follow-up

The overall study duration will be approximately 18 calendar months. The study will consist of a 2-4-week Screening Period, a 6-week Loading Period, a 56-week Maintenance Period and a 12-week Post-Treatment Period $(for\ patients\ who\ will\ not\ enter\ the\ OLE\ Study\ BN40955)$. Please refer to the Schedule of Procedures in Appendix A.

Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Study Medical Monitor in consultation with the Investigator.

3.4.1 Screening Period

Patient eligibility for the study will be determined within 4 weeks prior to patient entry into the Treatment Period.

3.4.2 Treatment Period

Eligible patients will report to the Study Center for administration of *RO7234292* and for additional, non-dosing visits as described in the Schedule of Procedures in Appendix A. The Treatment Period consists of a 6-week Loading Period, in which all patients receive 2 doses of *RO7234292* at 28-day intervals, and a 56-week Maintenance Period, in which the Monthly Cohort receives doses at 28-day intervals (14 doses over 56 weeks) and the Bimonthly Cohort receives doses at 56-day intervals (7 doses over 56 weeks).

3.4.3 Post-Treatment Period

After completing study treatment in Study BN40697, the patient will be eligible to enroll in another OLE 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 meets approval by the relevant competent authorities, IRBs, and ECs.

Patients *who will not enter the OLE study* will return to the Study Center for one follow-up visit 14 weeks after the last dose of *RO7234292*. The final study visit will be *Study Day 428/Week 62 for patients who enter OLE Study BN40955 and* Study Day 519/Week 74 *for those patients who do not*.

3.5 End-of-Study

The End-of-Study is defined as last patient, last study visit.

4. PATIENT ENROLLMENT

4.1 Screening

Before patients may be enrolled into the Study, the Sponsor or designee requires a copy of the Study Center's written Independent Ethics Committee/Institutional Review Board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information and/or recruitment material.

Patients must sign the consent form before any screening tests or assessments are performed. At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening

procedures, are performed. Patients will also be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. Each patient will be assigned to the same screening and patient identification numbers as in the prior MAD study (Study ISIS 443139-CS1). The screening number and patient identification number must remain constant throughout the entire study. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2 Randomization

A patient will be randomized after all Screening assessments have been completed and after the Investigator has verified that the patient is eligible per criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

Eligible patients will be randomized centrally by an automated system to receive $RO7234292$ as part of the Monthly Cohort or the Bimonthly Cohort. Randomization between regimens (1:1) will be stratified by Study Center.

The Sponsor or designee will prepare the randomization list.

4.3 Replacement of Patients

Patients who withdraw from the study will not be replaced.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time point specified in the individual eligibility criterion listed.

5.1 Inclusion Criteria

Signed Written Informed Consent

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Must be capable of giving informed consent (in the opinion of the Investigator)

Target Population

3. Must have completed the Treatment Period of Study ISIS 443139-CS1
4. Able and willing to meet all study requirements in the opinion of the Investigator, including:
    a. Adequately supportive psychosocial circumstances
    b. Have a trial partner who is reliable, competent and at least 18 years of age, is willing to accompany the patient to select trial visits and to be available to the Study Center

by phone if needed, and who (in the opinion of the Investigator) is and will remain sufficiently knowledgeable of patient's ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to HDWF and PBA-s.

c. Able to undergo MRI scans and able to tolerate them (e.g., no metal implants including MRI incompatible IUDs, chorea of a severity that precludes MRI scans or any condition that renders testing intolerable for the patient)

d. Able to tolerate blood draws and lumbar puncture (LP)

e. Stable medical, psychiatric and neurological status for at least 12 weeks prior to Screening visit

Reproductive Status

5. Females must be non-pregnant, non-lactating and either

   a. surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy);

   b. post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved);

   c. abstinent* or,

   d. if engaged in sexual relations of child-bearing potential, agree to use highly effective contraception (refer to Section 6.3.1) from the time of signing the informed consent form until at least 5 months after the last dose of $RO7234292$

   If not surgically sterile, must have a negative HCG pregnancy test at Screening visit and prior to each dose administration

   Males must be surgically sterile, abstinent* or, if engaged in sexual relations with a female of child-bearing potential, must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 5 months after the last dose of $RO7234292$

   * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

5.2 Exclusion Criteria

Prohibited and Restricted Medications and Procedures

1. Treatment with an investigational drug (other than ISIS 443139 in Study ISIS-443139-CS1), biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer. Concurrent or planned concurrent participation in any clinical study (including observational and non-interventional studies) without approval of the Sponsor Medical Monitor
2. Antiplatelet or anticoagulant therapy within the 14 days prior to first lumbar puncture in the study or anticipated use during the study, including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban
3. Prior treatment with an antisense oligonucleotide including small interfering ribonucleic acid (siRNA) (other than ISIS 443139 in Study ISIS 443139-CS1)
4. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter

Medical History and Concurrent Disease

5. Clinically-relevant hematological, hepatic, cardiac or renal disease or event. Clinically-significant abnormal hepatic, renal or hematology lab tests at Screening must be discussed with the Sponsor Medical Monitor
6. Malignancy within 5 years of Screening, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated
7. Any condition that significantly increases risk of meningitis unless patient is receiving appropriate prophylactic treatment
8. History of bleeding diathesis or coagulopathy, platelet count < LLN *unless stable and assessed by the Investigator and Sponsor Medical Monitor to be not clinically significant*
9. Have any other condition which, in the opinion of the Investigator or Sponsor, would make the patient unsuitable for inclusion or could interfere with the patient participating in or completing the study

6. STUDY PROCEDURES

6.1 Study Schedule

All required study procedures are outlined in Appendices A, B and C. Additional patient visits may be scheduled if required for further evaluation of an abnormal laboratory value or a reported AE.

All reasonable attempts should be made to ensure compliance with the visit schedule and visit windows as outlined in Appendix A. However, in the event that a visit does not occur or is

delayed, all subsequent visits should be calculated based on the time elapsed since Study Day 1 rather than from the date of the previous visit.

6.1.1 Screening Period (Week -4 to Week -1)

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. During the Screening Period, inclusion/exclusion criteria will be evaluated to determine patient eligibility for the study. A single CSF sample will be collected during the Screening Period. At least 2 weeks must elapse between the screening CSF collection and Study Day 1. Abnormal laboratory screening results may be retested for review by the Study Medical Monitor for eligibility purposes.

6.1.2 Treatment Period (Week 1 to Week 62)

During the Loading Period, $RO7234292$ will be administered 2 times, with doses separated by 28 days. During the Maintenance Period, $RO7234292$ will be administered either every 28 days (Monthly Cohort) or every 56 days (Bimonthly Cohort) according to regimen assignment at randomization.

Eligible patients will report to the Study Center on Study Day -1 (the day prior to first $RO7234292$ administration) for baseline assessments. Assessments should be completed at approximately the same time of day from visit to visit. At the completion of assessments on Study Day -1, patients will be discharged unless the Investigator feels it is in the patient's best interest for him/her to remain in the Study Center overnight. Patients will return to the Study Center on Study Day 1 to undergo CSF sampling and $RO7234292$ administration via lumbar puncture, followed by overnight observation in the Study Center, safety assessments on Study Day 2 and then discharge. On Study Day 3, the Study Center will conduct a brief visit with the patients by phone to capture any AEs or changes in concomitant medication usage. (See Appendices A and C.) On Study Day 8, the patients will return to the Study Center for additional assessments.

Subsequent $RO7234292$ administrations will be conducted in a similar manner, with pre-dose assessments conducted either the day before or the day of $RO7234292$ administration, in-clinic observation of at least 5 hours after $RO7234292$ administration (longer or overnight if necessary for safety reasons) and in-clinic assessments or phone assessments on the days following $RO7234292$ administration.

All patients, regardless of cohort assignment, will appear at the Study Center at least every 4 weeks throughout the Treatment Period for routine monitoring.

6.1.3 Post-Treatment Period (Week 63 to Week 74) or Early Termination

After completion of the Treatment Period, patients $who\ do\ not\ enter\ the\ OLE\ Study\ BN40955$ will enter the 12-week Post-Treatment Period. This period consists of 1 Study Center visits during Week 74, as outlined in the Schedule of Procedures in Appendix A.

Patients who terminate early from the study for a reason other than withdrawal of consent should be encouraged to attend the final study visit (Study Day 519). This visit should be conducted approximately 14 weeks after last administration of $RO7234292$. (Also see Appendices A and C and Study Design and Treatment Schema.)

6.2 Study Assessments

All efforts should be made to adhere to a consistent order of assessments throughout the study. Patients should be permitted rest periods as needed to minimize testing fatigue.

6.2.1 Capacity to Consent

Patients' capacity to consent to participation in the study will be assessed using the Evaluation to Sign Consent tool (DeRenzo et al. 1998). This is a brief, 5-item questionnaire utilized by Study Center personnel during a targeted interview with the patient. The patient responses to the questionnaire will not be collected by the Sponsor and are intended only to guide Study Center personnel in their evaluation of each potential patient's capacity to consent.

6.2.2 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a structured tool to assess suicidal ideation and behavior. Four (4) 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 (C-CASA) and meets the criteria listed in the recent FDA draft guidance for assessment of suicidality in clinical trials (FDA Sept 2010). The C-SSRS will be used to assess eligibility for the study and to monitor the patients throughout the study.

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

6.2.3 Vital Signs Measurement

Vital signs are to be measured at visits indicated in Appendix A. Refer to the manufacturer's manual for proper operation, calibration, care and handling of the monitor. Select an appropriately sized BP cuff.

For each vital sign measurement, record the patient's position and the arm used for the measurement.

6.2.3.1 Seated Blood Pressure Measurement

Situate the patient in a quiet environment with feet flat on the floor, back against the chair and arm resting on a table or other support so that the midpoint of the cuff is at the level of the

heart. The patient must rest for at least 10 minutes in the seated position prior to measuring blood pressure (BP).

6.2.3.2 Standing Blood Pressure Measurement for Orthostatic Assessment

To assess for the presence of orthostatic hypotension, additional BP and pulse rate will be assessed at selected study visits (see Appendix A) or as needed at the discretion of the Investigator. After measurement of seated BP, the patient will change to a standing position. After 2 minutes of standing, BP and pulse rate will be measured 3 times, with each test separated by at least 1 minute from the prior test. If the diastolic BP readings from the 3 tests are not all within 5 mm Hg, 2 additional standing BP readings must be obtained (total of 5 BP readings), with each test separated by at least 1 minute from the prior test.

6.2.4 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be recorded at selected study visits (see Appendix A). The ECG will be performed in triplicate at the Screening visit only. A central ECG service will be utilized for reading all ECGs. Refer to the ECG Manual for proper operation, care and handling of the machine.

6.2.5 Physical Measurements (Height and Weight)

For measurements of body weight, the same weighing scales should be used to weigh a given patient throughout the study. Scales should be calibrated and reliable; scales should be zeroed just prior to each patient's weigh-in session. A patient should void just prior to being weighed. Weight should be recorded before a patient's meal (if applicable) and at approximately the same time of day at each visit. Patients should be minimally clothed (i.e., no shoes or heavy over-garments).

6.2.6 Physical/Neurological Examination

Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function and reflexes. Neurological examinations will be performed at the times/dates according to the schedule as shown in Appendix A (Schedule of Procedures).

6.2.7 Electrophysiological Assessments

Quantitative EEGs (qEEGs) will be performed to characterize cortical activity during the resting brain state, including quantification by standard measures such as alpha and delta power and the anterior-posterior (AP) gradient of relative alpha power. Huntington's disease patients have been shown to differ from healthy controls in these parameters, and relative alpha AP gradient loss is associated with lower total functional capacity and greater cognitive dysfunction (Hunter et al. 2010). QEEGs will be performed according to the schedule as shown in Appendix A (Schedule of Procedures).

6.2.8 Neuroimaging Assessments

Neuroimaging assessments will be conducted using a 3T MRI scanner, and scans must be reviewed locally by a trained radiologist.

A 3D T1-weighted structural MR scan will be used to quantitate whole brain, caudate and intraventricular volumes. In addition, the following scans will be performed: T2 flair, T2 star and T2 Fast Spin Echo (FSE)/Turbo Spin Echo (TSE).

[redacted]

[redacted]

6.2.13 HD Cognitive Battery

The HD Cognitive Battery was developed as a means of measuring cognitive dysfunction in late premanifest and early manifest HD patients (Stout et al. 2014). The 6 tests that comprise the battery were selected based on test sensitivity, practice effects, reliability, domain coverage, feasibility for use in clinical trials and tolerability. A composite cognitive score can be calculated by the average z-score of the 6 individual tests. [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.18 Collection of CSF

Patients will have CSF collected at the Screening Visit, prior to administration of each dose of $RO7234292$ and at the Post-Treatment Visit. At each collection, 20 mL of CSF fluid is to be collected for analyses. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 15 mL should be collected. A 24G atraumatic needle (Whitacre or other if approved by Sponsor prior to use) will be used. Depending on institutional guidelines, local anesthesia may be used for the procedure. Sedation may not be used. Spinal ultrasound may be used for the LP procedure, if deemed necessary, but is not required.

6.2.19 Laboratory Assessments

Samples for assessment of laboratory analytes will be collected throughout the study. A list of these analytes is contained in Appendix B.

6.2.19.1 Plasma and Serum Laboratory Assessments

Routine chemistry and hematology panels will be conducted as indicated in the Schedule of Assessments (Appendix A). [redacted] immunogenicity (anti-$RO7234292$ antibody assessment) will be conducted using samples collected as described in Appendices A and C.

[redacted]

For each scheduled lumbar puncture, local laboratory analysis of coagulation factors (prothrombin time [PT], International normalized ratio [INR] and activated partial thromboplastin time [aPTT]) and platelets must be conducted and results reviewed prior to performing the lumbar puncture. Collection for these local labs may occur at any time in the 72 hours prior to the lumbar puncture.

6.2.19.2 CSF Laboratory Assessments

CSF will be used for standard laboratory measurement of cells, glucose, protein and for $RO7234292$ pharmacokinetic analyses. CSF will also be used for evaluation of CSF biomarkers, shown in Appendix B.

Any CSF remaining after performing the planned analyses will be stored for investigation of possible biomarkers of HD; the pharmacodynamic effects of $RO7234292$; for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes) or to assess other actions of $RO7234292$ with CSF constituents.

6.2.19.3 Urine Laboratory Assessments

Urine will be collected for routine testing and for $RO7234292$ concentration analysis and pharmacokinetic analyses.

6.2.20 Pregnancy Testing

Pregnancy tests will be conducted in all female patients who are not surgically sterile, as shown in the Schedule of Assessments (Appendix A).

6.3 Restriction on the Lifestyle of Patients

6.3.1 Contraception Requirements

All male patients and women patients of childbearing potential must refrain from sperm/egg donation and practice effective contraception from the time of signing the informed consent form until at least 5 months after the last dose of $RO7234292$.

Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent through the end of the study.

For the purposes of this study, women of childbearing potential are defined as any female who has experienced menarche and does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral tubal occlusion, hysterectomy, bilateral salpingectomy or bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, effective contraception is defined as follows:

For male patients:

- Effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the $RO7234292$

For female patients:

- Surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or using 2 methods from signing ICF until at least 5 months after the last dose of $RO7234292$. The 2 methods should include at least 1, highly-effective barrier method (e.g., intrauterine device or any of the following in combination with spermicidal foam/gel/film/cream/suppository: male condom*, female condom*, diaphragm, sponge, cervical cap) and at least 1 other method (e.g., oral, injected or implanted hormonal methods).

For female partners of male patients:

- Using any of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy); oral, injected or implanted hormonal contraception; intrauterine contraception/device; or any 2 barrier methods (a combination of male or female condom* with diaphragm, sponge or cervical cap) together with spermicidal foam/gel/film/cream/suppository

***Note: A female condom and a male condom should not be used together as friction between the 2 can result in either or both products failing.**

6.3.2 Other Requirements

Patients should be encouraged to maintain consistency throughout the study with respect to smoking, caffeine consumption and alcoholic beverage consumption.

Patients who have a unique Huntington's disease identification number (HDID) will be asked to provide the number. If the patient does not have an HDID number, the number should be created via a web portal. The HDID is a nine-digit number created by a secure one-way algorithm, based on unchanging information (date of birth, birth name, place of birth, and mother's maiden name). The identifying data are used for the immediate generation of the HDID and are never stored electronically on the web portal or in the study database. The Investigator should store the original data and the HDID in the patient's source documents and in the Investigator file.

The HDID is a unique coded identifier for patients participating in Huntington's disease studies. A patient's HDID will remain the same for all studies. The use of such a unique identifier will ensure that patients are only enrolled once in large observational studies, including Enroll-HD, REGISTRY, COHORT, PREDICT, and TRACK-HD, and also will allow approved comparison and combination of data among studies (see Section 11.4).

7. STUDY DRUG

7.1 Study Drug Description

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

7.1.2 *Roche Study Drug Provision after Change in Sponsor (Protocol BN40697, Amendment 4 and Subsequent Versions)*

[redacted]

[redacted]

[redacted]

[redacted]

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

7.2 Packaging and Labeling

7.2.1 *Packaging and Labeling until Change in Sponsor (Original Protocol ISIS 443139-CS2 and Amendments 1–3)*

The Sponsor *(Ionis)* will provide the Investigator with packaged ISIS 443139 and diluent labeled in accordance with specific country regulatory requirements.

7.2.2 *Packaging and Labeling after Change in Sponsor (Protocol BN40697, Amendment 4 and Subsequent Versions)*

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

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

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of *RO7234292* provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

8.1 Study Drug Administration

RO7234292 dosing will occur at the Study Center. On administration days, each patient will undergo an LP procedure for collection of CSF (see Section 6.2.18) followed by a single IT bolus (1-3 minute) LP injection of *RO7234292*. A 24G atraumatic needle (Whitacre or other if approved by Sponsor prior to use) will be used, oriented with the opening rostral (toward the patient's head). The target site for needle insertion is the L3/L4 space but may be 1 segment above or 1-2 segments below this level, if needed. Depending on institutional guidelines, local anesthesia may be used for the LP procedure. Sedation may not be used. Spinal ultrasound may be used for the LP procedure, if deemed necessary, but is not required.

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for dose preparation and administration, including volume of administration. These instructions must be followed for each dose administration.

8.2 Other Protocol-Required Drugs

There are no other protocol required drugs. Depending on institutional guidelines, local anesthesia may be used for the LP procedure, following institutional procedures. Sedation may not be used.

8.3 Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures.

8.4 Treatment Precautions

Patients will be discouraged from resting supine after the lumbar puncture procedure and will be encouraged to mobilize immediately.

Throughout the study, patients will be monitored for post-LP headache and for any signs or symptoms of infection. The Study Manual will provide guidance for site personnel on differentiating between and managing treatment of pressure headaches and encephalitic/meningitic headaches.

Epinephrine for subcutaneous injection, diphenhydramine for intravenous injection and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be close to the location where the injection is being performed.

8.5 Safety Monitoring Rules

Please refer to the Guidance to Investigator section of the Investigator Brochure.

8.6 Stopping Rules

Please refer to Section 8.8 *and the current RO7234292 Investigator's Brochure. T*he Investigator should discuss significant concerns relating to individual patients with the *Sponsor* Medical Monitor to ensure that it is appropriate for the patient to continue in the study.

8.7 Adjustment of Dose and/or Treatment Schedule

For a given patient, no adjustment of dose is planned. If a situation prevents the dosing procedure (i.e., lumbar puncture) from being performed safely but discontinuation of *RO7234292* is not warranted, an adjustment in the dose schedule may be permitted at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Examples of situations where the dosing schedule may be altered include the following:

- If a clinically significant abnormality is observed in the laboratory tests conducted prior to lumbar puncture (protocol Section 6.2.19.1) that increases lumbar puncture-related risk to the patient, further lumbar punctures must be delayed to allow for investigation into the finding. Prior to resuming treatment, the Investigator and Medical Monitor must agree to resume dosing.
- If patient is experiencing a concurrent illness that increases lumbar puncture-related risk to the patient, such as a skin infection near the area for injection, further lumbar punctures must be delayed until Investigator and Medical Monitor agree to resume dosing.

8.8 Discontinuation of Study Drug

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of *RO7234292*

The reason for discontinuation of Study Drug must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Patients who terminate early from the study during the Treatment Period (for reason other than withdrawal of consent) should be encouraged to complete the Study Day 519/Study Week 74 visit. This visit should be conducted approximately 14 weeks after last administration of *RO7234292*. (Also see Appendices A and C and Study Design and Treatment Schema.)

8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request.

For patients withdrawn from the study during the Treatment Period for reasons other than withdrawal of consent, every effort should be made to encourage the patient to participate in the Week 74 visit as an Early Termination Visit. This visit should be conducted approximately 14 weeks after last administration of *RO7234292*.

8.10 Access to Treatment after Study Completion

The Sponsor will offer continued access to Roche investigational medicinal product (IMP) (RO7234292) free of charge to eligible patients in accordance with the Roche

Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (RO7234292) after completing Study BN40697 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 Study BN40697 if any of the following conditions are met:

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

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

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

Patients may be eligible to receive Roche IMP (RO7234292) as part of an extension study, as described in Section 3.4.3.

8.11 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. AEs related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.11.1 Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between date of first dose of *RO7234292* and end of study.

Patients should consult with the Site Investigator or qualified designee prior to initiating any new medication, including non-prescription compounds or any other non-drug therapy.

Allowed Concomitant Therapy

Throughout the study, Site Investigators or designated licensed physicians involved in the study may prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care.

In addition, the following therapies are permitted:

- Contraceptive agents, as described in Section 6.3.1
- Supplements (e.g., coenzyme Q10, vitamins, creatine) if at a stable dose for at least 6 weeks prior to Screening and dosage is not anticipated to change during the study
- Antipsychotics (only if prescribed for motor symptoms or as a mood stabilizer) and/or tetrabenazine/deutetrabenazine if at a stable dose for at least 12 weeks prior to Screening and the dose is not anticipated to change during the study
- Antidepressant or benzodiazepine if at a stable dose for at least 12 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study
- Aspirin at doses ≤ 81 mg/day
- Depending on institutional guidelines, local anesthesia may be used for the lumbar puncture procedure. Sedation may not be used.
- Anti-anxiety medication use for imaging-related anxiety is prohibited during the Screening Period and strongly discouraged during scheduled scans in the Post-Treatment Period. If anti-anxiety medication is used for a Post-Treatment scan, the scan must be performed at the end of the assessment day or, preferably on a different day, so as not to impact other assessments.

Disallowed Concomitant Therapy

Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental doses that are being tested for the treatment of HD. The following agents are specifically prohibited:

- Antipsychotics unless prescribed for motor symptoms or mood stabilization (not psychosis) and at a stable dose for at least 12 weeks prior to Screening and the dose is not anticipated to change during the study
- Cholinesterase inhibitors
- Memantine
- Amantadine

- Tetrabenazine or deutetrabenazine unless at a stable dose for at least 12 weeks prior to Screening and the dose is not anticipated to change during the study
- Riluzole
- Supplements (e.g., coenzyme Q10, vitamins, creatine) unless at a stable dose for at least 6 weeks prior to Screening and the dose is not anticipated to change during the study
- Antidepressant or benzodiazepine use unless stable dose for at least 12 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study
- Antiplatelet or anticoagulant therapy including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban
- Sedation is not permitted for any procedures in the study

8.11.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between date of first dose of $RO7234292$ and End-of-Study.

8.12 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded in the CRF by Study Center staff.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the Safety Management Plan throughout the conduct of the clinical trial.

9.2 Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations.

The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that the $RO7234292$ caused the AE and, therefore, meets the definition of a SUSAR.

9.3 Definitions

9.3.1 Adverse Event

An adverse event is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product.

9.3.2 Adverse Reaction and Suspected Adverse Reaction

An adverse reaction is any AE caused by the Study Drug.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3 Serious Adverse Event (SAE)

A serious adverse event is any AE that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do

not result in inpatient hospitalization, or the development of drug dependency or drug abuse

9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the Study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible.

9.4.1 Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period which is defined as Study Day 519 $or\ the\ time\ of\ enrollment\ in\ OLE\ Study\ BN40955$. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. An Initial Serious Adverse Event Form should be completed and a copy should be faxed to the Sponsor or designee. The fax number for reporting SAEs can be found in the Study Reference Manual.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2 Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period, which is defined as Study Day 519 $or\ the\ time\ of\ enrollment\ in\ OLE\ Study\ BN40955$. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

9.4.3.1 Relationship to the Study Drug

The event's relationship to the $RO7234292$ is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and $RO7234292$ administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to $RO7234292$ administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

9.4.3.2 Severity

For laboratory AEs, the severity should be indicated according to Appendix D, which is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) guidelines, Version 4.03.

For AEs not listed in Appendix D, the event's severity is characterized by 1 of the following:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient 's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

9.4.3.3 Action Taken with Study Drug

Action taken with $RO7234292$ due to the event is characterized by 1 of the following:

- **None:** No changes were made to $RO7234292$ administration and dose
- **Permanently Discontinued:** $RO7234292$ was discontinued and not restarted
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose

9.4.3.4 Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.3.5 Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

9.5 Procedures for Handling Special Situations

9.5.1 Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically-significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents.

9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the Study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the Study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3 Dosing Errors

RO7234292 dosing errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of *RO7234292* that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

Should an overdose occur, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4 Contraception and Pregnancy

Patients must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the Study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the Study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with $RO7234292$. However, the patient will be encouraged to complete the post-treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested for the mother and infant. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Subsets, and Covariates

There is no single primary endpoint for this study. Important endpoints that will be evaluated are identified in the following sections.

10.1.1 Safety and Tolerability Endpoints

- Columbia - Suicide Severity Rating Scale (C-SSRS)
- Physical examination and standard neurological assessment (including fundi)
- Pregnancy testing
- Vital signs (heart rate [HR], BP, orthostatic changes, weight)
- ECG
- AEs and concomitant medications
- CSF safety labs (cell counts, protein, glucose)
- Plasma laboratory tests (clinical chemistry, hematology)
- Urinalysis
- Safety neuroimaging assessments

10.1.2 Pharmacokinetic Endpoints

[redacted] CSF elimination half-life and trough drug levels will be assessed, where appropriate. Urinary excretion parameters such as amount of drug excreted and renal clearance will be determined, as appropriate.

10.1.3 Pharmacodynamic and Clinical Endpoints

- Biochemical
  - CSF levels of mutant Htt, [redacted]
  - [redacted]
- Neuroimaging volumes, including but not limited to:
  - Structural MRI
    - Caudate volume
    - Whole brain volume
    - Ventricular volume
  - [redacted]
- Electrophysiological
  - qEEG
- Clinical
  - [redacted]
  - Cognitive and motor tests:
    - HD Cognitive Battery
      - [redacted]

10.2 Sample Size Considerations

The sample size is dictated by the number of patients enrolled in the prior MAD study (Study ISIS 443139-CS1). Based on experience with generation 2 ASOs administered by IT injection, this number of patients (N ≈ 46) is expected to be sufficient to ensure that the safety, tolerability, pharmacokinetics and pharmacodynamics are adequately assessed.

10.3 Populations

Safety Population: All patients who are randomized and receive at least 1 dose of $RO7234292$.

Per Protocol Population: All patients who are randomized and receive all protocol-specified doses of $RO7234292$.

PK Population: All patients who are randomized to $RO7234292$ and receive at least 1 dose of $RO7234292$ and have sufficient sampling to permit pharmacokinetic evaluation.

10.4 Definition of Baseline

For vital signs (BP, HR, respiration rate and temperature), baseline will be defined as the average of the values collected prior to first dose (Screening, Study Day -1 and Study Day 1). For CSF laboratory tests, baseline will be defined as the average of the values collected prior to first dose (Screening and Study Day 1). For all other measures and parameters, baseline will be defined as the last non-missing measure prior to the first dose.

10.5 Interim Analysis

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

10.6 Planned Methods of Analysis

All CRF data, lab data transfers, and any outcomes derived from the data will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, comparisons between regimens may be conducted and p-values may be reported. Statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated in the Statistical Analysis Plan (SAP).

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by regimen. Patient disposition will be summarized by regimen. All patients enrolled will be included in a summary of patient disposition.

10.6.2 Safety Analysis

The safety analysis will be conducted on the Safety Population.

Treatment duration and amount of $RO7234292$ received will be summarized by regimen.

All treatment-emergent adverse events (TEAEs) and SAEs will be summarized for each regimen and for all patients using the Medical Dictionary for Regulatory Activities (MedDRA) coding system by system organ class, preferred term, relationship to Study Drug, and severity.

Narratives of “on-study” deaths, serious and significant AEs, including early withdrawals due to AEs, will be provided.

Laboratory tests to ensure patient safety including chemistry panel, hematology panel, CSF safety labs (cell counts, protein, glucose) and urinalysis, will be summarized by study visit for each regimen. These safety variables will also be presented as change and percent change from baseline over time, as appropriate.

Vital sign and ECG measures will be tabulated by regimen. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by regimen.

Columbia – Suicide Severity Rating Scale will be summarized by study visit for each regimen. Physical examination, standard neurological assessment (including fundi), and clinical and neuroimaging results will be summarized, if appropriate, and listed.

10.6.3 Pharmacokinetic Analysis

The pharmacokinetic analysis will be conducted on the PK Population.

The CSF concentrations will be summarized using descriptive statistics and the *RO7234292* half-life in CSF will be calculated, if possible.

[redacted]

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Additional details regarding the PK analysis will be described in the SAP.

10.6.4 Pharmacodynamic and Clinical Analysis

The analyses of pharmacodynamic and clinical endpoints will be conducted on the Per Protocol and Safety Populations.

These evaluations will be summarized using descriptive statistics by study visit and regimen. Change and percent change from baseline over time will be summarized as appropriate. Comparison between regimens may be performed.

Additional analyses to investigate the relationship between the disease burden score (i.e., calculated from patients' age and CAG repeat length, CAG_n, using the formula: (CAG_n - 35.5) x age) and these endpoints may be performed as where deemed appropriate.

Details will be described in the SAP.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

Huntington's disease is known to cause behavioral changes, and patients who wish to participate in this study may have disturbances in judgment and decision-making (Walker 2007). During the consent process, the Investigator must carefully evaluate the patient's capacity to consent. To facilitate this evaluation, the Evaluation to Sign Consent questionnaire will be administered (DeRenzo et al. 1998). In cases where the Investigator is uncertain as to whether the patient possesses capacity to consent, the patient should be referred to an independent expert for further assessment of capacity. A prospective patient's consent will be sought only if

he or she demonstrates during the consent process an adequate level of understanding of the study, its requirements and its risks.

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor or designee.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or $RO7234292$ is administered. The patient must be given sufficient time to consider whether to participate in the study. Consent for genetic testing within the study will be obtained separately from consent for participation in the other aspects of the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2 Ethical Conduct of the Study

The Guidelines of the World Medical Association Declaration of Helsinki dated October 2002 the applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements will be strictly followed.

11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent/assent forms, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor or designee before recruitment of patients into the Study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of patients into the Study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the Study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRFs) or other documents submitted to the Sponsor or designee, patients should be identified by initials, if permitted by local law, and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. Linking of data will be facilitated by the HDID number (see Section 6.3.2).

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

12.2 Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, eCRFs may not be used as source documents.

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the CRFs at regular intervals throughout the Study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research.

The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this Study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period	Screen	Treatment Period (62 weeks)												Post-Treatment Period** (12 weeks)
		Loading Period (6 weeks)									Maintenance Period[1] (56 weeks)			
Study Week	**-4 to -1**	**1**				**2**	**5**			**6**	**7-62**			**74/ET**
Study Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**8**	**28**	**29**	**30**	**36**	**57, 85, … 421**	**58, 86, … 422**	**64, 92, … 428**	**519**
Visit Window (days)*	**-**	*	**0**	*	*	**±2**	*	**±5**	*	**±2**	**±5**	*	**±2**	**±21**
Visit Type (cl = clinic, ph = phone)	**cl**	**cl**	**cl**	**cl**	**ph**	**cl**	**cl**	**cl**	**ph**	**ph**	**cl**	**ph**	**ph**	**cl**
Overnight Stay			X →											
Capacity to Consent Assessment and Informed Consent	X													
Inclusion/Exclusion	X													
Medical History	X													
Vital Signs (BP, HR, RR, T)	X[2]	X	X[a]	X		X	X	X[a]			X[a]			X
Orthostasis	X[2]		X[b]											X
Physical and Neurological Exam[3]	X[2]	X	X[a]	X[c]		X	X	X[a]			X[a]			X
Height	X													
Body Weight	X[2]	X					X				X			X
C-SSRS[4]	X	X	X[b]	X		X	X	X[b]			X[b]			X
Pregnancy Test[5]	X[2]	X					X				X[b]			X
FSH	X[5]													
Chemistry, Hematology, Urinalysis	X[6]	X					X				X[b]			X
24-hour urine collection[7]			X →											
Serum Biomarker Sample	X[6]	X					X				X[b]			X
PT, INR, aPTT	X[6]	X					X				X[b]			X
Archived Serum Sample[8]	X[6]	X					X				X[b]			X

Appendix A Schedule of Procedures *Continued*

Study Period	Screen	Treatment Period (62 weeks)												Post-Treatment Period** (12 weeks)
		Loading Period (6 weeks)									Maintenance Period[1] (56 weeks)			
Study Week	**-4 to -1**	**1**				**2**	**5**			**6**	**7-62**			**74/ET**
Study Day	**-29 to -2**	**-1**	**1**	**2**	**3**	**8**	**28**	**29**	**30**	**36**	**57, 85, … 421**	**58, 86, … 422**	**64, 92, … 428**	**519**
Visit Window (days)*	**-**	*****	**0**	*****	*****	**±2**	*****	**±5**	*****	**±2**	**±5**	*****	**±2**	**±21**
Visit Type (cl = clinic, ph = phone)	**cl**	**cl**	**cl**	**cl**	**ph**	**cl**	**cl**	**cl**	**ph**	**ph**	**cl**	**ph**	**ph**	**cl**
Local PT, INR, aPTT, Platelets[9]	X	X					X[b]				X[b, 10]			X
Thyroid Panel		X					X				X[b]			X
[redacted]														
Plasma Sampling for Immunogenicity Testing			X[b]					X[b]			X[b]			X
CSF Sample for PK/Safety/Biomarkers/Archive	X[11]		X[b]					X[b]			X[b, 10]			X
[redacted]														
ECG (12-lead; in Triplicate at Screening Visit Only)	X[6]	X		X							X[b, 14]			X
qEEG	X[13]										X[b, 14]			X
Structural MRI	X[13]										X[b, 14]			X[15]
T2 flair, T2 star, T2 FSE/TSE MRI	X[13]										X[b, 14]			X[15]
[redacted]														
[redacted]														
RO7234292 Administration			X					X			X[10]			
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures *Continued*

Note: If not specifically labeled, "X" means anytime; ET = early termination

* All visits windows are calculated relative Study Day 1, i.e., the date of first dose administration in this protocol. Visits with an asterisk (*) do not have a visit window and must be conducted on the exact day shown relative to the corresponding dosing day.

** *Only patients who do not enter the open-label extension study (Study BN40955) will attend the Post-Treatment/End-of-Study visit.*

1 Patients are randomized to the Monthly Cohort or the Bimonthly Cohort. Patients in the Monthly Cohort receive *RO7234292* every 28 days during the Maintenance Period (14 doses in the Maintenance Period). Patients in the Bimonthly Cohort receive *RO7234292* every 56 days during the Maintenance Period (7 doses in the Maintenance Period). Study visits are shown below.

Monthly Cohort Study Visits during the Maintenance Period:

Study Weeks	Study Visit Day (Clinic Visit)	*RO7234292* Dosing Visit?	Day After Dosing Visit (Phone Visit)	Seven Days After Dosing Visit (Phone Visit)
9/10	57	Y	58	64
13/14	85	Y	86	92
17/18	113	Y	114	120
21/22	141	Y	142	148
25/26	169	Y	170	176
29/30	197	Y	198	204
33/34	225	Y	226	232
37/38	253	Y	254	260
41/42	281	Y	282	288
45/46	309	Y	310	316
49/50	337	Y	338	344
53/54	365	Y	366	372
57/58	393	Y	394	400
61/62	421	Y	422	428

Appendix A Schedule of Procedures *Continued*

Bimonthly Cohort Study Visits during the Maintenance Period:

Study Weeks	Study Visit Day (Clinic Visit)	*RO7234292* Dosing Visit?	Day After Dosing Visit (Phone Visit)	Seven Days After Dosing Visit (Phone Visit)
9/10	57	N		
13/14	85	Y	86	92
17/18	113	N		
21/22	141	Y	142	148
25/26	169	N		
29/30	197	Y	198	204
33/34	225	N		
37/38	253	Y	254	260
41/42	281	N		
45/46	309	Y	310	316
49/50	337	N		
53/54	365	Y	366	372
57/58	393	N		
61/62	421	Y	422	428

2 If the Screening visit is conducted on the same day as the patient's last visit in Study ISIS 443139-CS1 and this assessment was performed at that visit, this assessment does not need to be performed separately for Study *BN40697* (i.e., the result from the patient's last visit in Study ISIS 443139-CS1 may serve as the Screening result for Study *BN40697*).

3 Full physical and neurological exam (including fundi) to be given at Screening and abbreviated physical (but full neurological) exam to be given during Treatment and Post-Treatment Periods as indicated to assess changes from Screening.

4 The C-SSRS must be administered on the study days shown. It may also be administered at any time that the Investigator feels is necessary. At the Screening visit, the "Baseline/Screening" version of the C-SSRS must be administered, capturing patient's suicidal ideation and behavior over the prior year. In some cases, this collection period will overlap with the time period captured in Study ISIS 443139-CS1. If the Screening visit is conducted on the same day as the patient's last visit in Study ISIS 443139-CS1, then 2 forms must be completed: the "Since Last Visit" C-SSRS must be completed for Study ISIS 443139-CS1, and the "Baseline/Screening" C-SSRS much be completed for Study *BN40697*. In this situation, it is expected that a single interview with the patient will yield sufficient information to complete the C-SSRS forms for both studies.

5 Women who are not surgically sterile. Serum pregnancy at Screening visit (unless result from the patient's last visit in Study ISIS 443139-CS1 serves as the Screening result for Study *BN40697*); dipstick at post-screen visits.

6 If the Screening visit is conducted within 4 weeks of the patient's last visit in Study ISIS 443139-CS1 and this assessment was performed at that visit, this assessment does not need to be performed separately for Study *BN40697* (i.e., the result from the patient's last visit in Study ISIS 443139-CS1 may serve as the Screening result for Study *BN40697*).

7 Ensure patient has voided bladder prior to start of *RO7234292* administration procedure. Start 24-hour urine collection immediately after *RO7234292* administration. Pool and record total urine volume.

8 Stored at -80 °C for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies) in this or subsequent clinical studies of *RO7234292*.

9 Local laboratory analysis of PT, INR, aPTT and platelets must be conducted and results reviewed prior to performing the lumbar puncture. Sample collection may occur at at any time within 72 hours prior to the planned lumbar puncture.

10 Only at dosing visits. (See tables in Footnote 1.)

11 Screening CSF sample collected at least 2 weeks prior to Study Day 1. Screening sample is for Safety/Biomarkers/Archive only.

[redacted]

13 If the Screening visit is conducted within 3 months of the patient's last visit in Study ISIS 443139-CS1 and this assessment was performed at that visit, this assessment does not need to be performed separately for Study *BN40697* (i.e., the result from the patient's last visit in Study ISIS 443139-CS1 may serve as the Screening result for Study *BN40697*).

14 This assessment is conducted on Study Days 85, 253 and 421 only. If necessary for ease of logistics, the assessment may be performed on a different calendar day than the dose administration (must be prior to the dose administration and within the required visit window).

15 If imaging is conducted after CSF collection, at least 1 day must elapse between the LP and the imaging session to avoid LP-related artifacts on the images.

[redacted]

Time (in reference to time of *RO7234292* administration):

a Pre-dose; also 3 and 5 hours after administration of *RO7234292* (3- and 5-hour assessments are only performed if *RO7234292* has been administered)

b Pre-dose at dosing visits (otherwise, at any time during the visit)

c Approximately 24 hours after administration of *RO7234292*

d Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours after administration of *RO7234292*

e On Study Day 197: samples collected pre-dose and 0.5, 1, 2, 3, 4 and 5 hours after administration of *RO7234292*. On all other Study Days (57, 85, … 421): 1 sample collected pre-dose (if *RO7234292* will be administered at the visit) or anytime during the visit (if *RO7234292* will not be administered at the visit)

Appendix B List of Laboratory Analytes

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of *RO7234292* or other similar oligonucleotides.

Clinical Chemistry

- Sodium
- Potassium
- Chloride
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Bicarbonate
- Glucose
- BUN
- Creatinine
- Total serum Bilirubin
- Uric acid
- Alkaline phosphatase
- AST (SGOT)
- ALT (SGPT)
- GGT
- CPK

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- Platelets
- MCV, MCH, MCHC
- White blood cells (WBC)
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Urinalysis

- Specific gravity
- pH
- Protein
- P/C ratio
- Glucose
- Ketones
- Urobilinogen
- Leukocyte esterase
- Nitrite
- Bilirubin
- Blood
- Red blood cells
- WBC
- Epithelial cells
- Bacteria
- Casts
- Crystals
- Color
- Appearance

Thyroid Panel

- TSH
- Free T4
- Free T3

Coagulation

- aPTT
- PT
- INR

Screening Tests

- FSH (women only)
- Serum βhCG

PK[1]

- CSF *RO7234292* levels
- Urine *RO7234292* levels
- Anti-*RO7234292* antibodies

Pregnancy

- Urine hCG

CSF Biomarker Panel

- mu Htt

Appendix B List of Laboratory Analytes *Continued*

1 Any of the collected PK [redacted], CSF and urine samples from the study patients may also be used by *Sponsor* for investigation of possible biomarkers of disease or the pharmacodynamic effects of *RO7234292* or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes) or to assess other actions of *RO7234292* with [redacted] CSF or urine constituents. Also, if a relationship between genetic markers and disease progression becomes apparent during the study or within 5 years after the end of the study, the genetic markers may be identified in archived samples for investigation of association with drug effect.

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

Study Period	Treatment Period (62 weeks)						Post-Treatment Period or Early Termination Visit** (12 Weeks)
	Loading Period (6 weeks)			Maintenance Period (56 Weeks)			
Study Week	**1**		**5**	**9-28**	**29**	**30-62**	**74**
Study Day	**1**	**2**	**29**	**57, 85, 113, 141, 169**	**197**	**225, 253, 281, 309, 337, 365, 393, 421**	**519**
CSF Sampling	Pre-dose	--	Pre-dose	Pre-dose †	Pre-dose	Pre-dose †	Anytime
[redacted]							
Urine Sampling	24-hour collection	--	--	--	--	--	--

† Pre-dose at dosing visits only. (See tables in Appendix A, Footnote 1.)

‡ Pre-dose at dosing visits; otherwise, sample to be collected at any time during the visit.

** *Only patients who do not enter the open-label label extension study (Study BN40955) will attend the Post-Treatment/End-of-Study visit.*

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010.

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 D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

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

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

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)