This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

ISIS PHARMACEUTICALS, INC.

ISIS 443139-CS1

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Original Protocol – 6 March 2015

EudraCT No: 2015-000381-66

Sponsor:

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

ISIS 443139-CS1

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PPD

PPD MD
Vice President, Clinical Development

ISIS 443139

Isis Protocol Number ISIS 443139-CS1

Original Protocol

EudraCT No: 2015-000381-66

Clinical Phase: 1/2a

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

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Date: 6 March 2015

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 443139-CS1
Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease
Amendment:	Original Protocol
Date:	6 March 2015

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease," dated 6 March 2015, and agree to conduct the Study as described herein.

I agree to comply with the International Conference on Harmonization 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 Isis Pharmaceuticals, Inc.

_____

Investigator's Signature

_____ _____

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease
Study Phase	Phase 1/2a
Primary Objectives	To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 443139 to patients with Huntington's disease (HD)
Secondary Objectives	To characterize the cerebrospinal fluid (CSF) pharmacokinetics of ascending dose-levels of multiple IT administrations of ISIS 443139
Exploratory Objectives	To explore effects of multiple doses of ISIS 443139 on pharmacodynamic biomarkers and clinical endpoints relevant to HD. Plasma pharmacokinetic properties will also be assessed.
Study Design	ISIS 443139-CS1 is a multi-center, Phase 1/2a, randomized, double-blind, placebo-controlled study of ascending dose levels of multiple IT administrations of ISIS 443139 ("slow push" IT bolus) in patients with early manifest HD aged 25-65 years, inclusive. Four dose level cohorts (A, B, C and D) will be enrolled sequentially, with patients randomized to Study Drug or to placebo in a 3 to 1 ratio. Cohort A will comprise 4 patients, Cohorts B and C will comprise 8 patients and Cohort D will comprise 16 patients. All patients will be disease "Stage 1" out of a possible five stages, where 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. These stages also correlate with scores on the 13-point UHDRS Total Functional Capacity (TFC) Scale, with Stage 1 corresponding to TFC scores of 11-13. Randomization in Cohort D will be stratified by early Stage 1 (TFC ≥ 12) or late Stage 1 (TFC = 11) disease. Each patient will receive 4 doses of Study Drug with a 28-day interval between doses. Patients not completing a course of 4 IT bolus injections may be replaced up to a limit of 25% of the cohort sample and only if the reason for premature discontinuation from the Treatment Period does not involve a dose-limiting toxicity (DLT). Following the 3-month Treatment Period, there will be a 4-month Post-treatment Period. After study completion, an open-label extension study of ISIS 443139 will be implemented if this is warranted based on review of safety, tolerability, pharmacokinetic and exploratory pharmacodynamic findings.
Number of Patients	Approximately 36 patients will be enrolled in this study. The number of patients enrolled may be higher if some patients need to be replaced and/or if the sizes of certain cohorts are expanded to obtain further experience with particular dose levels. A maximum of 48 patients may be enrolled.
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 2. Must be capable of giving informed consent (in the opinion of the Investigator) *Target Population* 3. Early manifest, Stage 1 HD (defined as TFC of 11-13, inclusive), aged 25 to 65 years, inclusive, at the time of informed consent, with genetically confirmed disease (CAG repeat length ≥ 36 in huntingtin gene by direct DNA testing) 4. Body Mass Index (BMI) ≥ 18 and ≤ 32 kg/m^2; total body weight > 50 kg (110 lbs)

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	5. Able and willing to meet all study requirements in the opinion of the Investigator, including travel to Study Center, procedures, measurements and visits, 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 and at the time of enrollment f. Patients must reside in a proximity to the Study Center that permits prompt appearance at the facility if requested by the Investigator (maximum of 4-hour travel to Study Center) *Reproductive Status* 6. 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 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo) If not surgically sterile, must have a negative β-HCG pregnancy test at Screening and prior to each dose administration 7. 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 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo) **Exclusion Criteria:** *Target Disease-Related Exclusions* 1. Any condition, including severe chorea, that would prevent either writing or performing rapid computer tasks *Physical, Mental and Laboratory Test Findings* 2. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 12 months prior to Screening. For patients with (i) a suicide ideation score ≥ 4 on the Columbia Suicide Severity Rating Scale (C-SSRS) within the last 12 months, (ii) a score of 3 or 4 on question 2 of the Problems Behavior Assessment for Huntington's Disease – short form or (iii) suicidal behaviors within the last 12 months (as measured by the answer "Yes" on any of the C-SSRS Suicidal Behavior Items), a risk assessment should be done by an appropriately-qualified mental health professional (e.g., a Psychiatrist or licensed Clinical Psychologist) to assess whether it is safe for the patient to participate in the study. In addition, patients deemed by the Investigator to be at significant risk of suicide, major depressive episode, psychosis, confusional state or violent behavior should be excluded

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	3. Clinically significant laboratory, vital sign or ECG abnormalities at Screening (including heart rate (HR) < 45 bpm; SBP < 90 mmHg; confirmed BP readings > 170/105 mmHg) 4. Positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B at Screening *Prohibited and Restricted Medications and Procedures* 5. Treatment with another investigational drug, biological agent, or device within one 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 6. Current or recent (within the last 6 months) use of antipsychotics (prescribed for psychosis), cholinesterase inhibitors, memantine, amantadine or riluzole. Stable use of antipsychotics (prescribed for treatment of motor symptoms) and/or tetrabenazine is not permitted 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 7. 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 8. Supplement use (e.g., coenzyme Q10, vitamins, creatine) unless stable dose for 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study 9. Antiplatelet or anticoagulant therapy within the 14 days prior to Screening or anticipated use during the study, including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban 10. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed at least 3 days prior to the first day Study Drug is administered to the patient (Study Day 1) 11. Prior treatment with an antisense oligonucleotide (including siRNA) 12. Any history of gene therapy or cell transplantation or any other experimental brain surgery 13. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter *Medical History and Concurrent Disease* 14. Significant history of alcoholism or drug/chemical abuse 15. Clinically relevant hematological, hepatic, cardiac or renal disease or event (e.g., previous acute coronary syndrome within 6 months of Screening). Abnormal hepatic, renal or hematology lab tests must be discussed with the Sponsor Medical Monitor 16. Known history of human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 17. Any condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment 18. History of bleeding diathesis or coagulopathy, platelet count < LLN 19. A medical history of brain or spinal disease that would interfere with the LP process, CSF circulation or safety assessment, including tumors or abnormalities by MRI or computed tomography (CT), subarachnoid hemorrhage, suggestion of raised intracranial pressure on MRI or ophthalmic examination, spinal stenosis or curvature, chiari malformation, hydrocephalus, syringomyelia, tethered spinal cord syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome

PROTOCOL SYNOPSIS *Continued*

<table>
<tr><td>Study Population
Continued</td><td>20. History of post-lumbar-puncture headache of moderate or severe intensity and/or blood patch
21. 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
22. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
23. Have any other conditions which, in the opinion of the Investigator, would make the patient unsuitable for inclusion or could interfere with the patient participating in or completing the study</td></tr>
<tr><td>Treatment Groups</td><td>ISIS 443139, Placebo

There will be 4 multiple-dose cohorts (n = 4, 8 or 16 per cohort, randomized 3 active: 1 placebo). Patients will receive 4 IT bolus doses of Study Drug at 4 week intervals during the 3 month Treatment Period (Days 1, 29, 57, 85). For patients who receive ISIS 443139, planned total dose is shown in the table below.
<table>
<tr><th>Planned Dose of Active Study Drug</th><th># of doses</th><th>Total ISIS 443139</th></tr>
<tr><td>Cohort A: 10 mg ISIS 443139</td><td>4</td><td>40 mg</td></tr>
<tr><td>Cohort B: 30 mg ISIS 443139</td><td>4</td><td>120 mg</td></tr>
<tr><td>Cohort C: 50 mg ISIS 443139</td><td>4</td><td>200 mg</td></tr>
<tr><td>Cohort D: 70 mg ISIS 443139</td><td>4</td><td>280 mg</td></tr>
</table></td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>Each dose of ISIS 443139 or placebo 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.

Dosing instructions and details regarding administration will be provided in the Study Drug manual. The site pharmacist will be blinded to treatment assignment.</td></tr>
<tr><td>Dose Escalation</td><td>Four dose level cohorts (Cohorts A, B, C and D) will be enrolled sequentially, with patients each receiving 4 doses of Study Drug at 28-day intervals. The progression of the study from one cohort to the next will be determined by the Sponsor in collaboration with the Data and Safety Monitoring Board (DSMB) and will generally be based on the number of DLTs observed in patients treated with ISIS 443139.

Beginning with Cohort B, dose administration in a cohort may commence only after (1) all patients in the prior cohort have been enrolled, (2) at least 4 patients in the prior cohort have received a cumulative dose that is equal to or greater than the initial dose planned for the cohort and safety in these patients has been monitored for at least 7 days post-treatment after reaching that cumulative dose, and (3) safety results for all patients enrolled in the prior cohorts have been reviewed by the DSMB. The occurrence of DLTs in 2 patients in a cohort will result in the dose tested in the cohort being dose limiting in this study.

If a single DLT is encountered in Cohort A, the cohort may be expanded up to 8 patients to assess safety at that dose. Other dose cohorts (Cohorts B, C and D) may also be expanded up to 100% if a single DLT is encountered in those cohorts. If dosing in higher dose cohort(s) is ongoing at the time a single DLT is encountered in a lower dose cohort, further enrollment in the higher dose cohort(s) will stop until all current patients have completed dosing and at least 7 days of post-dose safety evaluations. In addition, the DSMB will convene to decide if further measures are required such as pausing or reducing dosing in ongoing patients in the higher dose cohort(s).</td></tr>
</table>

PROTOCOL SYNOPSIS *Continued*

Dose Escalation ***Continued***	The occurrence of DLTs in (i) 2 patients in a cohort or (ii) a single SAE that is life threatening and that is evaluated by the Sponsor as related to Study Drug in a cohort will result in termination of further dosing in that cohort and any higher dose cohort that is also ongoing.
Rationale for Dose and Schedule Selection	ISIS 443139 dose levels and dose interval for ISIS 443139-CS1 were selected based on preclinical toxicology and pharmacokinetic observations. CCI [redacted] Monthly dosing is expected to achieve ISIS 443139 brain cortex tissue levels at steady state by Day 92, and is expected to be safe and well-tolerated by patients.
Study Visit Schedule and Procedures	After informed consent is obtained, patients will undergo a screening evaluation during a 6-week period prior to baseline. Patients who meet the eligibility criteria will visit the Study Center on Study Day -1 to undergo baseline clinical, blood, and electrophysiological evaluations and for re-assessment of eligibility. On Study Day 1, patients will be admitted to the Study Center, undergo pre-dose evaluations of vital signs and then receive an IT bolus injection (slow push) of ISIS 443139 or placebo (3:1). Following the initial LP injection on Day 1, patients will be kept at the Study Center for at least 24 hours and carefully monitored for any adverse clinical symptoms or signs. This inpatient post-dose assessment may be reduced to a minimum of 6 hours following the 2nd, 3rd and 4th dose administrations provided a visit is made to the Study Center the next day. Assessments during these admission periods include neurological, electrophysiological and physical examination, vital signs, ECGs, blood sampling and clinical laboratory analyses. Full standard neurological assessment (including fundi) will be performed 3 hours post-dosing with Study Drug and prior to discharge from the Study Center. Study Drug administration will take place on Study Days 1, 29, 57 and 85. In the Treatment Period, Study Center visits are held on Study Days 1, 2, 8, 28, 29, 30, 36, 56, 57, 58, 84, 85 and 86. During the Post-Treatment Period, patients will visit the Study Center on Study Days 113, 169 and 197 (study completion visit). In addition, the Study Center will monitor the patient's condition through telephone contact on Study Day 3, 31, 59, 64, 87 and 92. CSF samples will be taken pre-dose on each Study Drug IT injection day (Days 1, 29, 57, 85) and on Day 113 or 169. These samples will be utilized for PK, Htt protein and other biomarker and laboratory analyses. If a patient terminates early from the Treatment Period of the study, he/she will be encouraged to return for the near-term follow-up visits associated with the most recent dose of Study Drug and for the Post-Treatment Period (Days 113-197).
Safety and Tolerability Evaluations	Safety and tolerability evaluations will 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 • Clinical and neuroimaging (including safety sequences) assessments

PROTOCOL SYNOPSIS *Continued*

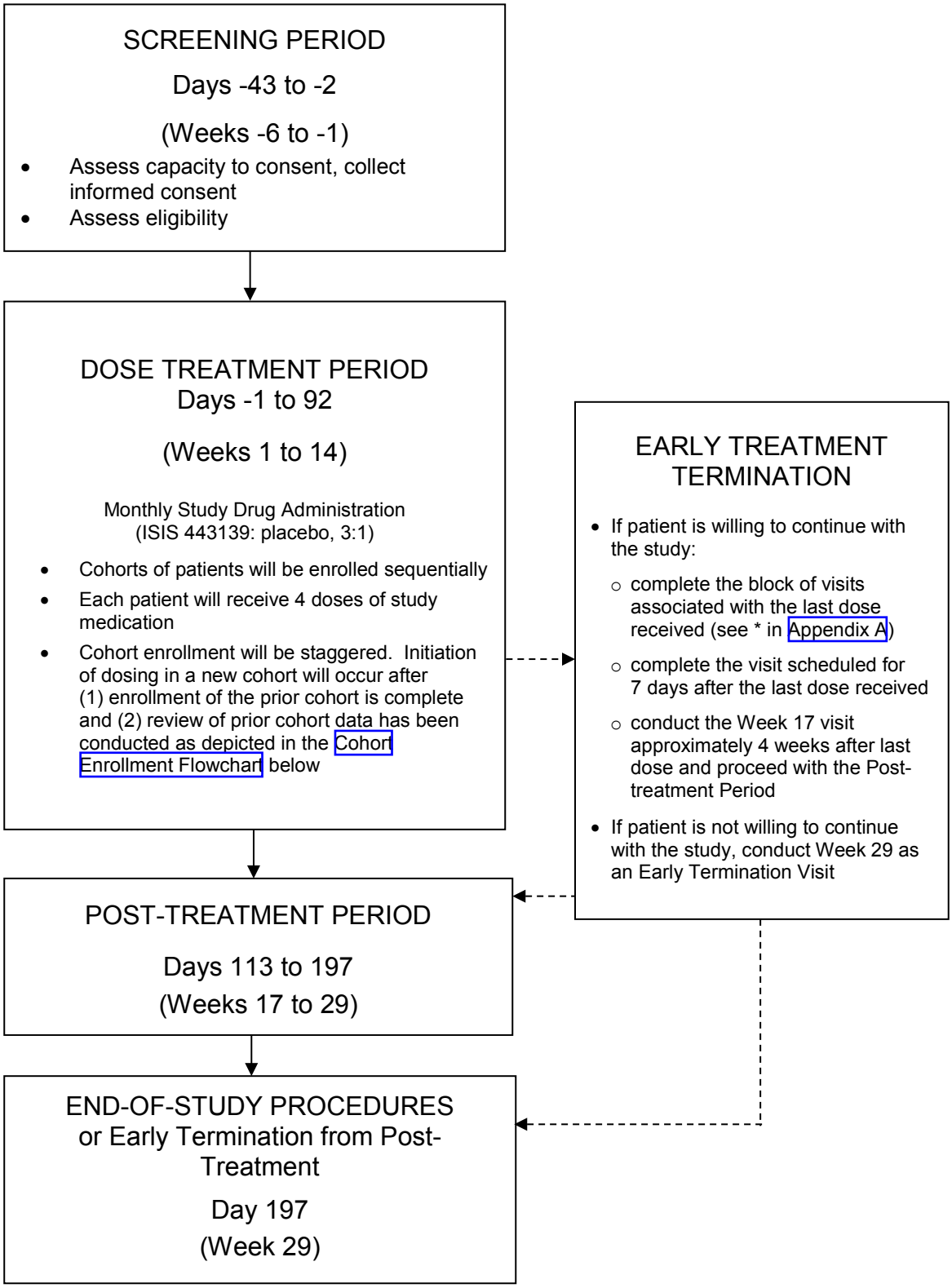
Safety and Tolerability Evaluations *Continued*	The safety and tolerability of ISIS 443139 will be assessed by determining the incidence, severity and dose-relationships of AEs and changes in laboratory parameters by dose. In addition, clinical, electrophysiological and volumetric neuroimaging assessments will be used to monitor for unexpected deterioration. Safety results in patients dosed with ISIS 443139 will be compared with those from patients dosed with placebo. Placebo-treated patients will be pooled for analysis.
Pharmacokinetic Evaluations	A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at one Post-Treatment Period visit (either Study Day 113 or 169) for PK analyses. The CSF concentrations will be summarized using descriptive statistics and the ISIS 443139 half-life in CSF will be calculated, if possible. Analysis of the levels of ISIS 443139 in CSF is of key importance. In addition, plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses. Plasma maximum concentration (C_{max}), area under the curve (AUC), elimination half-life and trough and post-distribution drug levels will be assessed, where appropriate.

Exploratory Evaluations	Exploratory evaluations will include:
	• Biochemical
	  ○ CSF levels of mutant Htt[7] and total Htt
	  ○ Potential biomarkers of HD disease progression
	  ▪ CSF: neurofilament light chain[8], proenkephalin, clusterin, factor H (FH), C3, interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), MCP-1, chitinase-3-like protein 1 (YKL-40), visinin-like protein 1 (VILIP1), apolipoprotein, chromogranin B, neurogranin, SNAP25, S100B and tau
	  ▪ Plasma: IL-6, TNFα and 24S-hydroxycholesterol
	• Neuroimaging
	  ○ Structural MRI volumes, including but not limited to:
	  ▪ Caudate
	  ▪ Whole brain
	  ▪ Ventricular[9]
	  ○ MRS spectroscopy for frontal lobe myoinositol and N-Acetylaspartic acid (NAA)
	  ○ Resting state functional MRI
	  ○ Neurite orientation dispersion and density imaging (NODDI)
	• Electrophysiological
	  ○ qEEG
	• Clinical
	  ○ Functioning/ability to perform activities of daily living
	  ▪ UHDRS Total Functional Capacity Scale (TFC)
	  ▪ UHDRS Independence Scale
	  ▪ HD Work Function Scale
	  ○ Cognitive and motor tests:
	  ▪ HD Cognitive Battery[8]
	  • Self-Paced Tapping
	  • Emotion Recognition
	  • CANTAB One Touch Stockings
	  • Symbol Digit Modalities Test
	  • Hopkins Verbal Learning Test Revised
	  • Trail Making Test Part B
	  ▪ UHDRS Total Motor Scale
	  ▪ Map Search Test
	  ▪ Stroop Word Reading Test
	  ▪ Speeded Tapping
	  ○ Neuropsychiatric evaluation
	  ▪ Problems Behavior Assessment for Huntington's disease-short form (PBA-s)

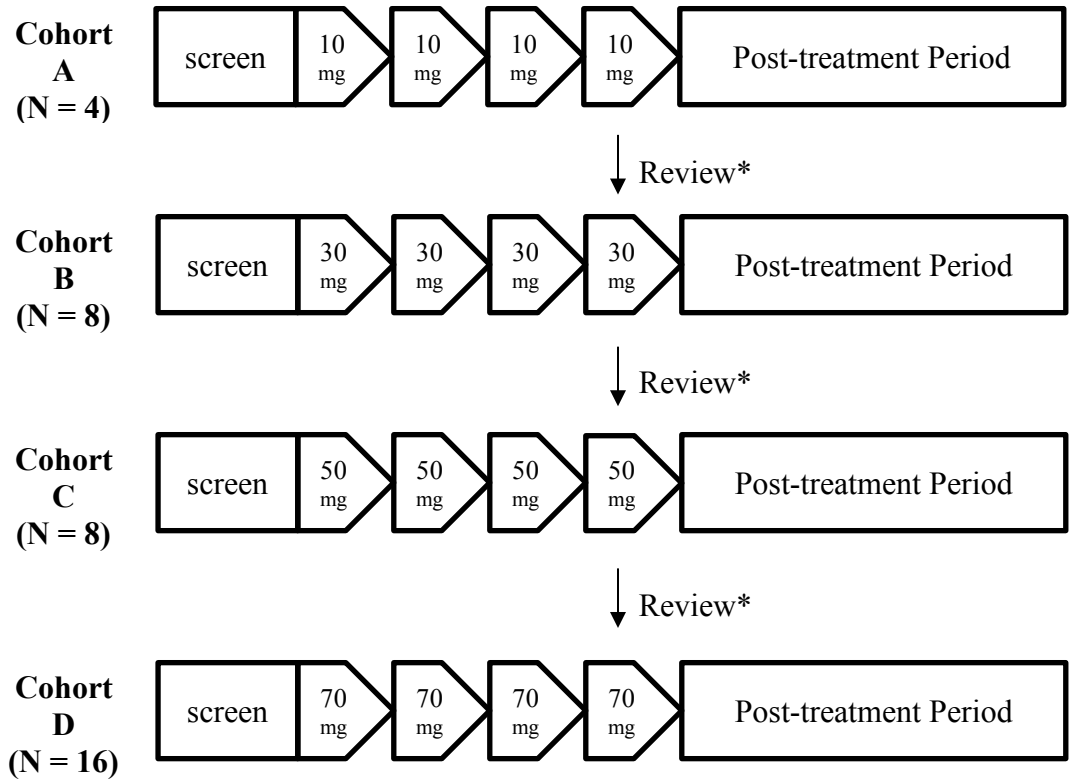
PROTOCOL SYNOPSIS *Continued*

Exploratory Evaluations ***Continued***	Evaluations will include comparisons between ISIS 443139-treated patients and placebo-treated patients of the above biomarkers and clinical evaluations. If CSF Htt protein level is reflective of target engagement, exploratory evaluations will be conducted to relate dose and PK to CSF Htt protein level. Placebo-treated patients will be pooled for analysis. * Key exploratory biochemical, neuroimaging, electrophysiological and clinical assessments
Statistical Considerations	While there is no statistical basis for the sample size, it has been selected based on prior experience with generation 2 ASOs given by IT injection to ensure that the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.
Sponsor	Isis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



COHORT ENROLLMENT FLOWCHART



* DSMB and Sponsor review of data to permit initiation of dosing in a new cohort will occur when:

- at least 4 patients in the current cohort have received multiple doses of Study Drug such that the cumulative dose received by each of these patients meets or exceeds the initial dose planned for the new cohort and
- safety data have been collected in these patients through at least 7 days after receipt of the necessary cumulative dose.

Prior to initiating dosing in a new cohort, the DSMB will review the safety data described above (at minimum) and make a recommendation regarding initiation of the new cohort.

Additionally, the Sponsor may conduct a blinded review (or reviews) of accumulating pharmacokinetic data and compare those data to the ISIS 443139 levels that are expected to produce a pharmacologic effect (according to the preclinical PK/PD model). Based on this review, the dose level(s) for future cohort(s) may be adjusted. The maximum dose level tested in a cohort will not exceed 70 mg.

Note: Each ▷ represents one dose followed by a 28-day observation period.
The Post-treatment Period is 15 weeks.

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)
AUC	Area under the curve
AUC_t	Area under the plasma concentration-time curve from time zero to time t
βhCG	Beta-subunit of human chorionic gonadotropin (pregnancy test)
BCHE-K	Butyrylcholinesterase K variant
BP	Blood pressure
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
cl	Clinic
CRF	Case report form
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DSMB	Data And Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
FH	Factor H
FSE	Fast spin echo
GCP	Good Clinical Practice
^{1}H-MRS	Proton magnetic resonance spectroscopy
HD	Huntington's disease
HDWF	Huntington's disease work function

Htt	Huntingtin protein
HIV	Human Immunodeficiency Virus
HR	Heart rate
HVLT-R	Hopkins verbal learning test - revised
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
INR	International normalized ratio
IRB	Institutional Review Board
ISIS 443139	Antisense inhibitor of Htt
IT	Intrathecal(ly)
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein-1
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mI	Myo-inositol
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRS	Magnetic resonance spectroscopy
MTD	Maximum tolerated dose
NAA	N-Acetyl-aspartate
NCS	Not clinically significant
NODDI	Neurite orientation dispersion and density imaging
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
PK	Pharmacokinetic(s)

PBA-s	Problems behavior assessment for Huntington's disease – short form
PT	Prothrombin time
qEEG	Quantitative EEG
rsfMRI	Resting state functional MRI
RNase H	Ribonuclease H (a non-specific endonuclease and catalyzes the cleavage of RNA via a hydrolytic mechanism)
S100B	S100 calcium binding protein B
SAD	Single ascending dose
SAE	Serious adverse event
siRNA	Small interfering ribonucleic acid
SAP	Statistical Analysis Plan
SNAP25	Synaptosomal-associated protein 25
Study Day 1	Defined as the first day Study Drug is administered to the patient
Study Drug	ISIS 443139 or placebo
SUSAR	Suspected unexpected serious adverse reaction
SDMT	Symbol digit modalities test
TEAE	Treatment-emergent adverse event
TFC	Total functional capacity
T_{max}	Time to maximal concentration
TMS	Total motor scale
TMT-A	Trail-making test part A
TMT-B	Trail-making test part B
TNFα	Tumor necrosis factor alpha
TSE	Turbo spin echo
UHDRS	Unified Huntington's disease rating scale
VILIP1	Visinin-like protein 1
WBC	White blood cell
YKL-40	Chitinase-3-like protein 1

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of an antisense inhibitor of Htt (ISIS 443139) to patients with Huntington's disease (HD)

1.2 Secondary Objectives

To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT administrations of ISIS 443139.

1.3 Exploratory Objectives

To explore effects of multiple doses of ISIS 443139 on potential target engagement and disease progression biomarkers and clinical endpoints relevant to HD. Plasma pharmacokinetic properties of ISIS 443139 will also be assessed. Disease progression markers are included primarily as a safety measure to document any marked worsening. A lesser objective is to gain experience with these measures in an ISIS 443139 clinical study as preparation for subsequent, longer-term clinical studies. It is not expected that the majority of biomarkers and clinical measures will be impacted significantly by the 3 months of dosing planned for this study. For the current study, select disease progression markers are considered to be key exploratory target engagement, biochemical, neuroimaging and cognitive assessments based on their potential to evidence changes in disease progression in early HD. These key exploratory endpoints are mutant Htt in CSF, neurofilament light chain in CSF, ventricular volume as assessed by structural MRI and the composite cognitive score resulting from assessment of the components of the HD Cognitive Battery.

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 has been elusive, studies suggest that Htt 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 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* 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. 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 five 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 five stages also correlate with score on the UHDRS Total Functional Capacity (TFC) Scale, with Stage 1 corresponding to TFC scores of 11-13, Stage 2 to scores of 7-10, Stage 3 to scores of 3-6, Stage 4 to scores of 1-2 and Stage 5 to a score of 0 (Shoulson et al. 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 et al. 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), a vesicular monoamine transporter 2 inhibitor, is the only drug currently approved for HD, and its label is specific for hyperkinetic motor disorders with Huntington's chorea. Tetrabenazine is approved in the United States, New Zealand, Australia, Canada, Israel and some European countries. However, the drug has been linked to many significant adverse events (AEs), including Parkinsonism, akathisia, sedation, depression and suicidal thoughts (Xenazine label 2011). Tetrabenazine is contraindicated in patients who are actively suicidal and in patients with untreated or inadequately treated depression (Xenazine label 2011), a population that includes approximately > 40% of HD patients (Chen et al. 2012). Additionally, tetrabenazine 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 (muHtt) (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 one gene, inhibiting *HTT* expression is a promising therapeutic option (Stanek et al. 2013).

ISIS 443139 is being developed to reduce the synthesis of Htt by targeting *HTT* mRNA and directing its catalytic degradation through the action of ribonuclease H (RNase H), 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 muHtt 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 ISIS 443139 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 ISIS 443139

2.3.1 Mechanism of Action

ISIS 443139 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 ISIS 443139 to the cognate mRNA results in the RNase H-mediated degradation of the *HTT* mRNA, thus preventing production of the Htt protein. Both wild-type and mutant *HTT* mRNA are targeted by ISIS 443139.

2.3.2 Chemistry

Chemically, ISIS 443139 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer). CCI . The nucleotide sequence of ISIS 443139 (Figure 1) is complementary to a 20-nucleotide stretch CCI of the *HTT* mRNA. CCI . These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003) and (3) amelioration of some high dose toxicities resulting in an improved safety profile compared to first generation

antisense drugs containing phosphorothioate-modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The central portion of the oligonucleotide is composed of CCI ISIS 443139 employs this chimeric structure to enable use of the RNase H-mechanism for antisense activity. While the 2′-MOE modification confers increased stability and affinity, it does not support RNase H catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999) because conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids are not recognized by RNase H enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H recognition.

Figure 1 Design of ISIS 443139

2.3.3 Preclinical Experience

CCI

2.3.4 Clinical Experience

ISIS 443139 has not been evaluated in any clinical setting.

2.4 Rationale for Study Design

2.4.1 Rationale for the Study Population

This is the first study of ISIS 443139 in humans, and it will be conducted in patients with early manifest HD. Early manifest HD patients are generally active and independent in most areas of functioning (often still working or driving). These patients are fully capable of informed consent. It is necessary to conduct this study in patients, rather than in healthy volunteers, for two reasons. First, a better understanding of the safety of ISIS 443139 in its intended target population will be achieved in patients since the intended target of the Study Drug (i.e., mutant *HTT* mRNA transcripts) is not present in healthy volunteers. Second, ISIS 443139 must be administered via intrathecal (IT) administration, and consideration of the balance between risk and benefit justifies investigation in a patient population only. Although assessment of safety is the primary objective of this study, HD patients who enroll in this study will be relatively early in the manifest disease process and may experience benefit from the investigational treatment if it addresses the primary pathogenesis of the disease.

Eligible patients will be aged ≥ 25 years of age to avoid very high CAG repeats associated with early disease onset (e.g., > 55 repeats) as such patients are considered to have a somewhat different, rapidly-progressing phenotype. Eligible patients will also be ≤ 65 years of age to avoid undesirable comorbidity that is more common above this age.

2.4.2 Rationale for a Multiple Ascending Dose Design

This is a first-in-man, multiple ascending dose (MAD) study in patients with HD. This design is rational given the prolonged time between doses and the rarity of the patient population. Also, the study is designed with a focus on patient safety.

The study is designed to capture the information that would ordinarily be obtained in two separate studies – a single ascending dose (SAD) study and a MAD study. The length of the dosing interval makes this design feasible. With Study Drug dosing at 28-day intervals, comprehensive safety, tolerability and pharmacokinetic evaluations can be conducted in each patient for 28 days after the first dose. This is comparable to the evaluation that would be conducted in a SAD study. At the conclusion of this 28-day period, monthly dosing will continue (in the absence of significant safety issues related to Study Drug) for three additional doses, allowing for evaluation of safety, tolerability and pharmacokinetics during a multiple-dose regimen.

This design, which eliminates the need for a SAD study, is appropriate because of the nature of the patients under investigation. These are rare patients with a devastating disease, and Study Drug has to be administered by IT injection. Therefore, it is important to obtain a maximum amount of information from each patient enrolled in each study conducted in this population.

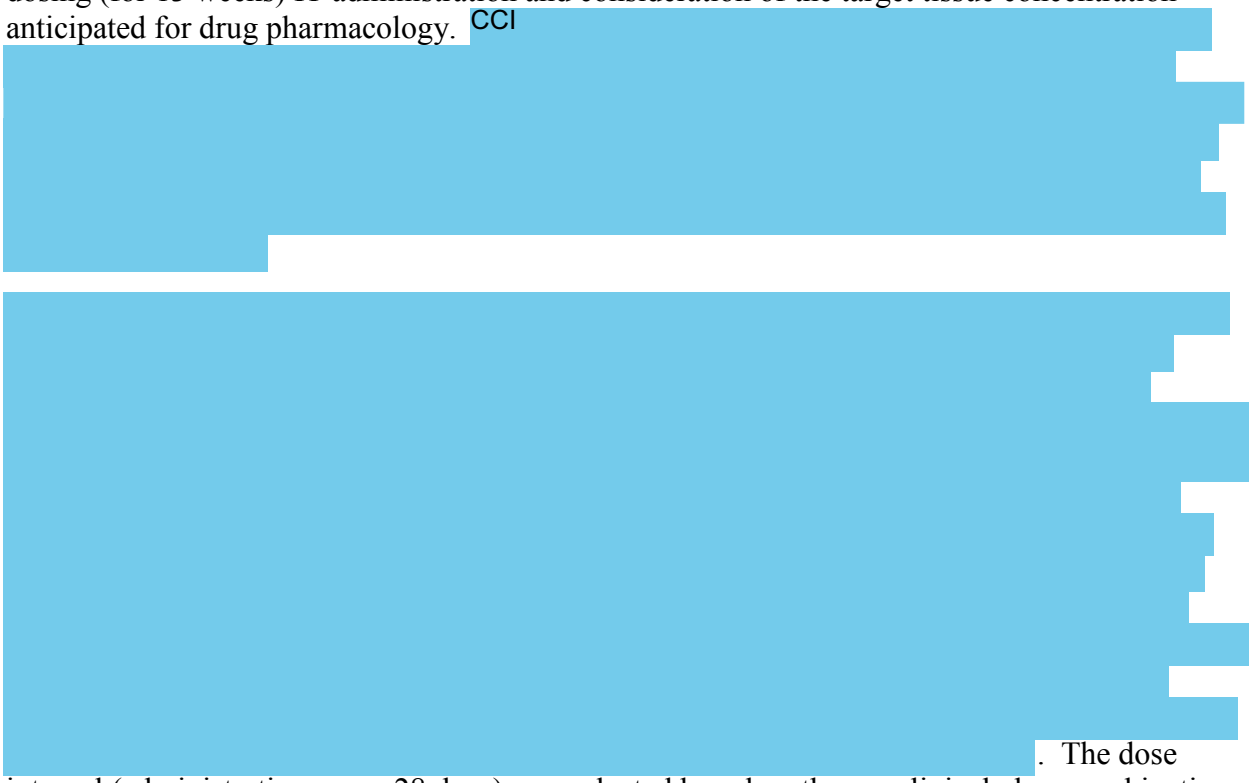
Patient safety is paramount with this study design. For example, only clinical research facilities with capabilities for 24-hour in-patient monitoring will be utilized, and patients will be required to live close enough to the facility to permit prompt appearance at the facility if requested. Each patient will be required to have a trial partner (i.e., a reliable and competent individual with a close relationship with the patient), and the Investigator will seek supplemental information about the patient's condition from the trial partner using validated assessment tools. In addition,

patient safety during the study will be monitored closely and on an ongoing basis by an independent, unblinded Data Safety Monitoring Board (DSMB).

2.4.3 Rationale for Dose Levels and Dosing Schedule

The proposed study will test the safety, tolerability, and PK of multiple doses of ISIS 443139 administered as IT injections. Four dose levels will be evaluated . The doses are predicted to produce a range of pharmacologic effect but are not intended to elicit dose-limiting toxicities.

ISIS 443139 dose levels and dose interval for ISIS 443139-CS1 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. CCI



. The dose interval (administration every 28 days) was selected based on the nonclinical pharmacokinetic and pharmacodynamic (*HTT* mRNA reduction) data required to achieve ISIS 443139 brain cortex tissue levels that are predicted to be at steady state by Day 92 and to achieve reduction in *HTT* mRNA levels. Also, monthly dosing is expected to be safe and well-tolerated by patients.

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

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 1/2a, multi-center, double-blind, randomized, placebo-controlled, dose-escalation study conducted in patients with early manifest HD. The study consists of four cohorts (n = 4-16 per cohort, randomized 3 active:1 placebo). The doses planned for the study are shown below. Based on emerging safety data from this study, one or more cohorts may be expanded by

enrolling additional patients. Additionally, pharmacokinetic and pharmacodynamic measures will be collected at each dose level and compared to the results that are predicted by models constructed from preclinical data. The doses utilized in remaining cohorts may be adjusted, or an additional cohort may be added, if necessary to achieve pharmacologically relevant levels. The maximum dose tested in a cohort will not exceed 70 mg.

Cohort A: N = 4, 10 mg ISIS 443139 or placebo (3:1)

Cohort B: N = 8, 30 mg ISIS 443139 or placebo (6:2)

Cohort C: N = 8, 50 mg ISIS 443139 or placebo (6:2)

Cohort D: N = 16, 70 mg ISIS 443139 or placebo (12:4)

Randomization in Cohort D will be stratified by early Stage 1 (TFC ≥ 12) or late Stage 1 (TFC = 11) disease, where Stage 1 represents the highest level of capacity of the 5 stages of manifest disease.

Patients will receive 4 monthly IT doses of Study Drug (ISIS 443139 or placebo). Cohorts will be enrolled sequentially. Initiation of dosing in a new cohort may begin after three conditions have been met: (1) all patients in the lower-dose cohorts have been enrolled; (2) at least four patients in the lower-dose cohort have been followed for 7 days after receipt of a cumulative dose that meets or exceeds the initial dose for the next higher dose level cohort; and (3) a review of data collected in the lower-dose cohorts has been conducted by the DSMB and a decision has been made to proceed with the next cohort (see Section 3.7).

After study completion, an open-label extension study of ISIS 443139 may be implemented if warranted based on review of safety, tolerability, pharmacokinetic and exploratory pharmacodynamic findings and subject to approval by the relevant Competent Authorities and Ethics Committees.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Approximately 36 patients are planned to be enrolled in this study. The number of patients enrolled may be higher if some patients need to be replaced and/or if the sizes of the cohorts are expanded to obtain further experience with particular dose levels. A maximum of 48 patients may be enrolled.

3.4 Overall Study Duration and Follow-up

The overall study duration will be approximately 7-8 months. The study will consist of a Screening Period of up to 6 weeks, a 13-week Treatment Period and a 15-week Post-Treatment Period. Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Screening Period

Patient eligibility for the study will be determined within 6 weeks prior to patient entry into the Treatment Period.

3.4.2 Treatment Period

Eligible patients will report to the Study Center for monthly administration of Study Drug and for additional, non-dosing visits as described in the Schedule of Procedures in Appendix A.

In Cohorts A and B, no more than one patient may begin the Treatment Period on a given day. In later cohorts, the first two patients in the cohort may not begin the Treatment Period on a given day.

3.4.3 Post-Treatment Period

Patients will return to the Study Center for follow-up visits 4, 12 and 16 weeks after the last dose of Study Drug. The final study visit will be Study Day 197/Week 29.

3.5 End of Study

The end of study is defined as last patient, last study visit.

3.6 Data and Safety Monitoring Board

An independent and unblinded DSMB will be assembled to review data collected on ISIS 443139 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 443139, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. The progression of the study from the one cohort to the next will be determined by the Sponsor and the DSMB, and this determination will generally be based on the number of dose-limiting toxicities (DLTs) observed in patients treated with ISIS 443139.

Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data will be outlined in the DSMB Charter. The DSMB will consist of at least three voting members, all medical doctors experienced in the conduct of clinical studies in patients with neurodegenerative diseases and otherwise independent from the conduct of the study. Additional non-voting members may join the DSMB as required. A majority of voting members must agree before escalation dose can proceed. The decisions of the DSMB will be recorded in minutes of the meeting.

3.7 Dose Escalation

Four dose level cohorts (Cohorts A, B, C and D) will be enrolled sequentially, with patients each receiving 4 doses of Study Drug at 28-day intervals. In Cohorts A and B, no more than one patient may begin the Treatment Period on a given day. In later cohorts, the first two patients in the cohort may not begin the Treatment Period on a given day. The progression of the study from initiation of dosing in one cohort to the next will be determined by the Sponsor and the DSMB.

Beginning with Cohort B, dose administration in the cohort may commence only after the following minimum requirements are met in the prior cohort:

- All patients in the prior cohort have been enrolled
- At least 4 patients in the prior cohort have received multiple doses of Study Drug (ISIS 443139 or placebo) such that the cumulative dose received by each patient is equal to or greater than the dose level planned for patients in the new cohort. This corresponds

to a requirement for multiple dose administration in all patients in Cohort A (when considering escalation to Cohort B) and multiple dose administration in at least 50% of patients in Cohorts B or C (when considering escalation to Cohort C or D, respectively).

- Patient safety in the prior cohort has been monitored for at least 7 days post-treatment after receipt of the cumulative dose that meets or exceeds the dose planned for the new cohort, and those data are available for review.
- Safety data in the prior cohort have been reviewed by the DSMB and the DSMB has recommended initiation of the new cohort.

Additionally, the Sponsor may conduct a blinded review (or reviews) of accumulating CSF pharmacokinetic data and compare those data to the ISIS 443139 levels that are expected to produce a pharmacologic effect (according to the preclinical PK/PD model). This review will be conducted in a manner that does not associate individual data with particular patients for those involved in the conduct of the study. Based on this review, the dose level(s) for future cohort(s) may be adjusted. The maximum single and cumulative doses administered in a cohort will not exceed 70 and 280 mg, respectively.

If a single DLT is encountered in Cohort A, the cohort may be expanded from to up to 8 patients to assess safety at that dose. Other dose cohorts (Cohorts B, C and D) may also be expanded by up to 100% if a single DLT is encountered in those cohorts. If dosing in higher dose cohort(s) is ongoing at the time a single DLT is encountered in a lower dose cohort, further enrollment in the higher dose cohort(s) will stop until all current patients have completed dosing and at least 7 days of post-treatment safety evaluations. In addition, the DSMB will convene to decide if further measures are required such as pausing or reducing dose in ongoing patients in the higher dose cohort(s).

The occurrence of DLTs in (i) 2 patients in a cohort or (ii) a single SAE that is life threatening and that is evaluated by the Sponsor as related to Study Drug in a cohort will result in termination of further dosing in that cohort and any higher dose cohort that is also ongoing. In this situation, the DSMB will determine if the previous (lower) tolerated dose is the maximum tolerated dose (MTD). The Sponsor and DSMB will determine if enrollment of additional patients at the previous (lower) tolerated dose is required to confirm that there is an acceptable toxicity profile at the lower dose prior to its designation as the MTD.

3.8 Dose Limiting Toxicity

A DLT is defined as an adverse event (AE) that, in the judgment of the Investigator, is of sufficient significance to be dose limiting, is possibly or definitely related to Study Drug (i.e., the AE is substantially less likely to occur in patients not administered the Study Drug) and that it is not a known sign or symptom of HD or effect of any study procedure (e.g., LP, venipuncture, MRI scan).

If a suspected DLT occurs during IT injection of the Study Drug, administration of Study Drug to the patient should be stopped (i.e., the injection should be discontinued immediately and no further Study Drug injections should be administered in this patient). The Investigator should contact the Isis Medical Monitor as soon as possible to discuss the case. The DSMB should

convene and determine (based on unblinded data review, if necessary) if any relevant findings have been observed in other patients in the study.

Patients that experience a DLT will discontinue study treatment but should complete any follow-up visits associated with the most recent dose (see Section 8.9) and should complete the Post-Treatment Period.

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 or their legally acceptable representatives 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. At the time of randomization, patients will 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. The screening number and patient identification number must remain constant throughout the entire study. In the event the patient is re-consented and re-screened, the patient must be given a new screening number. 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 ISIS 443139 or placebo. Within each cohort, randomization will be 3:1 ISIS 443139:placebo as outlined in Section 3.1.

The Sponsor or designee will prepare the randomization list.

4.3 Replacement of Patients

Patients withdrawn early from the Study who do not complete all scheduled doses of Study Drug (ISIS 443139 or placebo) may be replaced at the discretion of the Sponsor unless the Investigator and Sponsor Medical Monitor agree that this should not be done for reasons of safety. Replacement patients will be assigned to the same Study Drug (ISIS 443139 or placebo) as the patients who are being replaced without unblinding any study personnel. No more than 48 patients may be enrolled.

Patients whose randomization code has been broken will not be replaced.

4.4 Unblinding of Treatment Assignment

The Sponsor and all patients, monitors and Study Center personnel related to the study will be blinded throughout the Study. However, if a patient has suffered a Serious Adverse Event (SAE) (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient through an automated system. The Sponsor or designee will be informed of the unblinding of a patient within 24 hours. An unblinded randomization schema will be maintained securely at the Sponsor's (or designee's) Quality Assurance Department. In addition, all SUSARs will be unblinded by the Sponsor's or designee's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendices A and B) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

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. Early manifest, Stage 1 HD (defined as TFC of 11-13, inclusive), aged 25 to 65 years, inclusive, at the time of informed consent, with genetically confirmed disease (CAG repeat length ≥ 36 in huntingtin gene by direct DNA testing)
4. Body Mass Index (BMI) ≥ 18 and ≤ 32 kg/m^2; total body weight > 50 kg (110 lbs)
5. Able and willing to meet all study requirements in the opinion of the Investigator, including travel to Study Center, procedures, measurements and visits, 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 and at the time of enrollment

f. Patients must reside in a proximity to the Study Center that permits prompt appearance at the facility if requested by the Investigator (maximum of 4-hour travel to Study Center)

Reproductive Status

6. 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 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo)

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

7. Males must be surgically sterile, abstinent or, if engaged in sexual relations with a female of child-bearing potential, the patient must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo)

5.2 Exclusion Criteria

Target Disease-Related Exclusions

1. Any condition, including severe chorea, that would prevent either writing or performing rapid computer tasks

Physical, Mental and Laboratory Test Findings

2. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 12 months prior to Screening. For patients with (i) a suicide ideation score ≥ 4 on the Columbia Suicide Severity Rating Scale (C-SSRS)

within the last 12 months, (ii) a score of 3 or 4 on question 2 of the Problems Behavior Assessment for Huntington's Disease – short form or (iii) suicidal behaviors within the last 12 months (as measured by the answer "Yes" on any of the C-SSRS Suicidal Behavior Items), a risk assessment should be done by an appropriately-qualified mental health professional (e.g., a Psychiatrist or licensed Clinical Psychologist) to assess whether it is safe for the patient to participate in the study. In addition, patients deemed by the Investigator to be at significant risk of suicide, major depressive episode, psychosis, confusional state or violent behavior should be excluded

3. Clinically significant laboratory, vital sign or ECG abnormalities at Screening (including heart rate (HR) < 45 bpm; SBP < 90 mmHg; confirmed BP readings > 170/105 mmHg)

4. Positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B at Screening

Prohibited and Restricted Medications and Procedures

5. Treatment with another investigational drug, biological agent, or device within one 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

6. Current or recent (within the last 6 months) use of antipsychotics (prescribed for psychosis), cholinesterase inhibitors, memantine, amantadine or riluzole. Stable use of antipsychotics (prescribed for treatment of motor symptoms) and/or tetrabenazine is not permitted 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

7. 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

8. Supplement use (e.g., coenzyme Q10, vitamins, creatine) unless stable dose for 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study

9. Antiplatelet or anticoagulant therapy within the 14 days prior to Screening or anticipated use during the study, including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban

10. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed at least 3 days prior to the first day Study Drug is administered to the patient (Study Day 1)

11. Prior treatment with an antisense oligonucleotide (including siRNA)

12. Any history of gene therapy or cell transplantation or any other experimental brain surgery

13. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter

Medical History and Concurrent Disease

14. Significant history of alcoholism or drug/chemical abuse
15. Clinically relevant hematological, hepatic, cardiac or renal disease or event (e.g., previous acute coronary syndrome within 6 months of Screening). Abnormal hepatic, renal or hematology lab tests must be discussed with the Sponsor Medical Monitor
16. Known history of human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
17. Any condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment
18. History of bleeding diathesis or coagulopathy, platelet count < LLN
19. A medical history of brain or spinal disease that would interfere with the LP process, CSF circulation or safety assessment, including tumors or abnormalities by MRI or computed tomography (CT), subarachnoid hemorrhage, suggestion of raised intracranial pressure on MRI or ophthalmic examination, spinal stenosis or curvature, chiari malformation, hydrocephalus, syringomyelia, tethered spinal cord syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome
20. History of post-lumbar-puncture headache of moderate or severe intensity and/or blood patch
21. 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
22. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
23. Have any other conditions which, in the opinion of the Investigator, 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 -6 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. 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 14)

Study Drug will be administered four times, with doses separated by 28 days (Section 8.1).

Eligible patients will report to the Study Center on Study Day -1 (the day prior to first Study Drug 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 Study Drug 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 adverse events 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.

Each subsequent Study Drug administration will be conducted in the same manner, with most pre-dose assessments conducted on the day before Study Drug administration; post-dose, in-clinic observation of at least 6 hours after Study Drug administration (longer or overnight if necessary for safety reasons); in-clinic assessments on the day after Study Drug administration; telephonic contact with patients two days after Study Drug administration and in-clinic assessments one week after Study Drug administration.

6.1.3 Post-Treatment Period (Week 17 to Week 29) or Early Termination

After completion of the Treatment Period, patients will enter the 15-week Post- Treatment Period. This period consists of three Study Center visits on Weeks 17, 21 and 29, as outlined in the Schedule of Procedures in Appendix A.

Patients who terminate early from the Treatment or Post-Treatment Periods (for reasons other than withdrawal of consent) should be encouraged to submit to additional visit(s) as described in detail in Section 8.9. (Also see Appendices A and C and Study Design and Treatment Schema.)

6.2 Study Assessments

The order of study assessments will be defined in the Study Manual. All efforts should be made to adhere to a consistent order of assessments throughout the study. Rest periods will be scheduled during the testing, and the patient should be permitted additional 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 International Standard Classification of Education (ISCED)

The ISCED is used to capture each patient's level of education based on categories ranging from pre-primary education through advanced degree programs.

6.2.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a structured tool to assess suicidal ideation and behavior. Four constructs are measured: severity of ideation, intensity of ideation, behavior and lethality of actual suicide attempts. Binary (yes/no) data are collected for 10 categories, and composite endpoints based on the categories are followed over time to monitor patient safety (Posner et al. 2011). It maps to the Columbia-Classification Algorithm for Suicide Assessment (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.

A referral for psychiatric evaluation is required for any increase in the most severe suicidal ideation score from baseline. 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.

6.2.4 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.

6.2.4.1 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).

6.2.4.2 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 two minutes of standing, BP and pulse rate will be measured three times, with each test separated by at least 1 minute from the prior test. If the diastolic BP readings from the three tests

are not all within 5 mm Hg, two 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.

6.2.5 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 Study Day -1 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.

6.2.6 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).

6.2.7 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).

6.2.8 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. HD 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).

6.2.9 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 at Screening and during the Post-Treatment Period. Ventricular volume as assessed by structural MRI is a key exploratory endpoint for the study.

Ventricular expansion as assessed by structural MRI is a key exploratory endpoint for the study.

At the Screening and Study Day 197/Week 29 visits, the following scans will be performed to characterize the patients' pre-treatment and end-of-study state: T2 flair, T2 star and T2 Fast Spin Echo (FSE)/Turbo Spin Echo (TSE).

Additionally, at the Study Day 113/Week 17 visit, MRI will be used to image the CSF space.

Metabolic disturbances in the frontal lobe of the brain will be assessed using proton magnetic resonance spectroscopy (^{1}H-MRS). Using ^{1}H-MRS, the concentrations of particular metabolites, N-Acetyl-aspartate (NAA) and myo-inositol (mI), can be measured relative to the signal of unsuppressed water. Normal, healthy tissues present a constant proton spectrum, and relative changes in metabolites may be reflective of aberrant biochemical transformations (Walecki et al. 2011). NAA serves as a marker or neuronal health, as it is found only in mature neurons, and has been shown to decline in patients with cognitive impairment (Kantarci et al. 2003). Myo-inositol serves as a marker of glial cells, and elevated levels are associated with regional gliosis (Walecki et al. 2011). A recent study demonstrated elevated mI and decreased NAA in HD (Sturrock and Leavitt 2010) suggesting that these metabolites might serve as endpoints in HD clinical trials.

Corticostriatal connectivity loss occurs early in Huntington's disease. The functional and effective connectivity between brain regions will be examined using resting state functional MRI (rsfMRI). Seed connectivity will be used to identify brain regions which are simultaneously activated at rest. Dynamic causal modelling will be used to explore causal interactions between the brain and these regions. Brain cellular microstructure and structural connectivity will be examined using volumetric MRI combined with neurite orientation dispersion and density imaging (NODDI). Computational approaches will be applied to visualize neural tracts and to determine the relative strength of anatomical connections between brain regions. Graph theory will be used to detect changes in the organization of brain networks such as integration and efficiency. The rsfMRI and NODDI scans require approximately 25 minutes in the scanner. It is recognized that some patients may be unwilling to submit to this additional burden; therefore, while patients will be encouraged to receive these scans, they will not be required.

6.2.10 Speeded Tapping

The speeded tapping test is a measure of psychomotor speed and has been used as a longitudinal marker of disease severity in manifest and pre-manifest HD. For the test, the patient taps the index finger of his/her non-dominant hand as quickly as possible. A brief rest period is held between trials.

6.2.11 Unified Huntington's Disease Rating Scale (UHDRS)

The UHDRS, developed by the Huntington Study Group to provide a uniform assessment of the clinical features and course of HD has undergone reliability and validity testing that support its use in longitudinal studies (Huntington Study Group 1996). The scale assesses four domains associated with HD: motor function, cognitive function, behavioral abnormalities and functional capacity.

For this study, only the UHDRS components required to calculate the total functional capacity scale, the independence scale and the total motor scale will be collected. These components are simple, multiple-choice questions based on patient interview, physical exam and observation during motor activities, such as speeded tapping (Section 6.2.10) and walking. The components are described further below.

6.2.11.1 UHDRS Total Functional Capacity Scale (TFC)

The TFC represents the Investigator's assessment of the patient's capacity to perform a wide range of activities of daily living including working, chores, managing finances, eating, dressing and bathing. It is based on a brief interview with the patient and the study partner. Scores range from 0 to 13, and higher scores represent better functioning.

6.2.11.2 UHDRS Independence Scale

The patient's independence scale is the Investigator's assessment of the patient's degree of independence. The scale consists of 19 discrete levels ranging from 10 to 100 (by 5) where no special care needed corresponds to a scale of 100 and tube fed and total bed care corresponds to a scale of 10.

6.2.11.3 UHDRS Total Motor Scale (TMS)

The TMS is the sum of the individual motor ratings obtained during administration of the motor assessment portion of the UHDRS. Scores range from 0 to 124, and higher scores represent more severe impairment.

6.2.12 HD Work Function (HDWF) Scale

The HDWF scale is a measure of work role limitations and effort, which are areas that may be affected by the cognitive, behavioral and motor changes associated with HD (Brossman et al. 2012). It was developed for prodromal HD, the stage prior to overt motor impairment and HD diagnosis in which structural and functional brain changes lead to subtle changes in cognition and motor function. Patients complete the questionnaire consisting of 20 questions, where the response to each is based on a 7-point Likert scale ranging from "not at all like me" to "very much like me". Scores range from 20 to 140, and higher scores represent higher work function ability.

A companion scale was developed as a proxy indicator of the patient's work function, acknowledging that insight may diminish in some individuals in the prodromal or early stages of HD. During for development of the HDWF scale, correlation between the patient and companion scores were statistically significant (Brossman et al. 2012). If the patient suffers from diminished insight, information from the companion, i.e., trial partner, may provide important supporting information.

6.2.13 Montreal Cognitive Assessment (MoCA)

The MoCA is a screening test for cognitive impairment that spans the visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation domains that has been shown to be sensitive in HD (Nasreddine et al. 2005; Videnovic et al. 2010). The test administrator prompts the patient through a series of tests and follows a simple algorithm to document the patient's score. Total scores range from 0 to 30 points, with lower numbers representative of more cognitive impairment. This test will be performed at Screening only to characterize the patient population relative to published populations.

6.2.14 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 six 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 six individual tests. This composite cognitive score is a key exploratory endpoint for the study. The individual tests that comprise the battery are described below.

6.2.14.1 Self-Paced Tapping

Self-paced tapping measures cognitive and motor timing. The patient listens to a repeating tone at 3Hz and taps in time with the tone, alternating between left and right thumbs. The patient continues to tap after the tone stops, attempting to maintain the same rate of tapping. Four trials are conducted.

Scoring of each effort is based on the precision of taps, which is directly estimated, and timing precision, which is calculated as the reciprocal of the standard deviation of the intertap interval.

6.2.14.2 Emotion Recognition

For this test, patients view faces depicting a neutral expression or an emotion (anger, disgust, fear, sadness, surprise, happiness). After a practice trial for each category, the patient views 70 test trials and categorizes each face by emotion. The number of correct responses for negative emotions (anger, disgust, fear, sadness) are tallied (Johnson et al. 2007).

6.2.14.3 CANTAB One Touch Stockings (OTS)

The OTS test measures executive function, spatial planning and working memory. On a computer or tablet screen, the patient is shown two stacks of colored balls, which can be perceived balls stacked in hanging socks or stockings. The patient must move the balls between the stockings to achieve a particular color pattern. Rearranging the balls to make the target pattern may take one, two, three or four moves. Then, the patient is shown two stacks of colored balls and must determine, without moving the balls, the minimum number of moves necessary to achieve the target pattern.

Tests are scored based on accuracy in determining minimum number of moves and time to correct solution.

6.2.14.4 Symbol Digit Modalities Test (SDMT)

The SDMT is used to assess attention, visuoperceptual processing, working memory and psychomotor speed. It has been shown to have strong reliability and validity (Smith 1982; Hinton-Bayre et al. 1999). The patient must pair abstract symbols with specific numbers according to a translation key. The test measures the number of items correctly paired (maximum of 110) in 90 seconds.

6.2.14.5 Hopkins Verbal Learning Test – Revised (HVLT-R)

The HVLT-R is used to assess verbal memory through tests of recall and recognition. Patients must recall a series of 12 words over three immediate trials (learning), free recall after a 25-minute delay and a recognition trial.

6.2.14.6 Trail-Making Test

The Trail-Making Test Part B (TMT-B) is a test of executive functioning. Patients are presented with a picture of 25 circles, each labeled with a number (1 – 13) or a letter (A – L). The patient must draws lines to connect the circles in an ascending pattern that alternates between the numbers and letters (i.e., 1-A-2-B-3-C …). The patient is instructed to connect the circles as quickly as possible, and the time to complete the task is recorded.

The Trail-Making Test Part A (TMT-A) is also administered, but the results of the TMT-A are not considered to be part of the battery. For the TMT-A, patients are presented with 25 circles, each labeled with a number (1-25) and are asked to connect the numbers. Administration of TMT-A prior to TMT-B provides practice to aid in administering TMT-B.

6.2.15 Problems Behavior Assessment for Huntington's Disease – Short Form (PBA-s)

The PBA-s assesses common behavioral and psychiatric manifestations of HD, including affect, irritability, loss of motivation, perseverative phenomena and psychotic symptoms. The test administrator interviews the patient and trial partner and rates the patient's behavior over the prior four weeks according to the guidelines for the test.

6.2.16 Stroop Word Reading Test

The Stroop Word Reading Test is a measure of processing and psychomotor speed. Patients are presented with a page of color names printed in black ink and are asked to read aloud as many words as possible within a given amount of time. The number of words read correctly is counted.

6.2.17 Map Search Test

The Map Search Test is a test of sustained visual attention. Patients are presented with a visually cluttered map and asked to circle as many target symbols on the map as possible within a fixed period of time. Scoring is based on the number of correctly identified symbols.

6.2.18 Collection of CSF

Patients will have CSF collected pre-dose during the LP procedure on Study Days 1, 29, 57 and 85 for safety and PK analyses. A sample will also be collected during the Post Treatment Period on either Study Day 113 or Study Day 169. Prior to the injection, 20 mL of CSF fluid is to be collected for analyses, using a standard LP collection kit. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 15 mL should be collected. A 24G Whitacre (atraumatic) needle 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. Fluoroscopy guidance should be used if attempts at lumbar puncture without imaging are unsuccessful.

6.2.19 Laboratory Assessments

Laboratory analyte samples 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). Pharmacokinetic analysis of ISIS 443139 in plasma will be conducted using samples collected as described in Appendices A and C.

In addition, assessments of exploratory biomarkers will include interleukin-6 (IL-6), TNFα and 24S-hydroxycholesterol.

6.2.19.2 CSF Laboratory Assessments

CSF will be used for standard laboratory measurement of cells, glucose, protein and ISIS 443139 pharmacokinetic analyses.

Key exploratory CSF biomarkers are muHtt level and neurofilament light chain. Additional CSF assessments are total Htt, proenkephalin, clusterin, factor H (FH), C3, IL-6, TNFα, IL-1β, monocyte chemoattractant protein-1 (MCP-1), chitinase-3-like protein 1 (YKL-40), visinin-like protein 1 (VILIP1), apolipoprotein E, chromogranin B, neurogranin, synaptosomal-associated protein 25 (SNAP25), S100 calcium binding protein B (S100B) and tau.

Extra CSF will be stored for investigation of possible biomarkers of HD or the pharmacodynamic effects of ISIS 443139 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 ISIS 443139 with CSF constituents.

6.2.20 Pregnancy Testing

Pregnancy tests will be conducted in all female patients who are not surgically sterile, as described 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 13 weeks after the last dose of study drug (ISIS 443139 or placebo).

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 one 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 Study Drug

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 13 weeks after the last dose of Study Drug. 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 two 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.

7. STUDY DRUG

7.1 Study Drug Description

ISIS 443139 Study Drug and artificial CSF diluent are manufactured by Isis Pharmaceuticals, Inc., Carlsbad, CA, USA. The Study Drug is supplied as a 5 mL fill volume in a 6 mL clear glass vial. The diluent (artificial CSF) is supplied as a 20 mL fill volume in a 20 mL clear glass vial. These configurations allow for various clinical doses by using different dilution procedures between the Study Drug and diluent vials. Study Drug characteristics are described in Table 1. More details are provided in the Study Drug Manual.

Table 1 Study Drug Characteristics

Study Drug	ISIS 443139	Placebo	Diluent (artificial CSF)
Strength	20 mg/mL	NA	NA
Volume/vial	5 mL solution per vial	5 mL solution per vial	20 mL solution per vial
Route of Administration	IT injection	IT injection	IT injection

ISIS 443139 Study Drug and the diluent (artificial CSF) must be stored securely at 2° C to 8° C. ISIS 443139 Study Drug must be protected from light.

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 443139 or placebo) and diluent labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drug (ISIS 443139 or placebo) and diluent supplies provided by the Sponsor. The Study Center must return all used and unused Study Drug and diluent vials to the Sponsor or designee.

8. TREATMENT OF PATIENTS

8.1 Study Drug Administration

Study Drug dosing will occur at the Study Center on Study Days 1, 29, 57 and 85. On each of these Study 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 Study Drug. A 24G Whitacre (atraumatic) needle 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. Fluoroscopy guidance should be used if attempts at lumbar puncture without imaging are unsuccessful.

Table 2 outlines the dose equivalent and ISIS 443139 concentration for delivery. See Section 3.1 for a description of adjustments that might be made to doses and the maximum dose that will be tested.

Table 2 Study Drug Dosing Information

Cohort	Volume to Administer	Nominal ISIS 443139 Concentration	ISIS 443139 Per Dose
Cohort A	20 mL	0.50 mg/mL	10 mg or placebo
Cohort B	20 mL	1.5 mg/mL	30 mg or placebo
Cohort C	20 mL	2.5 mg/mL	50 mg or placebo
Cohort D	20 mL	3.5 mg/mL	70 mg or placebo

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug preparation and administration. These instructions must be followed for each Study Drug 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. There are no additional specific stopping rules for this study but the Investigator should discuss significant concerns relating to individual patients with the Isis Medical Monitor to ensure that it is appropriate for the patient to continue Study Drug.

8.7 Adjustment of Dose and/or Treatment Schedule

For a given patient, no adjustment of dose is permitted. In the event of a concurrent illness that would prevent the dosing procedure from being performed safely, an adjustment in the dose schedule may be permitted at the discretion of the Sponsor Medical Monitor.

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 adverse event that necessitates permanent discontinuation of Study Drug
- The patient experiences a DLT as defined in Section 3.7

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 Treatment or Post-Treatment Periods (for reasons other than withdrawal of consent) should be encouraged to submit to additional visit(s) as described in detail in Section 8.9. (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 (a) conduct the full block of visits associated with the last dose received (see description of "visit blocks" below), (b) conduct the visit scheduled for 7 days after the last dose received, (c) and proceed to the Week 17 visit approximately 4 weeks after last dose and conduct all visits in the Post-Treatment Period (see Appendix A).

> "Visit blocks": Each dose of Study Drug is associated with a series of visits that are timed to assess acute safety and tolerability of ISIS 443139. There are four "visit blocks" in this study: Study Days -1, 1, 2 and 3; Study Days 28, 29, 30 and 31; Study Days 56, 57, 58 and 59 and Study Days 84, 85, 86 and 87.

For patients who terminate early from the Treatment Period for reasons other than withdrawal of consent every effort and are not willing to participate in the Post-Treatment Period, every effort should be made to (a) conduct the full block of visits associated with the last dose received (see description of "visit blocks" above), (b) conduct the visit scheduled for 7 days after the last dose received and (c) conduct the Week 29 visit as an Early Termination Visit.

For patients who terminate early from the Post-Treatment Period for reasons other than withdrawal of consent, every effort should be made to conduct the Week 29 visit as an Early Termination Visit.

8.10 Concomitant Therapy and Procedures

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

8.10.1 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 study medication 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 adverse events 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) and/or tetrabenazine 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 (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 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

8.10.2 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 study medication and end of study.

8.11 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 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 DSMB will be notified of any SAE as specified in the DSMB charter.

The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that the Study Drug (ISIS 443139 or placebo) 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 adverse event. 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 adverse event 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 one 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 197. 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 Study Day 197. 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 Study Drug (ISIS 443139 or placebo) is characterized by one 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 Study Drug (ISIS 443139 or placebo) 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 Study Drug (ISIS 443139 or placebo) 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 asymptomatic adverse events, the toxicity grading system and toxicity grade should be indicated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) guidelines, version 4.0 or higher (available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

For symptomatic adverse events, the event's severity is characterized by one 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 Study Drug (ISIS 443139 or placebo) due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drug (ISIS 443139 or placebo) administration and dose
- **Permanently Discontinued:** Study drug 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 one 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 one 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

Study Drug (ISIS 443139 or placebo) 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 Study Drug (ISIS 443139 or placebo) 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 Study Drug. 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 (HR, BP, orthostatic changes, weight)
- ECG
- AEs and concomitant medications
- CSF safety labs (cell counts, protein, glucose)
- Plasma laboratory tests (clinical chemistry, hematology)
- Urinalysis
- Clinical assessments
- Volumetric and safety neuroimaging assessments

10.1.2 Pharmacokinetic Endpoints

A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at one Post-Treatment Period visit for PK analyses.

Plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses.

Plasma C_{max}, AUC, elimination half-life and trough and post-distribution drug levels will be assessed, where appropriate.

10.1.3 Exploratory Endpoints

- Biochemical
  - CSF levels of mutant Htt* and total Htt
  - CSF levels of neurofilament light chain*, proenkephalin, clusterin, FH, C3, IL-6, TNFα, IL-1β, MCP-1, YKL-40, VILIP1, apolipoprotein, chromogranin B, neurogranin, SNAP25, S100B and tau
  - Plasma levels of IL-6, TNFα and 24S-hydroxycholesterol
- Neuroimaging volumes, including but not limited to:
  - Structural MRI
    - Caudate
    - Whole brain
    - Ventricular*
  - MRS spectroscopy for frontal lobe myoinositol and N-Acetylaspartic acid (NAA)
  - Resting state functional MRI

- Neurite orientation dispersion and density imaging (NODDI)

- Electrophysiological
  - qEEG
- Clinical
  - Functioning/ability to perform activities of daily living
    - UHDRS Total Functional Capacity Scale (TFC)
    - UHDRS Independence Scale
    - HD Work Function Scale
  - Cognitive and motor tests:
    - HD Cognitive Battery*
      - Self-Paced Tapping
      - Emotion Recognition
      - CANTAB One Touch Stockings
      - Symbol Digit Modalities Test
      - Hopkins Verbal Learning Test Revised
      - Trail Making Test Part B
    - UHDRS Total Motor Scale
    - Stroop Word Reading Test
    - Map Search Test
    - Speeded Tapping
  - Neuropsychiatric evaluation
    - Problems Behavior Assessment for Huntington's disease-short form (PBA-s)

* Key exploratory biochemical, neuroimaging, electrophysiological and clinical assessments

10.2 Sample Size Considerations

While there is no statistical rationale for the sample size, it has been selected based on prior experience with generation 2.0 ASOs given by IT injection to ensure that the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.

10.3 Populations

Safety Population: All patients who are randomized and receive at least one dose of Study Drug.

Per Protocol Population: All patients who are randomized and receive all doses of the protocol-specified Study Drug (ISIS 443139 or placebo).

PK Population: All patients who are randomized to ISIS 443139 and receive at least one dose of ISIS 443139 and have sufficient sampling to permit pharmacokinetic evaluation.

10.4 Definition of Baseline

For vital signs (BP, heart rate, respiration rate and temperature), baseline will be defined as the average of the three values collected prior to first dose (Screening, Study Day -1 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

An unblinded interim analysis may be performed and the results summarized by treatment group at the end of each cohort upon completion of dosing for that cohort or at any time if needed to address a safety concern. The results of an analysis of this type will not be shared with patients or Investigators.

A DSMB will be assembled to review safety, tolerability, pharmacokinetic and target engagement/pharmacodynamic (as needed) data collected on ISIS 443139 during this study. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to DSMB prior to each DSMB meeting. Based on its ongoing assessment of the safety and tolerability of ISIS 443139, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB charter and/or the statistical analysis plan (SAP).

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, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

Since there are limited placebo-treated patients within each dose cohort, the placebo-treated patients will be pooled for analysis.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Patient disposition will be summarized by treatment group. 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 Study Drug received will be summarized by treatment group.

All treatment-emergent adverse events (TEAEs) and SAEs will be summarized for each treatment group 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, etc., will be summarized by study visit for each treatment group. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

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

Columbia – Suicide Severity Rating Scale will be summarized by study visit for each treatment group. 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.

A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at one Post-Treatment Period visit for PK analyses. The CSF concentrations will be summarized using descriptive statistics and the ISIS 443139 half-life in CSF will be calculated, if possible.

Plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses. Plasma PK parameters will be summarized using descriptive statistics.

Non-compartmental PK analysis of ISIS 443139 in plasma will be carried out on each individual patient data set. C_{max} and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. The plasma half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate using available data, from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, where λ_z is the rate constant associated with the apparent terminal elimination phase. Partial areas under the plasma concentration-time curve from zero time (predose) to selected times (t) after the administration (AUC_t) will be calculated using the linear trapezoidal rule.

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 Statistical Analysis Plan.

10.6.4 Exploratory Analysis

The exploratory analyses will be conducted on the Per Protocol and Safety Populations.

Exploratory evaluations (Section 10.1.3) will be summarized using descriptive statistics by study visit and treatment group. Change and percent change from baseline over time will be summarized as appropriate. Comparison between ISIS 443139 group and the pooled placebo group will be performed in an exploratory manner. Details will be described in the Statistical Analysis Plan.

Additional exploratory 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 exploratory endpoints may be performed as where deemed appropriate.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

HD 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). 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 any Study Drug (ISIS 443139 or placebo) are 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 patient s 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.

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.

13. REFERENCES

Altmann KH, Dean NM, Fabbro D, Freier SM, Geiger T, Häner R, Hüsken D, Martin P, Monia BP, Müller M, Natt F, Nicklin P, Phillips J, Pieles U, Sasmor H, Moser HE. Second generation of antisense oligonucleotides: from nuclease resistance to biological efficacy in animals. Chimia 1996; 50: 168-176.

Bañez-Coronel M, Porta S, Kagerbauer B, Mateu-Huertas E, Pantano L, Ferrer I, Guzmán M, Estivill X, Martí E. A pathogenic mechanism in Huntington's disease involves small CAG-repeated RNAs with neurotoxic activity. PLoS Genet 2012; 8(2): e1002481.

Brossman B, Williams JK, Downing N, Mills JA, Paulsen JS. Development of the Huntington disease work function scale. J Occup Environ Med 2012; 54(10): 1300-1308.

Cerritelli SM and Crouch RJ. Ribonuclease H: the enzymes in eukaryotes. FEBS J 2009; 276: 1494-1505.

Chen JJ, Ondo WG, Khashayar D, Swope DM. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. Clinical Therapeutics 2012; 34: 1487-1504.

Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington's Disease. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14(4): 219-226.

Crooke ST and Bennett CF. Progress in antisense oligonucleotide therapeutics. Annu Rev Pharmacol Toxicol 1996; 36: 107-129.

DeRenzo EG, Conley RR, Love R. Assessment of capacity to give consent to research participation: state-of-the-art and beyond. J Health Care Law Policy 1998; 1(1): 66-87.

Duyao M, Ambrose C, Myers R, Novelletto A, Persichetti F, Frontali M, Folstein S, Ross C, Franz M, Abbott M, Gray J, Conneally P, Young A, Penney J, Hollingsworth Z, Shoulson I, Lazzarini A, Falek A, Koroshetz W, Sax D, Bird E, Vonsattel J, Bonilla E, Alvir J, Bickham Conde J, Cha J-H, Dure L, Gomez F, Ramos M, Sanchez-Ramos J, Snodgrass S, de Young M, Wexler N, Moscowitz C, Penchaszadeh G, MacFarlane H, Anderson M, Jenkins B, Srinidhi J, Barnes G, Gusella J, MacDonald M. Trinucleotide repeat instability and age of onset in Huntington's disease. Nat Gen 1993; 4: 387-392.

Duyao MP, Auerbach AB, Ryan A, Persichetti F, Barnes GT, McNeil SM, Ge P, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME. Inactivation of the mouse Huntington's disease gene homolog Hdh. Science 1995; 269: 407-410.

FDA: DRAFT Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials, September 2010.

Folstein SE. The psychopathology of Huntington's disease. J Nerv Ment Dis 1989; 177: 645.

Geary RS, Yu RZ, Watanabe T, Henry SP, Hardee GE, Chappell A, Matson J, Sasmor H, Cummins L, Levin AL. Pharmacokinetics of a tumor necrosis factor-α phosphorothioate 2′-*O*-(2-methoxyethyl) modified antisense oligonucleotide: comparison across species. Drug Metab Dispos 2003; 31: 1419–1428.

Henry SP, Stecker K, Brooks D, Monteith D, Conklin B, Bennett CF. Chemically modified oligonucleotides exhibit decreased immune stimulation in mice. J Pharmacol Exp Ther 2000; 292: 468-479.

Hinton-Bayre AD, Geffen GM, Geffen LB, McFarland KA, Friis P. Concussion in contact sports: reliable change indices of impairment and recovery. Clin Exp Neuropsychol 1999; 21: 70-86.

Hogarth P, Kayson E, Kieburtz K, Marder K, Oakes D, Rosas D, Shoulson I, Wexler NS, Young AB, Zhao H. Interrater agreement in the assessment of motor manifestations of Huntington's disease. Mov. Disord 2005; 20: 293-297.

Hunter A, Bordelon Y, Cook I, Leuchter A. QEEG measures in Huntington's disease: a pilot study. PLoS Curr 2010 Oct 25; 2: RRN1192.

Huntington G. On chorea. Med Surg Reporter 1872; 26: 320–321.

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136-142.

Inoue H, Hayase Y, Iwai S, Ohtsuka E. Sequence-dependent hydrolysis of RNA using modified oligonucleotide splints and RNase H. FEBS Letters 1987; 215: 327-330.

Ismailoglu I, Chen Q, Popowski M, Yang L, Gross S, Brivanloui AH. Huntingtin protein is essential for mitochondrial metabolism, bioenergetics and structure in murin embryonic stem cells. Dev Biol 2014; 391: 230-240.

Johnson SA, Stout JC, Solomon AC, Langbehn DR, Aylward EH, Cruce CB, Ross CA, Nance M, Kayson E, Julian-Baros E, Hayden MR, Kieburtz K, Guttman M, Oakes D, Shoulson I, Beglinger L, Duff K, Penziner E, Paulsen JS, Predict-HD Investigators of the Huntington Study Group. Beyond disgust: impaired recognition of negative emotions prior to diagnosis in Huntington's disease. Brain 2007; 130: 732-744.

Kantarci K, Reynolds G, Petersen RC, Boeve BF, Knopman DS, Edland SD, Smith GE, Ivnik RJ, Tangalos EG, Jack Jr CR. Proton MR spectroscopy in mild cognitive impairment and Alzheimer disease: comparison of 1.5 and 3T. Am J Neuroradiol 2003; 24: 843–849.

Kordasiewicz HB, Stanek LM, Wancewicz EV, Mazur C, McAlonis MM, Pyrel KA, Artates JW, Weiss A, Cheng SH, Shihabuddin LS, Hung G, Bennett CF, Cleveland DW. Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron 2012; 74: 1031-1044.

Kuermmerle S, Gutekunst CA, Klein AM, Li XJ, Li SH, Beal MF, Hersch SM, Ferrante RJ. Huntingtin aggregates may not predict neuronal death in Huntington's disease. Ann Neurol 1999; 46: 842-843.

Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR, International Huntington's Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Gen 2004; 65(4): 267-277.

McKay RA, Miraglia LJ, Cummins LL, Owens SR, Sasmor H, Dean NM. Characterization of a potent and specific class of antisense oligonucleotide inhibitor of human protein kinase C-α expression. J of Biol Chem 1999; 274: 1715-1722.

Monia BP, Lesnik EA, Gonzalez C, Lima WF, McGee D, Guinosso CJ, Kawasaki AM, Cook PD, Freier SM. Evaluation of 2′-modified oligonucleotides containing 2′-deoxy gaps as antisense inhibitors of gene expression. J Biol Chem 1993; 268: 14514-14522.

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

Nance M, Paulsen JS, Rosenblatt A, Wheelock V. A physician's guide to the management of Huntington's disease, Third Edition, Huntington's Disease Society of America 2011.

Nasir J, Floresco SB, O'Kusky JR, Diewert VM, Richman JM, Zeisler J, Borowski A, Marth JD, Phillips AG, Hayden MR. Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. Cell 1995; 81(5): 811-823.

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal cognitive assessment (MoCA): a brief screening tool for mild cognitive impairment. J American Geriatrics Society 2005; 53: 695-699.

Papoutsi M, Labuschagne I, Tabrizi SJ, Stout JC. The cognitive burden in Huntington's disease: pathology, phenotype, and mechanisms of compensation. Mov Disord. 2014; 29(5): 673-683.

Paulsen J, Ready R, Hamilton J, Mega M, Cummins J. Neuropsychiatric aspects of Huntington's disease. J Neurol, Neurosugery and Psychiatry 2001; 97: 310-314.

Paulsen JS, Smith MM, Long JD, PREDICT HD Investigators and Coordinators of the Huntington Study Group. Cognitive decline in prodromal Huntington disease; implications for clinical trials. J Neurol Neurosurg Psychiatry 2013; 84: 1233-1239.

Paulson HL and Albin RL. Huntington's Disease. Clinical Features and Routes to Therapy. In: Lo DC, Hughes, RE, editors. Neurobiology of Huntington's disease: Applications to drug discovery. Boca Raton, FL. CRC Press 2011. Chapter 1.

Petersen A, Gil J, Maat-Shieman ML, Bjorkqvist M, Tanila H, Araujo IM, Smith R, Popvic N, Wierup N, Norlen P, Li JY, Roos RA, Sundler F, Mulder H, Brundin P. Orexin loss in Huntington's disease. Hum Mol Genet 2005; 14(1): 39-47.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin G, Greenhill L, Shen S, Mann JJ. The Columbia-suicide severity rating scales: initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry 2011; 168: 1266-1277.

Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord 2012; 27(9): 1083-1091.

Roos, R. Huntington's disease: A clinical review. Orphanet Journal of Rare Diseases 2010; 5: 40.

Ross CA, Aylward EH, Wild EJ, Langbehn DR, Long JD, Warner JH, Scahill RI, Leavitt BR, Stout JC, Paulsen JS, Reilmann R, Unschuld PG, Wexler A, Margolis RL, Tabrizi SJ. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol 2014; 10(4): 204-216.

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

Shoulson I, Kurlan R, Rubin AJ, Goldblatt D, Behr J, Miller C, Kennedy J, Bamford KA, Caine ED, Kido DK, Plumb S, Odoroff C. Assessment of functional capacity in neurodegenerative movement disorders: Huntington's disease as a prototype. In Munsat TL, ed. Quantification of neurological deficit. Boston. Butterworth 1989. Chapter 20.

Shoulson I and Young AB. Milestones in Huntington disease. Mov Disord 2011; 26: 1127-1133.

Smith A. Symbol digit modalities test: Manual. 1982; Los-Angeles: Western Psychological Services.

Stanek LM, Yang W, Angus S, Sardi PS, Hayden MR, Hung GH, Bennett CF, Cheng SH, Shihabuddin LS. Antisense oligonucleotide-mediated correction of transcriptional dysregulation is correlated with behavioral benefits in the YAC128 mouse model of Huntington's disease. J Huntington's Disease 2013; 217-228.

Stout JC, Queller S, Baker KN, Cowlishaw S, Sampaio C, Fitzer-Attas C, Borowsky B, HD-CAB Investigators. HD-CAB: A cognitive assessment battery for clinical trials in Huntington's disease. Mov Disord 2014; 29: 1281-1288.

Sturrock A and Leavitt B. The clinical and genetic features of Huntington's disease. J Geriatric Psychiatry and Neurology 2010; 23: 243-259.

Videnovic A, Bernard B, Fan W, Jaglin J, Leurgans S, Shannon KM. The Montreal cognitive assessment as a screening tool for cognitive dysfunction in Huntington's disease. Mov Disord 2010; 25(3): 401-404.

Walecki J, Barcikowska M, Cwikla JB, Gabryelewicz T. N-acetylaspartate, choline, myoinositol, glutamine and glutamate (glx) concentration changes in protocol MR spectroscopy (1H MRS) in patients with mild cognitive impairment (MCI). Med Sci Monit 2011; 17(12): MT105-111.

Walker FO. Huntington's disease. Lancet 2007; 369 (9557): 218–228.

Wexler NS, Young AB, Tanzi RE, Travers H, Starosta-Rubinstein, Penney JB, Snodgrass SR, Shoulson I, Gomez F, Ramos Arroyo MA, Penchaszadeh GK, Moreno H, Gibbons K, Faryniarz A, Hobbs W, Anderson MA, Bonilla E, Conneally PM, Gusella JF. Homozygote for huntinton's disease. Nature 1987; 326: 194-197.

White JK, Auerbach W, Duyao MP, Vonsattel JP, Gusella JF, Joyner AL, MacDonald ME. Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. Nat Genet 1997; 17(4): 404-410.

Xenazine (tetrabenazine) [package insert]. Deerfield, IL: Lundbeck; 2011.

Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A. Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. Nat Genet 1995; 11(2): 155-163.

14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																				Post-Treatment Period (15 Weeks)		
Study Week	-6 to -1	1				2	5				6	9				10	13				14	17/ ET [2]	21	29/ ET[2]
Study Day	-43 to -2	-1	1	2	3	8	28	29	30	31	36	56	57	58	59	64	84	85	86	87	92	113	141	197
Visit Window (days) [3]	-	*	0	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	±2	±7	±7
Visit Type [4]	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	ph	cl	cl	cl	ph	ph	cl	cl	cl
Overnight Stay [5]			X→					X→					X→					X→						
Capacity to Consent Assessment and Informed Consent	X																							
Inclusion/Exclusion	X																							
Medical History and ISCED	X																							
MoCA	X																							
Vital Signs (BP, HR, RR, T)	X	X	X [5]				X	X[a]				X	X[a]				X	X[a]				X	X	X
Orthostasis	X		X [5]															X[b]					X	X
Physical& Neurological Exam [6]	X	X	X [5]	X [5]		X	X	X[c]	X[d]		X	X	X[c]	X[d]			X	X[c]	X[d]			X	X	X
Body Weight and Height [5]	X	X					X					X					X					X	X	X
Functional, Cognitive, Motor and Neuropsychiatric assessments [5]	X	X															X						X	X
C-SSRS [7]	X	X	X[b]	X		X	X	X[b]	X		X	X	X[b]	X			X	X[b]	X			X	X	X
qEEG	X	X																				X	X	X
Structural MRI [5]	X																					X		X
T2 flair, T2 star, T2 FSE/TSE MRI[8]	X																							X
rsfMRI and NODDI[8, 5]	X																							X
MRI of the CSF space[8]																						X		

Appendix A Schedule of Procedures *Continued*

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																				Post-Treatment Period (15 Weeks)		
Study Week	-6 to -1	1				2	5				6	9				10	13				14	17/ ET [2]	21	29/ ET[2]
Study Day	-43 to -2	-1	1	2	3	8	28	29	30	31	36	56	57	58	59	64	84	85	86	87	92	113	141	197
Visit Window (days) [5]	-	*	0	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	±2	±7	±7
Visit Type [6]	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	ph	cl	cl	cl	ph	ph	cl	cl	cl
^{1}H-MRS [8]	X																					X		X
ECG (12-Lead) [10]	X	X		X																		X		X
Chemistry Panel	X	X					X										X						X	X
Hematology	X	X					X										X						X	X
Urinalysis	X	X					X										X						X	X
Genetic Tests	X																							
HIV, Hepatitis B & C	X																							
Drug/Alcohol Screen	X																							
FSH [11]	X																							
Pregnancy Test [12]	X	X					X					X					X					X	X	X
Serum Biomarker Sample	X	X					X					X					X					X	X	X
Thyroid Panel		X					X										X						X	X
PT, INR, aPTT	X	X					X										X						X	X
Plasma Sampling for PK			X [3]	X [3]				X [3]					X[b]					X [7]	X[d]			X	X	X
Archived Serum Sample [13]	X	X					X					X					X					X	X	X
CSF Sample for PK/Safety/Biomarkers			X[b]					X[b]					X[b]					X[b]				X [9]	X[g]	X [1]
Archived CSF Sample			X[b]					X[b]					X[b]					X[b]				X[g]	X[g]	X[h]
Study Drug Administration			X					X					X					X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	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	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

* Visit windows are calculated relative to Study Day 1. Note that within each block of visits associated with dose administration, the visits must occur on 4 consecutive days. There are four "visit blocks" in this study: (Study Days -1, 1, 2 and 3), (Study Days 28, 29, 30 and 31), (Study Days 56, 57, 58 and 59) and (Study Days 84, 85, 86 and 87).

1 cl = clinic visit; ph = phone visit

2 If the patient terminates early from the Treatment Period but is willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received, (c) proceed to the Week 17 visit approximately 4 weeks after last dose and conduct all visits in the Post-Treatment Period. If the patient terminates early from the Treatment Period and is not willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received and (c) conduct the Week 29 visit as an Early Termination Visit. If the patient terminates early from the Post-Treatment Period, conduct the Week 29 visit as an Early Termination Visit.

3 On Study Day 1, the patient must stay in the clinic overnight and undergo safety monitoring follow-up as scheduled on Study Day 2. On Study Days 29, 57 and 85, the patient may either stay in the clinic overnight or be discharged (after a minimum observation period of 6 hours after Study Drug administration), provided the patient returns to the clinic on the following day (Day 30, 58 or 86) for all required assessments.

4 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.

5 Height is measured at Screening only.

6 Functional, Cognitive, Motor and Neuropsychiatric Tests are speeded tapping, UHDRS total functional capacity scale, UHDRS independence scale, UHDRS total motor scale, HD work function scale, HD Cognitive Battery (self-paced tapping, emotion recognition, CANTAB one-touch stockings, symbol-digit modalities test, Hopkins verbal learning test – revised and trail making tests), Problems Behavior Assessment for Huntington's disease-short form, Stroop Word Reading test and Map Search test.

7 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.

8 For imaging during the Screening period, the scans should be conducted sufficiently early in the Screening Period to allow for repeat scanning if necessary. For imaging at post-Screening visits, efforts should be made to conduct the imaging within the visit window. If re-scanning at a post-Screening visit is necessary because the original scan is not usable, the re-scanning should be conducted within one week of the original scan if at all possible.

9 rsfMRI and NODDI scans are conducted only in patients who have consented for these assessments.

10 Measured in triplicate at the Study Day -1 visit only.

11 Women who are not surgically sterile as confirmation of menopause.

12 Women who are not surgically sterile. Serum test at Screen visit; dipstick at post-screen visits.

13 Stored at -80º C for follow-up exploration of laboratory findings and/or adverse events (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 ISIS 443139.

Appendix A Schedule of Procedures *Continued*

Time (in reference to time of Study Drug administration):

a Predose, 3 and 6 hours post IT injection

b Predose

c Predose and 3 hours post IT injection; also conduct at 6 hours post IT injection on any dosing day that the patient does not stay in the clinic overnight (overnight stays are optional on Study Days 29, 57 and 85)

d 24 hours after prior dose of Study Drug

e Predose, 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours post IT injection

f Predose, 0.5, 1, 2, 3, 4 and 5 hours post IT injection

g All patients in Cohort A will have CSF collected on Study Day 113 (Week 17) and not on Study Day 141 (Week 21). For all other cohorts, CSF sampling will be conducted in approximately 50% of patients on Study Day 113 (Week 17) and in the remaining 50% of patients on Study Day 141 (Week 21), as assigned by the Sponsor according to a predetermined, randomized assignment.

h CSF sampling will be conducted at Study Day 197 (Week 29) in only those patients who attend the visit as an early termination visit and did not undergo CSF sampling on either Study Day 113 (Week 17) or Study Day 141 (Week 21). If CSF sampling was conducted on Study Day 113 (Week 17) or Study Day 141 (Week 21), do not collect CSF at Study Day 197 (Week 29)

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 ISIS 443139 or other similar oligonucleotides.

Clinical Chemistry	**Urinalysis**	**Screening Tests**	**CSF Safety Panel (Minimum Requirements)**
Sodium	Specific gravity	Hepatitis B surface antigen	Red blood cells
Potassium	pH	Hepatitis C antibody	White blood cells
Chloride	Protein	HIV antibody	Glucose
Total protein	P/C ratio	FSH (women only)	Protein
Albumin	Glucose	Serum βhCG	
Calcium	Ketones	Drug/Alcohol screen[2]	**Exploratory CSF Biomarker Panel**
Magnesium	Urobilinogen		mu Htt
Phosphorus	Leukocyte esterase	**Genetics**	total Htt
Bicarbonate	Nitrite	CAG repeat length	Proenkephalin
Glucose	Bilirubin	apoE isoform genotype	Clusterin
BUN	Blood	BCHE-K	FH
Creatinine	Red blood cells		C3
Total serum Bilirubin	White blood cells	**PK**[1]	IL-6
Uric acid	Epithelial cells	Plasma ISIS 443139 levels	TNFα
Alkaline phosphatase	Bacteria	CSF ISIS 443139 levels	IL-1β
AST (SGOT)	Casts		MCP-1
ALT (SGPT)	Crystals	**Pregnancy**	YKL-40
GGT	Color	Urine hCG	VILIP1
CPK	Appearance		ApoE
			Chromogranin B
Hematology	**Thyroid Panel**		Neurogranin
Red blood cells	TSH		SNAP25
Hemoglobin	Free T4		S100B
Hematocrit	Free T3		Tau
Platelets			Neurofilament light chain
MCV, MCH, MCHC	**Coagulation**		
White blood cells	aPTT		**Exploratory Serum Biomarker Panel**
WBC Differential (% and absolute)	PT		IL-6
• Neutrophils	INR		TNFα
• Eosinophils			24S-hydroxycholesterol
• Basophils			
• Lymphocytes			
• Monocytes			

1 Any of the collected PK plasma and CSF samples from the study patients may also be used by Isis for investigation of possible biomarkers of disease or the pharmacodynamic effects of ISIS 443139 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 ISIS 443139 with plasma and CSF 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.

2 Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

Study Period	Treatment Evaluation Period (13 Weeks)						Post-Treatment Period or Early Termination Visit (15 Weeks)		
Study Week	**1**		**5**	**9**	**13**		**17**	**21**	**29**
Study Day	**1**	**2**	**29**	**57**	**85**	**86**	**113**	**141**	**197**
CSF sampling	predose		predose	predose	predose		anytime[1]		
Plasma sampling	Predose, 0.5, 1, 2, 3, 4, 5, 6, 8,12 hours post IT injection	24 hours post Day 1 IT injection	predose	predose	Predose, 0.5, 1, 2, 3, 4, 5 hours post IT injection	24 hours post Day 85 IT injection	any-time	any-time	any-time

1 All patients in Cohort A will have CSF sampling on Study Day 113 (Week 17) and not on Study Day 141 (Week 21). For all other cohorts, CSF sampling will be conducted in approximately 50% of patients in the cohort on Study Day 113 (Week 17) and in the remaining 50% of patients in the cohort on Study Day 141 (Week 21), as assigned by the Sponsor. CSF sampling will be conducted on Study Day 197 (Week 29) in only those patients who attend the visit as an early termination visit and did not undergo CSF sampling on either Study Day 113 (Week 17) or Study Day 141 (Week 21). If CSF sampling was conducted on Study Day 113 (Week 17) or Study Day 141 (Week 21), do not collect CSF on Study Day 197 (Week 29).

IONIS PHARMACEUTICALS, INC.

ISIS 443139-CS1

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Protocol Amendment 3 – 5 April 2017

EudraCT No: 2015-000381-66

Sponsor:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

ISIS 443139-CS1

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Protocol Amendment 3 – 5 April 2017

Protocol History:

Original Protocol: 6 March 2015

Protocol Amendment 1: 7 May 2015

Protocol Amendment 2: 25 May 2016

Sponsor:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

CCI

CCI MD
Vice President, Clinical Development

ISIS 443139

Ionis Protocol Number ISIS 443139-CS1

Protocol Amendment 3

EudraCT No: 2015-000381-66

Clinical Phase: 1/2a

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

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Date: 5 April 2017

Confidentiality Statement

Protocol Signature Page

Protocol Number: ISIS 443139-CS1

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Amendment: Amendment 3

Date: 5 April 2017

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease," dated 5 April 2017, and agree to conduct the Study as described herein.

I agree to comply with the International Conference on Harmonization 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 Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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See Protocol Changes Section

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease
Study Phase	Phase 1/2a
Primary Objectives	To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 443139 to patients with Huntington's disease (HD)
Secondary Objectives	To characterize the cerebrospinal fluid (CSF) pharmacokinetics of ascending dose-levels of multiple IT administrations of ISIS 443139
Exploratory Objectives	To explore effects of multiple doses of ISIS 443139 on pharmacodynamic biomarkers and clinical endpoints relevant to HD. Plasma pharmacokinetic properties will also be assessed.
Study Design	ISIS 443139-CS1 is a multi-center, Phase 1/2a, randomized, double-blind, placebo-controlled study of ascending dose levels of multiple IT administrations of ISIS 443139 ("slow push" IT bolus) in patients with early manifest HD aged 25-65 years, inclusive. Five (5) dose level cohorts (A, B, C, D and E) will be enrolled sequentially, with patients randomized to Study Drug or to placebo in a 3 to 1 ratio. Cohort A will comprise 4 patients, Cohorts B and C will comprise 8 patients and Cohorts D and E will comprise 12 patients. All patients will be disease "Stage 1" out of a possible 5 stages, where 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. These stages also correlate with scores on the 13-point UHDRS Total Functional Capacity (TFC) Scale, with Stage 1 corresponding to TFC scores of 11-13. Randomization in Cohort D will be stratified by early Stage 1 (TFC ≥ 12) or late Stage 1 (TFC = 11) disease. Each patient will receive 4 doses of Study Drug with a 28-day interval between doses. Patients not completing a course of 4 IT bolus injections may be replaced up to a limit of 25% of the cohort sample and only if the reason for premature discontinuation from the Treatment Period does not involve a dose-limiting toxicity (DLT). Following the 3-month Treatment Period, there will be a 4-month Post-treatment Period. After study completion, an open-label extension study of ISIS 443139 will be implemented if this is warranted based on review of safety, tolerability, pharmacokinetic and exploratory pharmacodynamic findings.
Number of Patients	Approximately 44 patients will be enrolled in this study. The number of patients enrolled may be higher if some patients need to be replaced and/or if the sizes of certain cohorts are expanded to obtain further experience with particular dose levels. A maximum of 48 patients may be enrolled.
Study Population	**<u>Inclusion Criteria:</u>** *Signed Written Informed Consent* 1. Must have given written informed consent (signed and dated) and any authorizations required by local law 2. Must be capable of giving informed consent (in the opinion of the Investigator) *Target Population* 3. Early manifest, Stage 1 HD (defined as TFC of 11-13, inclusive), aged 25 to 65 years, inclusive, at the time of informed consent, with genetically confirmed disease (CAG repeat length ≥ 36 in huntingtin gene by direct DNA testing) 4. Body Mass Index (BMI) ≥ 18 and ≤ 32 kg/m^2; total body weight > 50 kg (110 lbs)

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	**Inclusion Criteria** ***Continued*** 5. Able and willing to meet all study requirements in the opinion of the Investigator, including travel to Study Center, procedures, measurements and visits, 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 and at the time of enrollment f. Patients must reside in a proximity to the Study Center that permits prompt appearance at the facility if requested by the Investigator (maximum of 4-hour travel to Study Center) *Reproductive Status* 6. 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 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo) If not surgically sterile, must have a negative HCG pregnancy test at Screening and prior to each dose administration 7. 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 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo) * 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:** *Target Disease-Related Exclusions* 1. Any condition, including severe chorea, that would prevent either writing or performing rapid computer tasks

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	**Exclusion Criteria:** ***Continued*** *Physical, Mental and Laboratory Test Findings* 2. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 12 months prior to Screening. For patients with (i) a suicide ideation score ≥ 4 on the Columbia Suicide Severity Rating Scale (C-SSRS) within the last 12 months, (ii) a score of 3 or 4 on question 2 of the Problems Behavior Assessment for Huntington's Disease – short form or (iii) suicidal behaviors within the last 12 months (as measured by the answer "Yes" on any of the C-SSRS Suicidal Behavior Items), a risk assessment should be done by an appropriately-qualified mental health professional (e.g., a Psychiatrist or licensed Clinical Psychologist) to assess whether it is safe for the patient to participate in the study. In addition, patients deemed by the Investigator to be at significant risk of suicide, major depressive episode, psychosis, confusional state or violent behavior should be excluded 3. Clinically significant laboratory, vital sign or ECG abnormalities at Screening (including heart rate (HR) < 45 bpm; SBP < 90 mmHg; confirmed BP readings > 170/105 mmHg) 4. Positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B at Screening *Prohibited and Restricted Medications and Procedures* 5. Treatment with another investigational drug, 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 6. Current or recent (within the last 6 months) use of antipsychotics (prescribed for psychosis), cholinesterase inhibitors, memantine, amantadine or riluzole. Stable use of antipsychotics (prescribed for treatment of motor symptoms) and/or tetrabenazine is not permitted 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 7. 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 8. Supplement use (e.g., coenzyme Q10, vitamins, creatine) unless stable dose for 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study 9. Antiplatelet or anticoagulant therapy within the 14 days prior to Screening or anticipated use during the study, including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban 10. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed at least 3 days prior to the first day Study Drug is administered to the patient (Study Day 1) 11. Prior treatment with an antisense oligonucleotide (including siRNA) 12. Any history of gene therapy or cell transplantation or any other experimental brain surgery 13. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter

PROTOCOL SYNOPSIS *Continued*

<table>
<tr><td>Study Population
Continued</td><td><u>Exclusion Criteria:</u> Continued
Medical History and Concurrent Disease
14. Significant history of alcoholism or drug/chemical abuse
15. Clinically relevant hematological, hepatic, cardiac or renal disease or event (e.g., previous acute coronary syndrome within 6 months of Screening). Abnormal hepatic, renal or hematology lab tests must be discussed with the Sponsor Medical Monitor
16. Known history of human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
17. Any condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment
18. History of bleeding diathesis or coagulopathy, platelet count < LLN
19. A medical history of brain or spinal disease that would interfere with the LP process, CSF circulation or safety assessment, including tumors or abnormalities by MRI or computed tomography (CT), subarachnoid hemorrhage, suggestion of raised intracranial pressure on MRI or ophthalmic examination, spinal stenosis or curvature, chiari malformation, hydrocephalus, syringomyelia, tethered spinal cord syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome
20. History of post-lumbar-puncture headache of moderate or severe intensity and/or blood patch
21. 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
22. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
23. Have any other conditions which, in the opinion of the Investigator, would make the patient unsuitable for inclusion or could interfere with the patient participating in or completing the study</td></tr>
<tr><td>Treatment Groups</td><td>ISIS 443139, Placebo
There will be 5 multiple-dose cohorts (n = 4, 8 or 12 per cohort, randomized 3 active: 1 placebo). Patients will receive 4 IT bolus doses of Study Drug at 4-week intervals during the 3-month Treatment Period (Days 1, 29, 57, 85). For patients who receive ISIS 443139, planned total dose is shown in the table below.
<table>
<tr><th>Planned Dose of Active Study Drug</th><th># of doses</th><th>Total ISIS 443139</th></tr>
<tr><td>Cohort A: 10 mg ISIS 443139</td><td>4</td><td>40 mg</td></tr>
<tr><td>Cohort B: 30 mg ISIS 443139</td><td>4</td><td>120 mg</td></tr>
<tr><td>Cohort C: 60 mg ISIS 443139</td><td>4</td><td>240 mg</td></tr>
<tr><td>Cohort D: 90 mg ISIS 443139</td><td>4</td><td>360 mg</td></tr>
<tr><td>Cohort E: 120 mg ISIS 443139</td><td>4</td><td>480 mg</td></tr>
</table></td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>Each dose of ISIS 443139 or placebo 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.
Dosing instructions and details regarding administration will be provided in the Study Drug manual. The site pharmacist will be blinded to treatment assignment.</td></tr>
</table>

PROTOCOL SYNOPSIS *Continued*

Dose Escalation	Five (5) dose level cohorts (Cohorts A, B, C, D and E) will be enrolled sequentially, with patients each receiving 4 doses of Study Drug at 28-day intervals. The progression of the study from one cohort to the next will be determined by the Sponsor in collaboration with the Data and Safety Monitoring Board (DSMB) and will generally be based on the number of DLTs observed in patients treated with ISIS 443139. Beginning with Cohort B, dose administration in a cohort may commence only after (1) all patients in the prior cohort have been enrolled, (2) at least 4 patients in the prior cohort have received a cumulative dose that is equal to or greater than the initial dose planned for the cohort and safety in these patients has been monitored for at least 7 days post-treatment after reaching that cumulative dose, and (3) safety results for all patients enrolled in the prior cohorts have been reviewed by the DSMB. The occurrence of DLTs in 2 patients in a cohort will result in the dose tested in the cohort being dose limiting in this study. If a single DLT is encountered in Cohort A, the cohort may be expanded up to 8 patients to assess safety at that dose. Other dose cohorts (Cohorts B, C, D and E) may also be expanded up to 100% if a single DLT is encountered in those cohorts. If dosing in higher dose cohort(s) is ongoing at the time a single DLT is encountered in a lower-dose cohort, further enrollment in the higher dose cohort(s) will stop until all current patients have completed dosing and at least 7 days of post-dose safety evaluations. In addition, the DSMB will convene to decide if further measures are required such as pausing or reducing dosing in ongoing patients in the higher dose cohort(s). The occurrence of (i) DLTs in 2 patients in a cohort or (ii) a single SAE (excluding those attributable to the lumbar puncture, other study procedure or HD) that is evaluated by the Sponsor as related to Study Drug and is of sufficient significance to be dose limiting will result in termination of further dosing in that cohort and any higher dose cohort that is also ongoing.
Rationale for Dose and Schedule Selection	ISIS 443139 dose levels and dose interval for ISIS 443139-CS1 were selected based on preclinical toxicology and pharmacokinetic observations. CCI [redacted] Monthly dosing is expected to achieve ISIS 443139 brain cortex tissue levels at steady state by Day 92, and is expected to be safe and well-tolerated by patients.
Study Visit Schedule and Procedures	After informed consent is obtained, patients will undergo a screening evaluation during a 6-week period prior to baseline. Patients who meet the eligibility criteria will visit the Study Center on Study Day -1 to undergo baseline clinical, blood, and electrophysiological evaluations and for re-assessment of eligibility. On Study Day 1, patients will be admitted to the Study Center, undergo pre-dose evaluations of vital signs and then receive an IT bolus injection (slow push) of ISIS 443139 or placebo (3:1). Following the initial LP injection on Day 1, patients will be kept at the Study Center for at least 24 hours and carefully monitored for any adverse clinical symptoms or signs. This inpatient post-dose assessment may be reduced to a minimum of 6 hours following the 2nd, 3rd and 4th dose administrations provided a visit is made to the Study Center the next day. Assessments during these admission periods include neurological, electrophysiological and physical examination, vital signs, ECGs, blood sampling and clinical laboratory analyses. Full standard neurological assessment (including fundi) will be performed 3 hours post-dosing with Study Drug and prior to discharge from the Study Center. Study Drug administration will take place on Study Days 1, 29, 57 and 85. In the Treatment Period, Study Center visits are held on Study Days 1, 2, 8, 28, 29, 30, 36, 56, 57, 58, 84, 85 and 86.

PROTOCOL SYNOPSIS *Continued*

Study Visit Schedule and Procedures ***Continued***	During the Post-Treatment Period, patients will visit the Study Center on Study Days 113, 141 and 197 (study completion visit). In addition, the Study Center will monitor the patient's condition through telephone contact on Study Day 3, 31, 59, 64, 87 and 92. CSF samples will be taken pre-dose on each Study Drug IT injection day (Days 1, 29, 57, 85) and on Day 113 or 141. These samples will be utilized for PK, Htt protein and other biomarker and laboratory analyses. If a patient terminates early from the Treatment Period of the study, he/she will be encouraged to return for the near-term follow-up visits associated with the most recent dose of Study Drug and for the Post-Treatment Period (Days 113-197).
Safety and Tolerability Evaluations	Safety and tolerability evaluations will 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 • Clinical and neuroimaging (including safety sequences) assessments The safety and tolerability of ISIS 443139 will be assessed by determining the incidence, severity and dose-relationships of AEs and changes in laboratory parameters by dose. In addition, clinical, electrophysiological and volumetric neuroimaging assessments will be used to monitor for unexpected deterioration. Safety results in patients dosed with ISIS 443139 will be compared with those from patients dosed with placebo. Placebo-treated patients will be pooled for analysis.
Pharmacokinetic Evaluations	A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at 1 Post-Treatment Period visit (either Study Day 113 or 141) for PK analyses. The CSF concentrations will be summarized using descriptive statistics and the ISIS 443139 half-life in CSF will be calculated, if possible. Analysis of the levels of ISIS 443139 in CSF is of key importance. In addition, plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses. Plasma maximum concentration (C_{max}), area under the curve (AUC), elimination half-life and trough and post-distribution drug levels will be assessed, where appropriate.

Exploratory Evaluations	Exploratory evaluations will include:
	• Biochemical
	  ○ CSF levels of mutant Htt* and total Htt
	  ○ Potential biomarkers of HD disease progression
	• CSF: neurofilament light chain*, proenkephalin, clusterin, factor H (FH), C3, interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β), MCP-1, chitinase-3-like protein 1 (YKL-40), visinin-like protein 1 (VILIP1), apolipoprotein, chromogranin B, neurogranin, SNAP25, S100B and tau

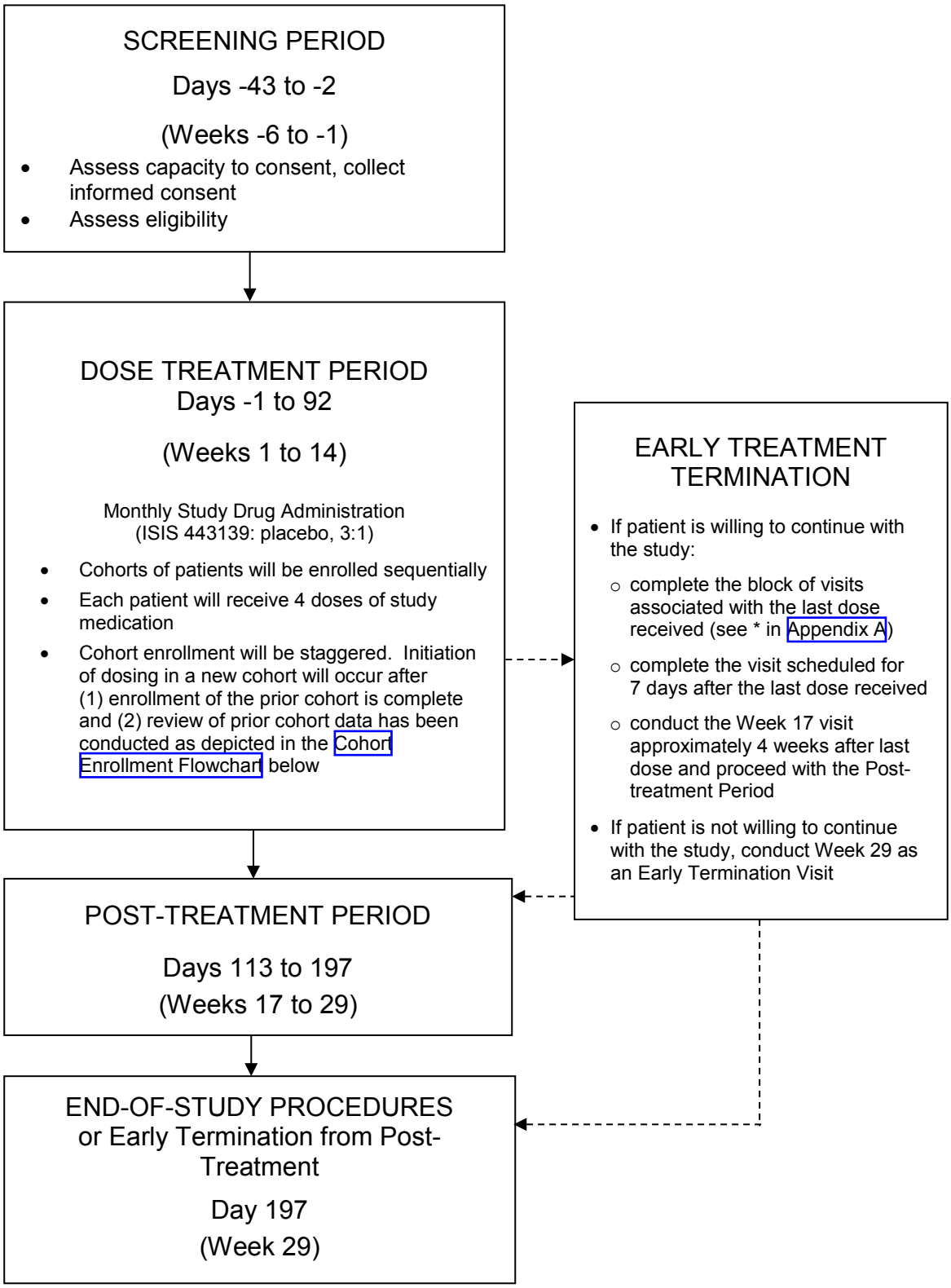
PROTOCOL SYNOPSIS *Continued*

Exploratory Evaluations *Continued*	Exploratory evaluations will include: *Continued*
	• Plasma or Serum: IL-6, TNFα and 24S-hydroxycholesterol
	• Neuroimaging
	  o Structural MRI volumes, including but not limited to:
	  ▪ Caudate
	  ▪ Whole brain
	  ▪ Ventricular*
	  o MRS spectroscopy for frontal lobe myoinositol and N-Acetylaspartic acid (NAA)
	  o Resting state functional MRI
	  o Neurite orientation dispersion and density imaging (NODDI)
	• Electrophysiological
	  o qEEG
	• Clinical
	  o Functioning/ability to perform activities of daily living
	  ▪ UHDRS Total Functional Capacity Scale (TFC)
	  ▪ UHDRS Independence Scale
	  ▪ HD Work Function Scale
	  o Cognitive and motor tests:
	  ▪ HD Cognitive Battery*
	  • Self-Paced Tapping
	  • Emotion Recognition
	  • CANTAB One Touch Stockings
	  • Symbol Digit Modalities Test
	  • Hopkins Verbal Learning Test Revised
	  • Trail Making Test Part B
	  ▪ UHDRS Total Motor Scale
	  ▪ Map Search Test
	  ▪ Stroop Word Reading Test
	  ▪ Speeded Tapping
	  o Neuropsychiatric evaluation
	  ▪ Problems Behavior Assessment for Huntington's disease-short form (PBA-s)
	Evaluations will include comparisons between ISIS 443139-treated patients and placebo-treated patients of the above biomarkers and clinical evaluations. If CSF Htt protein level is reflective of target engagement, exploratory evaluations will be conducted to relate dose and PK to CSF Htt protein level. Placebo-treated patients will be pooled for analysis.
	* Key exploratory biochemical, neuroimaging, electrophysiological and clinical assessments

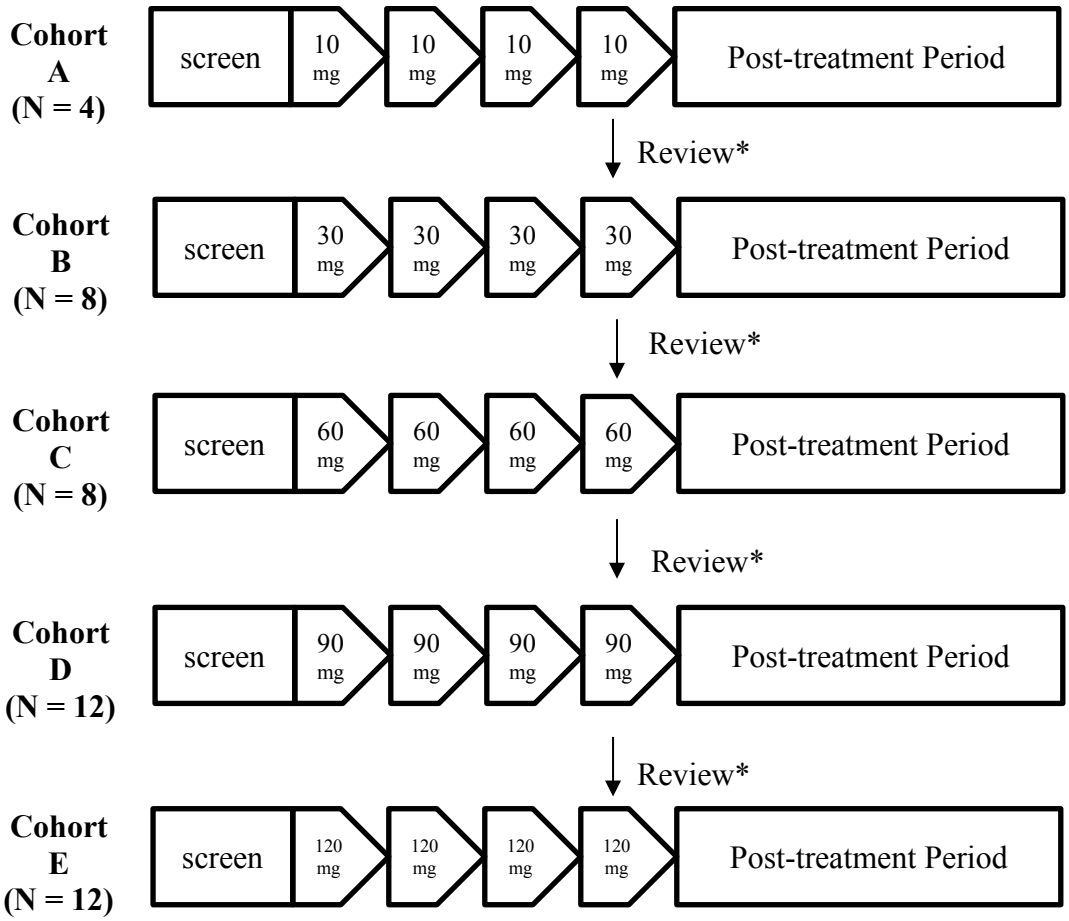
PROTOCOL SYNOPSIS *Continued*

Statistical Considerations	While there is no statistical basis for the sample size, it has been selected based on prior experience with generation 2 ASOs given by IT injection to ensure that the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.
Sponsor	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



COHORT ENROLLMENT FLOWCHART



* DSMB and Sponsor review of data to permit initiation of dosing in a new cohort will occur when:

- at least 4 patients in the current cohort have received multiple doses of Study Drug such that the cumulative dose received by each of these patients meets or exceeds the initial dose planned for the new cohort and
- safety data have been collected in these patients through at least 7 days after receipt of the necessary cumulative dose.

Prior to initiating dosing in a new cohort, the DSMB will review the safety data described above (at minimum) and make a recommendation regarding initiation of the new cohort.

Additionally, the Sponsor may conduct a blinded review (or reviews) of accumulating pharmacokinetic data and compare those data to the ISIS 443139 levels that are expected to produce a pharmacologic effect (according to the preclinical PK/PD model). Based on this review, the dose level(s) for future cohort(s) may be adjusted. The maximum dose level tested in a cohort will not exceed 120 mg. Beginning with Cohort C, the dose level for a cohort will not exceed 2 times the dose tested in the prior cohort.

Note: Each  represents 1-dose followed by a 28-day observation period.
The Post-treatment Period is 15 weeks.

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)
AUC	Area under the curve
AUC_t	Area under the plasma concentration-time curve from time zero to time t
βhCG	Beta-subunit of human chorionic gonadotropin (pregnancy test)
BCHE-K	Butyrylcholinesterase K variant
BP	Blood pressure
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
cl	Clinic
CRF	Case report form
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DSMB	Data And Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
FH	Factor H
FSE	Fast spin echo
GCP	Good Clinical Practice
^{1}H-MRS	Proton magnetic resonance spectroscopy
HD	Huntington's disease
HDWF	Huntington's disease work function

Htt	Huntingtin protein
HIV	Human Immunodeficiency Virus
HR	Heart rate
HVLT-R	Hopkins verbal learning test - revised
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
INR	International normalized ratio
IRB	Institutional Review Board
ISIS 443139	Antisense inhibitor of Htt
IT	Intrathecal(ly)
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein-1
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mI	Myo-inositol
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRS	Magnetic resonance spectroscopy
MTD	Maximum tolerated dose
NAA	N-Acetyl-aspartate
NCS	Not clinically-significant
NODDI	Neurite orientation dispersion and density imaging
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
PK	Pharmacokinetic(s)

PBA-s	Problems behavior assessment for Huntington's disease – short form
PT	Prothrombin time
qEEG	Quantitative EEG
rsfMRI	Resting state functional MRI
RNase H	Ribonuclease H (a non-specific endonuclease and catalyzes the cleavage of RNA via a hydrolytic mechanism)
S100B	S100 calcium binding protein B
SAD	Single ascending dose
SAE	Serious adverse event
siRNA	Small interfering ribonucleic acid
SAP	Statistical Analysis Plan
SNAP25	Synaptosomal-associated protein 25
Study Day 1	Defined as the first day Study Drug is administered to the patient
Study Drug	ISIS 443139 or placebo
SUSAR	Suspected unexpected serious adverse reaction
SDMT	Symbol digit modalities test
TEAE	Treatment-emergent adverse event
TFC	Total functional capacity
T_{max}	Time to maximal concentration
TMS	Total motor scale
TMT-A	Trail-making test part A
TMT-B	Trail-making test part B
TNFα	Tumor necrosis factor alpha
TSE	Turbo spin echo
UHDRS	Unified Huntington's disease rating scale
VILIP1	Visinin-like protein 1
WBC	White blood cell
YKL-40	Chitinase-3-like protein 1

1. OBJECTIVES

1.1 Primary Objectives

To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of an antisense inhibitor of Htt (ISIS 443139) to patients with Huntington's disease (HD)

1.2 Secondary Objectives

To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT administrations of ISIS 443139.

1.3 Exploratory Objectives

To explore effects of multiple doses of ISIS 443139 on potential target engagement and disease progression biomarkers and clinical endpoints relevant to HD. Plasma pharmacokinetic properties of ISIS 443139 will also be assessed. Disease progression markers are included primarily as a safety measure to document any marked worsening. A lesser objective is to gain experience with these measures in an ISIS 443139 clinical study as preparation for subsequent, longer-term clinical studies. It is not expected that the majority of biomarkers and clinical measures will be impacted significantly by the 3 months of dosing planned for this study. For the current study, select disease progression markers are considered to be key exploratory target engagement, biochemical, neuroimaging and cognitive assessments based on their potential to evidence changes in disease progression in early HD. These key exploratory endpoints are mutant Htt in CSF, neurofilament light chain in CSF, ventricular volume as assessed by structural MRI and the composite cognitive score resulting from assessment of the components of the HD Cognitive Battery.

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 has been elusive, studies suggest that Htt 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 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* 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. 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 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 et al. 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), a vesicular monoamine transporter 2 inhibitor, is the only drug currently approved for HD, and its label is specific for hyperkinetic motor disorders with Huntington's chorea. Tetrabenazine is approved in the United States, New Zealand, Australia, Canada, Israel and some European countries. However, the drug has been linked to many significant adverse events (AEs), including Parkinsonism, akathisia, sedation, depression and suicidal thoughts (Xenazine label 2011). Tetrabenazine is contraindicated in patients who are actively suicidal and in patients with untreated or inadequately treated depression (Xenazine label 2011), a population that includes approximately > 40% of HD patients (Chen et al. 2012). Additionally, tetrabenazine 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 (muHtt) (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).

ISIS 443139 is being developed to reduce the synthesis of Htt by targeting *HTT* mRNA and directing its catalytic degradation through the action of ribonuclease H (RNase H), 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 muHtt 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 ISIS 443139 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 ISIS 443139

2.3.1 Mechanism of Action

ISIS 443139 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 ISIS 443139 to the cognate mRNA results in the RNase H-mediated degradation of the *HTT* mRNA, thus preventing production of the Htt protein. Both wild-type and mutant *HTT* mRNA are targeted by ISIS 443139.

2.3.2 Chemistry

Chemically, ISIS 443139 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer). CCI The nucleotide sequence of ISIS 443139 (Figure 1) is complementary to a 20-nucleotide stretch CCI of the *HTT* mRNA. CCI These MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003) and (3) amelioration of some high dose toxicities resulting in an improved safety profile compared to first generation

antisense drugs containing phosphorothioate-modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The central portion of the oligonucleotide is composed of CCI . ISIS 443139 employs this chimeric structure to enable use of the RNase H-mechanism for antisense activity. While the 2′-MOE modification confers increased stability and affinity, it does not support RNase H catalysis of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999) because conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids are not recognized by RNase H enzymes (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H recognition.

Figure 1 Design of ISIS 443139

2.3.3 Preclinical Experience

CCI

2.3.4 Clinical Experience

ISIS 443139 has not been evaluated in any clinical setting.

2.4 Rationale for Study Design

2.4.1 Rationale for the Study Population

This is the first study of ISIS 443139 in humans, and it will be conducted in patients with early manifest HD. Early manifest HD patients are generally active and independent in most areas of functioning (often still working or driving). These patients are fully capable of informed consent. It is necessary to conduct this study in patients, rather than in healthy volunteers, for 2 reasons. First, a better understanding of the safety of ISIS 443139 in its intended target population will be achieved in patients since the intended target of the Study Drug (i.e., mutant *HTT* mRNA transcripts) is not present in healthy volunteers. Second, ISIS 443139 must be administered via intrathecal (IT) administration, and consideration of the balance between risk and benefit justifies investigation in a patient population only. Although assessment of safety is the primary objective of this study, HD patients who enroll in this study will be relatively early in the manifest disease process and may experience benefit from the investigational treatment if it addresses the primary pathogenesis of the disease.

Eligible patients will be aged ≥ 25 years of age to avoid very high CAG repeats associated with early disease onset (e.g., > 55 repeats) as such patients are considered to have a somewhat different, rapidly-progressing phenotype. Eligible patients will also be ≤ 65 years of age to avoid undesirable comorbidity that is more common above this age.

2.4.2 Rationale for a Multiple Ascending Dose Design

This is a first-in-man, multiple ascending dose (MAD) study in patients with HD. This design is rational given the prolonged time between doses and the rarity of the patient population. Also, the study is designed with a focus on patient safety.

The study is designed to capture the information that would ordinarily be obtained in 2 separate studies – a single ascending dose (SAD) study and a MAD study. The length of the dosing interval makes this design feasible. With Study Drug dosing at 28-day intervals, comprehensive safety, tolerability and pharmacokinetic evaluations can be conducted in each patient for 28 days after the first dose. This is comparable to the evaluation that would be conducted in a SAD study. At the conclusion of this 28-day period, monthly dosing will continue (in the absence of significant safety issues related to Study Drug) for 3 additional doses, allowing for evaluation of safety, tolerability and pharmacokinetics during a multiple-dose regimen.

This design, which eliminates the need for a SAD study, is appropriate because of the nature of the patients under investigation. These are rare patients with a devastating disease, and Study Drug has to be administered by IT injection. Therefore, it is important to obtain a maximum amount of information from each patient enrolled in each study conducted in this population.

Patient safety is paramount with this study design. For example, only clinical research facilities with capabilities for 24-hour in-patient monitoring will be utilized, and patients will be required to live close enough to the facility to permit prompt appearance at the facility if requested. Each patient will be required to have a trial partner (i.e., a reliable and competent individual with a close relationship with the patient), and the Investigator will seek supplemental information about the patient's condition from the trial partner using validated assessment tools. In addition,

patient safety during the study will be monitored closely and on an ongoing basis by an independent, unblinded Data Safety Monitoring Board (DSMB).

2.4.3 Rationale for Dose Levels and Dosing Schedule

The proposed study will test the safety, tolerability, and PK of multiple doses of ISIS 443139 administered as IT injections. Five (5) dose levels will be evaluated. The doses are predicted to produce a range of pharmacologic effect but are not intended to elicit dose-limiting toxicities.

ISIS 443139 dose levels and dose interval for ISIS 443139-CS1 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. CCI

CCI

. The dose interval (administration every 28 days) was selected based on the nonclinical pharmacokinetic and pharmacodynamic (*HTT* mRNA reduction) data required to achieve ISIS 443139 brain cortex tissue levels that are predicted to be at steady state by Day 92 and to achieve reduction in *HTT* mRNA levels. Also, monthly dosing is expected to be safe and well-tolerated by patients.

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

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 1/2a, multi-center, double-blind, randomized, placebo-controlled, dose-escalation study conducted in patients with early manifest HD. The study consists of 5 cohorts (n = 4-12 per cohort, randomized 3 active:1 placebo). The doses planned for the study are shown below. Based on emerging safety data from this study, 1 or more cohorts may be expanded by enrolling additional patients. Additionally, pharmacokinetic and pharmacodynamic measures will be collected at each dose level and compared to the results that are predicted by models constructed from preclinical data. The doses utilized in remaining cohorts may be adjusted, or an additional cohort may be added, if necessary to achieve pharmacologically relevant levels. The maximum dose tested in a cohort will not exceed 120 mg. Beginning with Cohort C, the dose level for a cohort will not exceed 2 times the dose tested in the prior cohort.

Cohort A: N = 4, 10 mg ISIS 443139 or placebo (3:1)

Cohort B: N = 8, 30 mg ISIS 443139 or placebo (6:2)

Cohort C: N = 8, 60 mg ISIS 443139 or placebo (6:2)

Cohort D: N = 12, 90 mg ISIS 443139 or placebo (9:3)

Cohort E: N = 12, 120 mg ISIS 443139 or placebo (9:3)

Randomization in Cohort D will be stratified by early Stage 1 (TFC $\geq$ 12) or late Stage 1 (TFC = 11) disease, where Stage 1 represents the highest level of capacity of the 5 stages of manifest disease.

Patients will receive 4 monthly IT doses of Study Drug (ISIS 443139 or placebo). Cohorts will be enrolled sequentially. Initiation of dosing in a new cohort may begin after 3 conditions have been met: (1) all patients in the lower-dose cohorts have been enrolled; (2) at least 4 patients in the lower-dose cohort have been followed for 7 days after receipt of a cumulative dose that meets or exceeds the initial dose for the next higher dose level cohort; and (3) a review of data collected in the lower-dose cohorts has been conducted by the DSMB and a decision has been made to proceed with the next cohort (see Section 3.7).

After study completion, an open-label extension study of ISIS 443139 may be implemented if warranted based on review of safety, tolerability, pharmacokinetic and exploratory pharmacodynamic findings and subject to approval by the relevant Competent Authorities and Ethics Committees.

3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3 Number of Patients

Approximately 44 patients are planned to be enrolled in this study. The number of patients enrolled may be higher if some patients need to be replaced and/or if the sizes of the cohorts are

expanded to obtain further experience with particular dose levels. A maximum of 48 patients may be enrolled.

3.4 Overall Study Duration and Follow-up

The overall study duration will be approximately 7-8 months. The study will consist of a Screening Period of up to 6 weeks, a 13-week Treatment Period and a 15-week Post-Treatment Period. Please refer to the Schedule of Procedures in Appendix A.

3.4.1 Screening Period

Patient eligibility for the study will be determined within 6 weeks prior to patient entry into the Treatment Period.

3.4.2 Treatment Period

Eligible patients will report to the Study Center for monthly administration of Study Drug and for additional, non-dosing visits as described in the Schedule of Procedures in Appendix A.

In Cohorts A and B, no more than 1 patient may begin the Treatment Period on a given day. In later cohorts, the first 2 patients in the cohort may not begin the Treatment Period on a given day.

3.4.3 Post-Treatment Period

Patients will return to the Study Center for follow-up visits 4, 8 and 16 weeks after the last dose of Study Drug. The final study visit will be Study Day 197/Week 29.

3.5 End-of-Study

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

3.6 Data and Safety Monitoring Board

An independent and unblinded DSMB will be assembled to review data collected on ISIS 443139 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 443139, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. The progression of the study from one cohort to the next will be determined by the Sponsor and the DSMB, and this determination will generally be based on the number of dose-limiting toxicities (DLTs) observed in patients treated with ISIS 443139.

Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data will be outlined in the DSMB Charter. The DSMB will consist of at least 3 voting members, all medical doctors experienced in the conduct of clinical studies in patients with neurodegenerative diseases and otherwise independent from the conduct of the study. Additional non-voting members may join the DSMB as required. A majority of voting members must agree before escalation dose can proceed. The decisions of the DSMB will be recorded in minutes of the meeting.

3.7 Dose Escalation

Five (5) dose level cohorts (Cohorts A, B, C, D and E) will be enrolled sequentially, with patients each receiving 4 doses of Study Drug at 28-day intervals. In Cohorts A and B, no more than 1 patient may begin the Treatment Period on a given day. In later cohorts, the first

2 patients in the cohort may not begin the Treatment Period on a given day. The progression of the study from initiation of dosing in one cohort to the next will be determined by the Sponsor and the DSMB.

Beginning with Cohort B, dose administration in the cohort may commence only after the following minimum requirements are met in the prior cohort:

- All patients in the prior cohort have been enrolled
- At least 4 patients in the prior cohort have received multiple doses of Study Drug (ISIS 443139 or placebo) such that the cumulative dose received by each patient is equal to or greater than the dose level planned for patients in the new cohort. This corresponds to a requirement for multiple-dose administration in all patients in Cohort A (when considering escalation to Cohort B) and multiple-dose administration in at least 50% of patients in Cohorts B or C (when considering escalation to Cohort C or D, respectively)
- Patient safety in the prior cohort has been monitored for at least 7 days post-treatment after receipt of the cumulative dose that meets or exceeds the dose planned for the new cohort, and those data are available for review
- Safety data in the prior cohort have been reviewed by the DSMB and the DSMB has recommended initiation of the new cohort

Additionally, the Sponsor may conduct a blinded review (or reviews) of accumulating CSF pharmacokinetic data and compare those data to the ISIS 443139 levels that are expected to produce a pharmacologic effect (according to the preclinical PK/PD model). This review will be conducted in a manner that does not associate individual data with particular patients for those involved in the conduct of the study. Based on this review, the dose level(s) for future cohort(s) may be adjusted. The maximum single and cumulative doses administered in a cohort will not exceed 120 and 480 mg, respectively. Beginning with Cohort C, the dose level for a cohort will not exceed 2 times the dose tested in the prior cohort.

If a single DLT is encountered in Cohort A, the cohort may be expanded from 4 to up to 8 patients to assess safety at that dose. Other dose cohorts (Cohorts B, C, D and E) may also be expanded by up to 100% if a single DLT is encountered in those cohorts. If dosing in higher dose cohort(s) is ongoing at the time a single DLT is encountered in a lower-dose cohort, further enrollment in the higher dose cohort(s) will stop until all current patients have completed dosing and at least 7 days of post-treatment safety evaluations. In addition, the DSMB will convene to decide if further measures are required such as pausing or reducing dose in ongoing patients in the higher dose cohort(s).

The occurrence of (i) DLTs in 2 patients in a cohort or (ii) a single SAE (excluding those attributable to the lumbar puncture, other study procedure or HD) that is evaluated by the Sponsor as related to Study Drug and is of sufficient significance to be dose limiting will result in termination of further dosing in that cohort and any higher dose cohort that is also ongoing. In this situation, the DSMB will determine if the previous (lower) tolerated dose is the maximum tolerated dose (MTD). The Sponsor and DSMB will determine if enrollment of additional patients at the previous (lower) tolerated dose is required to confirm that there is an acceptable

toxicity profile at the lower-dose or if a cohort of intermediate dose level (between the previous (lower) tolerated dose and the terminated dose) should be enrolled.

3.8 Dose Limiting Toxicity

A suspected DLT is defined as an adverse event (AE) that, in the judgment of the Investigator, is of sufficient significance to be dose limiting, is possibly or definitely related to Study Drug (i.e., the AE is substantially less likely to occur in patients not administered the Study Drug) and that it is not a known sign or symptom of HD or effect of any study procedure (e.g., LP, venipuncture, MRI scan).

If an Investigator considers an event to be a suspected DLT, the event will be referred to the unblinded DSMB which will determine whether it constitutes a DLT.

If a suspected DLT occurs during IT injection of the Study Drug, administration of Study Drug to the patient must be stopped (i.e., the injection must be discontinued immediately and no further Study Drug injections may be administered in this patient). The Investigator should contact the Ionis Medical Monitor as soon as possible to discuss the case. The DSMB should convene and determine (based on unblinded data review, if necessary) if any relevant findings have been observed in other patients in the study.

Patients that experience a DLT will discontinue study treatment but should complete any follow-up visits associated with the most recent dose (see Section 8.9) and should complete the Post-Treatment Period.

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. At the time of randomization, patients will 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. The screening number and patient identification number must remain constant throughout the entire study. In the event the patient is re-consented and re-screened, the patient must be given a new screening number. 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 ISIS 443139 or placebo. Within each cohort, randomization will be 3:1 ISIS 443139:placebo as outlined in Section 3.1.

The Sponsor or designee will prepare the randomization list.

4.3 Replacement of Patients

Patients withdrawn early from the Study who do not complete all scheduled doses of Study Drug (ISIS 443139 or placebo) may be replaced at the discretion of the Sponsor unless the Investigator and Sponsor Medical Monitor agree that this should not be done for reasons of safety. Replacement patients will be assigned to the same Study Drug (ISIS 443139 or placebo) as the patients who are being replaced without unblinding any study personnel. No more than 48 patients may be enrolled.

Patients whose randomization code has been broken will not be replaced.

4.4 Unblinding of Treatment Assignment

The Sponsor and all patients, monitors and Study Center personnel related to the study will be blinded throughout the Study. However, if a patient has suffered a Serious Adverse Event (SAE) (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient through an automated system. The Sponsor or designee will be informed of the unblinding of a patient within 24 hours. An unblinded randomization schema will be maintained securely at the Sponsor's (or designee's) Quality Assurance Department. In addition, all SUSARs will be unblinded by the Sponsor's or designee's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendices A and B) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

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. Early manifest, Stage 1 HD (defined as TFC of 11-13, inclusive), aged 25 to 65 years, inclusive, at the time of informed consent, with genetically confirmed disease (CAG repeat length ≥ 36 in huntingtin gene by direct DNA testing)

4. Body Mass Index (BMI) ≥ 18 and ≤ 32 kg/m^2; total body weight > 50 kg (110 lbs)

5. Able and willing to meet all study requirements in the opinion of the Investigator, including travel to Study Center, procedures, measurements and visits, 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 and at the time of enrollment

   f. Patients must reside in a proximity to the Study Center that permits prompt appearance at the facility if requested by the Investigator (maximum of 4-hour travel to Study Center)

Reproductive Status

6. 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 2 highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo)

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

7. Males must be surgically sterile, abstinent* or, if engaged in sexual relations with a female of child-bearing potential, the patient must be using an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo)

* 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

Target Disease-Related Exclusions

1. Any condition, including severe chorea, that would prevent either writing or performing rapid computer tasks

Physical, Mental and Laboratory Test Findings

2. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 12 months prior to Screening. For patients with (i) a suicide ideation score ≥ 4 on the Columbia Suicide Severity Rating Scale (C-SSRS) within the last 12 months, (ii) a score of 3 or 4 on question 2 of the Problems Behavior Assessment for Huntington's Disease – short form or (iii) suicidal behaviors within the last 12 months (as measured by the answer "Yes" on any of the C-SSRS Suicidal Behavior Items), a risk assessment should be done by an appropriately-qualified mental health professional (e.g., a Psychiatrist or licensed Clinical Psychologist) to assess whether it is safe for the patient to participate in the study. In addition, patients deemed by the Investigator to be at significant risk of suicide, major depressive episode, psychosis, confusional state or violent behavior should be excluded

3. Clinically significant laboratory, vital sign or ECG abnormalities at Screening (including heart rate (HR) < 45 bpm; SBP < 90 mmHg; confirmed BP readings > 170/105 mmHg)

4. Positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B at Screening

Prohibited and Restricted Medications and Procedures

5. Treatment with another investigational drug, 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

6. Current or recent (within the last 6 months) use of antipsychotics (prescribed for psychosis), cholinesterase inhibitors, memantine, amantadine or riluzole. Stable use of antipsychotics (prescribed for treatment of motor symptoms) and/or tetrabenazine is not permitted 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

7. 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

8. Supplement use (e.g., coenzyme Q10, vitamins, creatine) unless stable dose for 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study

9. Antiplatelet or anticoagulant therapy within the 14 days prior to Screening or anticipated use during the study, including but not limited to aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban and apixaban

10. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed at least 3 days prior to the first day Study Drug is administered to the patient (Study Day 1)

11. Prior treatment with an antisense oligonucleotide (including siRNA)

12. Any history of gene therapy or cell transplantation or any other experimental brain surgery

13. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter

Medical History and Concurrent Disease

14. Significant history of alcoholism or drug/chemical abuse

15. Clinically relevant hematological, hepatic, cardiac or renal disease or event (e.g., previous acute coronary syndrome within 6 months of Screening). Abnormal hepatic, renal or hematology lab tests must be discussed with the Sponsor Medical Monitor

16. Known history of human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B

17. Any condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment

18. History of bleeding diathesis or coagulopathy, platelet count < LLN

19. A medical history of brain or spinal disease that would interfere with the LP process, CSF circulation or safety assessment, including tumors or abnormalities by MRI or computed tomography (CT), subarachnoid hemorrhage, suggestion of raised intracranial pressure on MRI or ophthalmic examination, spinal stenosis or curvature, chiari malformation, hydrocephalus, syringomyelia, tethered spinal cord syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome

20. History of post-lumbar-puncture headache of moderate or severe intensity and/or blood patch

21. 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

22. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study

23. Have any other conditions which, in the opinion of the Investigator, 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 -6 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. 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 14)

Study Drug will be administered 4 times, with doses separated by 28 days (Section 8.1).

Eligible patients will report to the Study Center on Study Day -1 (the day prior to first Study Drug 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 Study Drug 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 adverse events 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.

Each subsequent Study Drug administration will be conducted in the same manner, with most pre-dose assessments conducted on the day before Study Drug administration; post-dose, in-clinic observation of at least 6 hours after Study Drug administration (longer or overnight if necessary for safety reasons); in-clinic assessments on the day after Study Drug administration; telephonic contact with patients 2 days after Study Drug administration and in-clinic assessments 1-week after Study Drug administration.

6.1.3 Post-Treatment Period (Week 17 to Week 29) or Early Termination

After completion of the Treatment Period, patients will enter the 15-week Post-Treatment Period. This period consists of 3 Study Center visits on Weeks 17, 21 and 29, as outlined in the Schedule of Procedures in Appendix A.

Patients who terminate early from the Treatment or Post-Treatment Periods (for reasons other than withdrawal of consent) should be encouraged to submit to additional visit(s) as described in detail in Section 8.9. (Also see Appendices A and C and Study Design and Treatment Schema.)

6.2 Study Assessments

The order of study assessments will be defined in the Study Manual. All efforts should be made to adhere to a consistent order of assessments throughout the study. Rest periods will be scheduled during the testing, and the patient should be permitted additional 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 International Standard Classification of Education (ISCED)

The ISCED is used to capture each patient's level of education based on categories ranging from pre-primary education through advanced degree programs.

6.2.3 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.

A referral for psychiatric evaluation is required for any increase in the most severe suicidal ideation score from baseline. 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.

6.2.4 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.

6.2.4.1 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).

6.2.4.2 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.

6.2.5 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 Study Day -1 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.

6.2.6 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).

6.2.7 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).

6.2.8 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. HD 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).

6.2.9 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 at Screening and during the Post-Treatment Period.

Ventricular expansion as assessed by structural MRI is a key exploratory endpoint for the study.

At the Screening and Study Day 197/Week 29 visits, the following scans will be performed to characterize the patients' pre-treatment and end-of-study state: T2 flair, T2 star and T2 Fast Spin Echo (FSE)/Turbo Spin Echo (TSE).

Additionally, at the Study Day 113/Week 17 visit, MRI will be used to image the CSF space.

Metabolic disturbances in the frontal lobe of the brain will be assessed using proton magnetic resonance spectroscopy (^{1}H-MRS). Using ^{1}H-MRS, the concentrations of particular metabolites, N-Acetyl-aspartate (NAA) and myo-inositol (mI), can be measured relative to the signal of unsuppressed water. Normal, healthy tissues present a constant proton spectrum, and relative changes in metabolites may be reflective of aberrant biochemical transformations (Walecki et al. 2011). NAA serves as a marker or neuronal health, as it is found only in mature neurons, and has been shown to decline in patients with cognitive impairment (Kantarci et al. 2003). Myo-inositol serves as a marker of glial cells, and elevated levels are associated with regional gliosis (Walecki et al. 2011). A recent study demonstrated elevated mI and decreased NAA in HD (Sturrock and Leavitt 2010) suggesting that these metabolites might serve as endpoints in HD clinical trials.

Corticostriatal connectivity loss occurs early in Huntington's disease. The functional and effective connectivity between brain regions will be examined using resting state functional MRI (rsfMRI). Seed connectivity will be used to identify brain regions which are simultaneously activated at rest. Dynamic causal modelling will be used to explore causal interactions between the brain and these regions. Brain cellular microstructure and structural connectivity will be examined using volumetric MRI combined with neurite orientation dispersion and density imaging (NODDI). Computational approaches will be applied to visualize neural tracts and to determine the relative strength of anatomical connections between brain regions. Graph theory will be used to detect changes in the organization of brain networks such as integration and efficiency. The rsfMRI and NODDI scans require approximately 25 minutes in the scanner. It is recognized that some patients may be unwilling to submit to this additional burden; therefore, while patients will be encouraged to receive these scans, they will not be required.

6.2.10 Speeded Tapping

The speeded tapping test is a measure of psychomotor speed and has been used as a longitudinal marker of disease severity in manifest and pre-manifest HD. For the test, the patient taps the index finger of his/her non-dominant hand as quickly as possible. A brief rest period is held between trials.

6.2.11 Unified Huntington's Disease Rating Scale (UHDRS)

The UHDRS, developed by the Huntington Study Group to provide a uniform assessment of the clinical features and course of HD has undergone reliability and validity testing that support its use in longitudinal studies (Huntington Study Group 1996). The scale assesses 4 domains associated with HD: motor function, cognitive function, behavioral abnormalities and functional capacity.

For this study, only the UHDRS components required to calculate the total functional capacity scale, the independence scale and the total motor scale will be collected. These components are simple, multiple-choice questions based on patient interview, physical exam and observation during motor activities, such as speeded tapping (Section 6.2.10) and walking. The components are described further below.

6.2.11.1 UHDRS Total Functional Capacity Scale (TFC)

The TFC represents the Investigator's assessment of the patient's capacity to perform a wide range of activities of daily living including working, chores, managing finances, eating, dressing and bathing. It is based on a brief interview with the patient and the study partner. Scores range from 0 to 13, and higher scores represent better functioning.

6.2.11.2 UHDRS Independence Scale

The patient's independence scale is the Investigator's assessment of the patient's degree of independence. The scale consists of 19 discrete levels ranging from 10 to 100 (by 5) where no special care needed corresponds to a scale of 100 and tube fed and total bed care corresponds to a scale of 10.

6.2.11.3 UHDRS Total Motor Scale (TMS)

The TMS is the sum of the individual motor ratings obtained during administration of the motor assessment portion of the UHDRS. Scores range from 0 to 124, and higher scores represent more severe impairment.

6.2.12 HD Work Function (HDWF) Scale

The HDWF scale is a measure of work role limitations and effort, which are areas that may be affected by the cognitive, behavioral and motor changes associated with HD (Brossman et al. 2012). It was developed for prodromal HD, the stage prior to overt motor impairment and HD diagnosis in which structural and functional brain changes lead to subtle changes in cognition and motor function. Patients complete the questionnaire consisting of 20 questions, where the response to each is based on a 7-point Likert scale ranging from "not at all like me" to "very much like me". Scores range from 20 to 140, and higher scores represent higher work function ability.

A companion scale was developed as a proxy indicator of the patient's work function, acknowledging that insight may diminish in some individuals in the prodromal or early stages of HD. During for development of the HDWF scale, correlation between the patient and companion scores were statistically significant (Brossman et al. 2012). If the patient suffers from diminished insight, information from the companion, i.e., trial partner, may provide important supporting information.

6.2.13 Montreal Cognitive Assessment (MoCA)

The MoCA is a screening test for cognitive impairment that spans the visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation domains that has been shown to be sensitive in HD (Nasreddine et al. 2005; Videnovic et al. 2010). The test administrator prompts the patient through a series of tests and follows a simple algorithm to document the patient's score. Total scores range from 0 to 30 points, with lower numbers representative of more cognitive impairment. This test will be performed at Screening only to characterize the patient population relative to published populations.

6.2.14 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. This composite cognitive score is a key exploratory endpoint for the study. The individual tests that comprise the battery are described below.

6.2.14.1 Self-Paced Tapping

Self-paced tapping measures cognitive and motor timing. The patient listens to a repeating tone at 3Hz and taps in time with the tone, alternating between left and right thumbs. The patient continues to tap after the tone stops, attempting to maintain the same rate of tapping. Four (4) trials are conducted.

Scoring of each effort is based on the precision of taps, which is directly estimated, and timing precision, which is calculated as the reciprocal of the standard deviation of the intertap interval.

6.2.14.2 Emotion Recognition

For this test, patients view faces depicting a neutral expression or an emotion (anger, disgust, fear, sadness, surprise, happiness). After a practice trial for each category, the patient views 70 test trials and categorizes each face by emotion. The number of correct responses for negative emotions (anger, disgust, fear, sadness) are tallied (Johnson et al. 2007).

6.2.14.3 CANTAB One Touch Stockings (OTS)

The OTS test measures executive function, spatial planning and working memory. On a computer or tablet screen, the patient is shown 2 stacks of colored balls, which can be perceived balls stacked in hanging socks or stockings. The patient must move the balls between the stockings to achieve a particular color pattern. Rearranging the balls to make the target pattern may take 1, 2, 3 or 4 moves. Then, the patient is shown 2 stacks of colored balls and must determine, without moving the balls, the minimum number of moves necessary to achieve the target pattern.

Tests are scored based on accuracy in determining minimum number of moves and time to correct solution.

6.2.14.4 Symbol Digit Modalities Test (SDMT)

The SDMT is used to assess attention, visuoperceptual processing, working memory and psychomotor speed. It has been shown to have strong reliability and validity (Smith 1982; Hinton-Bayre et al. 1999). The patient must pair abstract symbols with specific numbers according to a translation key. The test measures the number of items correctly paired (maximum of 110) in 90 seconds.

6.2.14.5 Hopkins Verbal Learning Test – Revised (HVLT-R)

The HVLT-R is used to assess verbal memory through tests of recall and recognition. Patients must recall a series of 12 words over 3 immediate trials (learning), free recall after a 25-minute delay and a recognition trial.

6.2.14.6 Trail-Making Test

The Trail-Making Test Part B (TMT-B) is a test of executive functioning. Patients are presented with a picture of 25 circles, each labeled with a number (1 – 13) or a letter (A – L). The patient must draw lines to connect the circles in an ascending pattern that alternates between the numbers and letters (i.e., 1-A-2-B-3-C …). The patient is instructed to connect the circles as quickly as possible, and the time to complete the task is recorded.

The Trail-Making Test Part A (TMT-A) is also administered, but the results of the TMT-A are not considered to be part of the battery. For the TMT-A, patients are presented with 25 circles, each labeled with a number (1-25) and are asked to connect the numbers. Administration of TMT-A prior to TMT-B provides practice to aid in administering TMT-B.

6.2.15 Problems Behavior Assessment for Huntington's Disease – Short Form (PBA-s)

The PBA-s assesses common behavioral and psychiatric manifestations of HD, including affect, irritability, loss of motivation, perseverative phenomena and psychotic symptoms. The test administrator interviews the patient and trial partner and rates the patient's behavior over the prior 4 weeks according to the guidelines for the test.

6.2.16 Stroop Word Reading Test

The Stroop Word Reading Test is a measure of processing and psychomotor speed. Patients are presented with a page of color names printed in black ink and are asked to read aloud as many words as possible within a given amount of time. The number of words read correctly is counted.

6.2.17 Map Search Test

The Map Search Test is a test of sustained visual attention. Patients are presented with a visually cluttered map and asked to circle as many target symbols on the map as possible within a fixed period of time. Scoring is based on the number of correctly identified symbols.

6.2.18 Collection of CSF

Patients will have CSF collected pre-dose during the LP procedure on Study Days 1, 29, 57 and 85 for safety and PK analyses. A sample will also be collected during the Post Treatment Period on either Study Day 113 or Study Day 141. Prior to the injection, 20 mL of CSF fluid is to be

collected for analyses, using a standard LP collection kit. 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. Fluoroscopy guidance should be used if attempts at lumbar puncture without imaging are unsuccessful.

6.2.19 Laboratory Assessments

Laboratory analyte samples 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). Pharmacokinetic analysis of ISIS 443139 in plasma will be conducted using samples collected as described in Appendices A and C.

In addition, assessments of exploratory biomarkers will include interleukin-6 (IL-6), TNFα and 24S-hydroxycholesterol.

For each scheduled lumbar puncture, local laboratory analysis of coagulation factors (PT, INR and aPTT) and platelets must be conducted and results reviewed prior to performing the lumbar puncture.

- For dosing visits (Days 1, 29, 57 and 85), collection for local labs may occur on the day prior to dosing at the same time that samples are collected for analysis at the central laboratory.
- For the lumbar puncture in the Post-Treatment Period (Day 113 or Day 141 or Day 197), collection for local labs may occur on the day of the lumbar puncture provided results can be obtained and reviewed prior to performing the lumbar puncture.

6.2.19.2 CSF Laboratory Assessments

CSF will be used for standard laboratory measurement of cells, glucose, protein and ISIS 443139 pharmacokinetic analyses.

Key exploratory CSF biomarkers are muHtt level and neurofilament light chain. Additional CSF assessments are total Htt, proenkephalin, clusterin, factor H (FH), C3, IL-6, TNFα, IL-1β, monocyte chemoattractant protein-1 (MCP-1), chitinase-3-like protein 1 (YKL-40), visinin-like protein 1 (VILIP1), apolipoprotein E, chromogranin B, neurogranin, synaptosomal-associated protein 25 (SNAP25), S100 calcium binding protein B (S100B) and tau.

Extra CSF will be stored for investigation of possible biomarkers of HD or the pharmacodynamic effects of ISIS 443139 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 ISIS 443139 with CSF constituents.

6.2.20 Pregnancy Testing

Pregnancy tests will be conducted in all female patients who are not surgically sterile, as described 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 13 weeks after the last dose of Study Drug (ISIS 443139 or placebo).

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 Study Drug

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 13 weeks after the last dose of Study Drug. 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[redacted], 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.

7. STUDY DRUG

7.1 Study Drug Description

ISIS 443139 Study Drug and artificial CSF diluent are manufactured by Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA. The Study Drug is supplied as a 5 mL fill volume in a 6 mL clear glass vial. The diluent (artificial CSF) is supplied as a 20 mL fill volume in a 20 mL clear glass vial. These configurations allow for various clinical doses by using different dilution procedures between the Study Drug and diluent vials. Study Drug characteristics are described in Table 1. More details are provided in the Study Drug Manual.

Table 1 Study Drug Characteristics

Study Drug	ISIS 443139	Placebo	Diluent (artificial CSF)
Strength	20 mg/mL	NA	NA
Volume/Vial	5 mL solution per vial	5 mL solution per vial	20 mL solution per vial
Route of Administration	IT injection	IT injection	IT injection

ISIS 443139 Study Drug and the diluent (artificial CSF) must be stored securely at 2° C to 8° C. ISIS 443139 Study Drug must be protected from light.

7.2 Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 443139 or placebo) and diluent labeled in accordance with specific country regulatory requirements.

7.3 Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return of Study Drug (ISIS 443139 or placebo) and diluent supplies provided by the Sponsor. The Study Center must return all used and unused Study Drug and diluent vials to the Sponsor or designee.

8. TREATMENT OF PATIENTS

8.1 Study Drug Administration

Study Drug dosing will occur at the Study Center on Study Days 1, 29, 57 and 85. On each of these Study 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 Study Drug. 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. Fluoroscopy guidance should be used if attempts at lumbar puncture without imaging are unsuccessful.

Table 2 outlines the dose equivalent and ISIS 443139 concentration for delivery. See Section 3.1 for a description of adjustments that might be made to doses and the maximum dose that will be tested.

Table 2 Study Drug Dosing Information

Cohort	Volume to Administer	Nominal ISIS 443139 Concentration	ISIS 443139 Per Dose
Cohort A	20 mL	0.50 mg/mL	10 mg or placebo
Cohort B	20 mL	1.5 mg/mL	30 mg or placebo
Cohort C	20 mL	3.0 mg/mL	60 mg or placebo
Cohort D	20 mL	4.5 mg/mL	90 mg or placebo
Cohort E	20 mL	6.0 mg/mL	120 mg or placebo

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug preparation and administration. These instructions must be followed for each Study Drug 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. There are no additional specific stopping rules for this study but the Investigator should discuss significant concerns relating to individual patients with the Ionis Medical Monitor to ensure that it is appropriate for the patient to continue Study Drug.

8.7 Adjustment of Dose and/or Treatment Schedule

For a given patient, no adjustment of dose is permitted except as mandated by the DSMB as described in Section 3.7. In the event of a concurrent illness that would prevent the dosing procedure from being performed safely, an adjustment in the dose schedule may be permitted at the discretion of the Sponsor Medical Monitor.

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 adverse event that necessitates permanent discontinuation of Study Drug
- The patient experiences a DLT as defined in Section 3.8

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 Treatment or Post-Treatment Periods (for reasons other than withdrawal of consent) should be encouraged to submit to additional visit(s) as described in detail in Section 8.9. (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 (a) conduct the full block of visits associated with the last dose received (see description of "visit blocks" below), (b) conduct the visit scheduled for 7 days after the last dose received, (c) and proceed to the Week 17 visit approximately 4 weeks after last dose and conduct all visits in the Post-Treatment Period (see Appendix A).

> "Visit blocks": Each dose of Study Drug is associated with a series of visits that are timed to assess acute safety and tolerability of ISIS 443139. There are 4 "visit blocks" in this study: Study Days -1, 1, 2 and 3; Study Days 28, 29, 30 and 31; Study Days 56, 57, 58 and 59 and Study Days 84, 85, 86 and 87.

For patients who terminate early from the Treatment Period for reasons other than withdrawal of consent every effort and are not willing to participate in the Post-Treatment Period, every effort should be made to (a) conduct the full block of visits associated with the last dose received (see description of "visit blocks" above), (b) conduct the visit scheduled for 7 days after the last dose received and (c) conduct the Week 29 visit as an Early Termination Visit.

For patients who terminate early from the Post-Treatment Period for reasons other than withdrawal of consent, every effort should be made to conduct the Week 29 visit as an Early Termination Visit.

8.10 Concomitant Therapy and Procedures

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

8.10.1 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 study medication 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 adverse events 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) and/or tetrabenazine 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 (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 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

8.10.2 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 study medication and end of study.

8.11 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 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 DSMB will be notified of any SAE as specified in the DSMB charter.

The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that the Study Drug (ISIS 443139 or placebo) 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 adverse event. 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 adverse event 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 197. 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 Study Day 197. 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 Study Drug (ISIS 443139 or placebo) 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 Study Drug (ISIS 443139 or placebo) 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 Study Drug (ISIS 443139 or placebo) 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 adverse events, 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 adverse events 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 Study Drug (ISIS 443139 or placebo) due to the event is characterized by 1 of the following:

- **None:** No changes were made to Study Drug (ISIS 443139 or placebo) administration and dose

- **Permanently Discontinued:** Study Drug 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

Study Drug (ISIS 443139 or placebo) 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 Study Drug (ISIS 443139 or placebo) 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 Study Drug. 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 (HR, BP, orthostatic changes, weight)
- ECG
- AEs and concomitant medications
- CSF safety labs (cell counts, protein, glucose)
- Plasma laboratory tests (clinical chemistry, hematology)
- Urinalysis
- Clinical assessments
- Volumetric and safety neuroimaging assessments

10.1.2 Pharmacokinetic Endpoints

A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at 1 Post-Treatment Period visit for PK analyses.

Plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses.

Plasma C_{max}, AUC, elimination half-life and trough and post-distribution drug levels will be assessed, where appropriate.

10.1.3 Exploratory Endpoints

- Biochemical
  - CSF levels of mutant Htt* and total Htt

- CSF levels of neurofilament light chain*, proenkephalin, clusterin, FH, C3, IL-6, TNFα, IL-1β, MCP-1, YKL-40, VILIP1, apolipoprotein, chromogranin B, neurogranin, SNAP25, S100B and tau
- Plasma or serum levels of IL-6, TNFα and 24S-hydroxycholesterol

- Neuroimaging volumes, including but not limited to:
  - Structural MRI
    - Caudate
    - Whole brain
    - Ventricular*
  - MRS spectroscopy for frontal lobe myoinositol and N-Acetylaspartic acid (NAA)
  - Resting state functional MRI
  - Neurite orientation dispersion and density imaging (NODDI)
- Electrophysiological
  - qEEG
- Clinical
  - Functioning/ability to perform activities of daily living
    - UHDRS Total Functional Capacity Scale (TFC)
    - UHDRS Independence Scale
    - HD Work Function Scale
  - Cognitive and motor tests:
    - HD Cognitive Battery*
      - Self-Paced Tapping
      - Emotion Recognition
      - CANTAB One Touch Stockings
      - Symbol Digit Modalities Test
      - Hopkins Verbal Learning Test Revised
      - Trail Making Test Part B

- UHDRS Total Motor Scale
- Stroop Word Reading Test
- Map Search Test
- Speeded Tapping

- Neuropsychiatric evaluation
  - Problems Behavior Assessment for Huntington's disease-short form (PBA-s)

* Key exploratory biochemical, neuroimaging, electrophysiological and clinical assessments

10.2 Sample Size Considerations

While there is no statistical rationale for the sample size, it has been selected based on prior experience with generation 2.0 ASOs given by IT injection to ensure that the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.

10.3 Populations

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

Per Protocol Population: All patients who are randomized and receive all doses of the protocol-specified Study Drug (ISIS 443139 or placebo).

PK Population: All patients who are randomized to ISIS 443139 and receive at least 1 dose of ISIS 443139 and have sufficient sampling to permit pharmacokinetic evaluation.

10.4 Definition of Baseline

For vital signs (BP, heart rate, respiration rate and temperature), baseline will be defined as the average of the 3 values collected prior to first dose (Screening, Study Day -1 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

An unblinded interim analysis may be performed and the results summarized by treatment group at the end of each cohort upon completion of dosing for that cohort or at any time if needed to address a safety concern. The results of an analysis of this type will not be shared with patients or Investigators.

A DSMB will be assembled to review safety, tolerability, pharmacokinetic and target engagement/pharmacodynamic (as needed) data collected on ISIS 443139 during this study. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to DSMB prior to each DSMB meeting. Based on its ongoing assessment of the safety and tolerability of ISIS 443139, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety

assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB charter and/or the statistical analysis plan (SAP).

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, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

Since there are limited placebo-treated patients within each dose cohort, the placebo-treated patients will be pooled for analysis.

10.6.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Patient disposition will be summarized by treatment group. 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 Study Drug received will be summarized by treatment group.

All treatment-emergent adverse events (TEAEs) and SAEs will be summarized for each treatment group 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, etc., will be summarized by study visit for each treatment group. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

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

Columbia – Suicide Severity Rating Scale will be summarized by study visit for each treatment group. 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.

A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at 1 Post-Treatment Period visit for PK analyses. The CSF concentrations will be summarized using descriptive statistics and the ISIS 443139 half-life in CSF will be calculated, if possible.

Plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses. Plasma PK parameters will be summarized using descriptive statistics.

Non-compartmental PK analysis of ISIS 443139 in plasma will be carried out on each individual patient data set. C_{max} and the time taken to reach C_{max} (T_{max}) will be obtained directly from the concentration-time data. The plasma half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate using available data, from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, where λ_z is the rate constant associated with the apparent terminal elimination phase. Partial areas under the plasma concentration-time curve from zero time (pre-dose) to selected times (t) after the administration (AUC_t) will be calculated using the linear trapezoidal rule.

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 Statistical Analysis Plan.

10.6.4 Exploratory Analysis

The exploratory analyses will be conducted on the Per Protocol and Safety Populations.

Exploratory evaluations (Section 10.1.3) will be summarized using descriptive statistics by study visit and treatment group. Change and percent change from baseline over time will be summarized as appropriate. Comparison between ISIS 443139 group and the pooled placebo group will be performed in an exploratory manner. Details will be described in the Statistical Analysis Plan.

Additional exploratory 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 exploratory endpoints may be performed as where deemed appropriate.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1 Informed Consent

HD 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). 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 any Study Drug (ISIS 443139 or placebo) are 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 patient s 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.

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.

13. REFERENCES

Altmann KH, Dean NM, Fabbro D, et al. Second generation of antisense oligonucleotides: from nuclease resistance to biological efficacy in animals. Chimia 1996; 50: 168-176.

Bañez-Coronel M, Porta S, Kagerbauer B, et al. A pathogenic mechanism in Huntington's disease involves small CAG-repeated RNAs with neurotoxic activity. PLoS Genet 2012; 8(2): e1002481.

Brossman B, Williams JK, Downing N, et al. Development of the Huntington disease work function scale. J Occup Environ Med 2012; 54(10): 1300-1308.

Cerritelli SM and Crouch RJ. Ribonuclease H: the enzymes in eukaryotes. FEBS J 2009; 276: 1494-1505.

Chen JJ, Ondo WG, Khashayar D, Swope DM. Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature. Clinical Therapeutics 2012; 34: 1487-1504.

Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington's Disease. Neuropsychiatry Neuropsychol Behav Neurol 2001; 14(4): 219-226.

Crooke ST and Bennett CF. Progress in antisense oligonucleotide therapeutics. Annu Rev Pharmacol Toxicol 1996; 36: 107-129.

DeRenzo EG, Conley RR, Love R. Assessment of capacity to give consent to research participation: state-of-the-art and beyond. J Health Care Law Policy 1998; 1(1): 66-87.

Duyao M, Ambrose C, Myers R, et al. Trinucleotide repeat instability and age of onset in Huntington's disease. Nat Gen 1993; 4: 387-392.

Duyao MP, Auerbach AB, Ryan A, et al. Inactivation of the mouse Huntington's disease gene homolog Hdh. Science 1995; 269: 407-410.

FDA: DRAFT Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials, September 2010.

Folstein SE. The psychopathology of Huntington's disease. J Nerv Ment Dis 1989; 177: 645.

Geary RS, Yu RZ, Watanabe T, et al. Pharmacokinetics of a tumor necrosis factor-α phosphorothioate 2′-*O*-(2-methoxyethyl) modified antisense oligonucleotide: comparison across species. Drug Metab Dispos 2003; 31: 1419-1428.

Henry SP, Stecker K, Brooks D, et al. Chemically modified oligonucleotides exhibit decreased immune stimulation in mice. J Pharmacol Exp Ther 2000; 292: 468-479.

Hinton-Bayre AD, Geffen GM, Geffen LB, et al. Concussion in contact sports: reliable change indices of impairment and recovery. Clin Exp Neuropsychol 1999; 21: 70-86.

Hogarth P, Kayson E, Kieburtz K, et al. Interrater agreement in the assessment of motor manifestations of Huntington's disease. Mov. Disord 2005; 20: 293-297.

Hunter A, Bordelon Y, Cook I, Leuchter A. QEEG measures in Huntington's disease: a pilot study. PLoS Curr 2010 Oct 25; 2: RRN1192.

Huntington G. On chorea. Med Surg Reporter 1872; 26: 320–321.

Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996; 11: 136-142.

Inoue H, Hayase Y, Iwai S, Ohtsuka E. Sequence-dependent hydrolysis of RNA using modified oligonucleotide splints and RNase H. FEBS Letters 1987; 215: 327-330.

Ismailoglu I, Chen Q, Popowski M, et al. Huntingtin protein is essential for mitochondrial metabolism, bioenergetics and structure in murin embryonic stem cells. Dev Biol 2014; 391: 230-240.

Johnson SA, Stout JC, Solomon AC, et al; and Predict-HD Investigators of the Huntington Study Group. Beyond disgust: impaired recognition of negative emotions prior to diagnosis in Huntington's disease. Brain 2007; 130: 732-744.

Kantarci K, Reynolds G, Petersen RC, et al. Proton MR spectroscopy in mild cognitive impairment and Alzheimer disease: comparison of 1.5 and 3T. Am J Neuroradiol 2003; 24: 843–849.

Kordasiewicz HB, Stanek LM, Wancewicz EV, et al. Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. Neuron 2012; 74: 1031-1044.

Kuermmerle S, Gutekunst CA, Klein AM, et al. Huntingtin aggregates may not predict neuronal death in Huntington's disease. Ann Neurol 1999; 46: 842-843.

Langbehn DR, Brinkman RR, Falush D, et al; and International Huntington's Disease Collaborative Group. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Gen 2004; 65(4): 267-277.

McKay RA, Miraglia LJ, Cummins LL, et al. Characterization of a potent and specific class of antisense oligonucleotide inhibitor of human protein kinase C-α expression. J of Biol Chem 1999; 274: 1715-1722.

Monia BP, Lesnik EA, Gonzalez C, et al. Evaluation of 2′-modified oligonucleotides containing 2′-deoxy gaps as antisense inhibitors of gene expression. J Biol Chem 1993; 268: 14514-14522.

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

Nance M, Paulsen JS, Rosenblatt A, Wheelock V. A physician's guide to the management of Huntington's disease, Third Edition, Huntington's Disease Society of America 2011.

Nasir J, Floresco SB, O'Kusky JR, et al. Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes. Cell 1995; 81(5): 811-823.

Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal cognitive assessment (MoCA): a brief screening tool for mild cognitive impairment. J American Geriatrics Society 2005; 53: 695-699.

Papoutsi M, Labuschagne I, Tabrizi SJ, Stout JC. The cognitive burden in Huntington's disease: pathology, phenotype, and mechanisms of compensation. Mov Disord. 2014; 29(5): 673-683.

Paulsen J, Ready R, Hamilton J, et al. Neuropsychiatric aspects of Huntington's disease. J Neurol Neurosugery and Psychiatry 2001; 97: 310-314.

Paulsen JS, Smith MM, Long JD; and PREDICT HD Investigators and Coordinators of the Huntington Study Group. Cognitive decline in prodromal Huntington disease; implications for clinical trials. J Neurol Neurosurg Psychiatry 2013; 84: 1233-1239.

Paulson HL and Albin RL. Huntington's Disease. Clinical Features and Routes to Therapy. In: Lo DC, Hughes RE, editors. Neurobiology of Huntington's disease: Applications to drug discovery. Boca Raton, FL. CRC Press 2011. Chapter 1.

Petersen A, Gil J, Maat-Shieman ML, et al. Orexin loss in Huntington's disease. Hum Mol Genet 2005; 14(1): 39-47.

Posner K, Brown GK, Stanley B, et al. The Columbia-suicide severity rating scales: initial validity and internal consistency findings from three multisite studies with adolescents and adults. American Journal of Psychiatry 2011; 168: 1266-1277.

Pringsheim T, Wiltshire K, Day L, et al. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord 2012; 27(9): 1083-1091.

Roos R. Huntington's disease: A clinical review. Orphanet Journal of Rare Diseases 2010; 5: 40.

Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol 2014; 10(4): 204-216.

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

Shoulson I, Kurlan R, Rubin AJ, et al. Assessment of functional capacity in neurodegenerative movement disorders: Huntington's disease as a prototype. In Munsat TL, editor, Quantification of Neurological Deficit. Boston. Butterworth 1989. Chapter 20.

Shoulson I and Young AB. Milestones in Huntington disease. Mov Disord 2011; 26: 1127-1133.

Smith A. Symbol digit modalities test: Manual. 1982; Los-Angeles: Western Psychological Services.

Stanek LM, Yang W, Angus S, et al. Antisense oligonucleotide-mediated correction of transcriptional dysregulation is correlated with behavioral benefits in the YAC128 mouse model of Huntington's disease. J Huntington's Disease 2013; 217-228.

Stout JC, Queller S, Baker KN, et al; and HD-CAB Investigators. HD-CAB: A cognitive assessment battery for clinical trials in Huntington's disease. Mov Disord 2014; 29: 1281-1288.

Sturrock A and Leavitt B. The clinical and genetic features of Huntington's disease. J Geriatric Psychiatry and Neurology 2010; 23: 243-259.

Videnovic A, Bernard B, Fan W, et al. The Montreal cognitive assessment as a screening tool for cognitive dysfunction in Huntington's disease. Mov Disord 2010; 25(3): 401-404.

Walecki J, Barcikowska M, Cwikla JB, Gabryelewicz T. N-acetylaspartate, choline, myoinositol, glutamine and glutamate (glx) concentration changes in protocol MR spectroscopy (1H MRS) in patients with mild cognitive impairment (MCI). Med Sci Monit 2011; 17(12): MT105-111.

Walker FO. Huntington's disease. Lancet 2007; 369 (9557): 218–228.

Wexler NS, Young AB, Tanzi RE, et al. Homozygote for huntinton's disease. Nature 1987; 326: 194-197.

White JK, Auerbach W, Duyao MP, et al. Huntingtin is required for neurogenesis and is not impaired by the Huntington's disease CAG expansion. Nat Genet 1997; 17(4): 404-410.

Xenazine (tetrabenazine) [package insert]. Deerfield, IL: Lundbeck; 2011.

Zeitlin S, Liu JP, Chapman DL, et al. Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue. Nat Genet 1995; 11(2): 155-163.

14. APPENDICES

Appendix A Schedule of Procedures

Appendix A Schedule of Procedures

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																				Post-Treatment Period (15 Weeks)		
Study Week	**-6 to -1**	**1**				**2**	**5**				**6**	**9**				**10**	**13**				**14**	**17/ ET[2]**	**21**	**29/ ET[2]**
Study Day	**-43 to -2**	**-1**	**1**	**2**	**3**	**8**	**28**	**29**	**30**	**31**	**36**	**56**	**57**	**58**	**59**	**64**	**84**	**85**	**86**	**87**	**92**	**113**	**141**	**197**
Visit Window (days)*	**-**	*	**0**	*	*	**± 2**	*	**±2**	*	*	**±2**	*	**±2**	*	*	**±2**	*	**±2**	*	*	**±2**	**±2**	**±7**	**±7**
Visit Type[1]	**cl**	**cl**	**cl**	**cl**	**ph**	**cl**	**cl**	**cl**	**cl**	**ph**	**cl**	**cl**	**cl**	**cl**	**ph**	**ph**	**cl**	**cl**	**cl**	**ph**	**ph**	**cl**	**cl**	**cl**
Overnight Stay[3]			X→					X→					X→					X→						
Capacity to Consent Assessment and Informed Consent	X																							
Inclusion/Exclusion	X																							
Medical History and ISCED	X																							
MoCA	X																							
Vital Signs (BP, HR, RR, T)	X	X	X[a]				X	X[a]				X	X[a]				X	X[a]				X	X	X
Orthostasis	X		X[b]															X[b]					X	X
Physical& Neurological Exam[4]	X	X	X[c]	X[d]		X	X	X[c]	X[d]		X	X	X[c]	X[d]			X	X[c]	X[d]			X	X	X
Body Weight and Height[5]	X	X					X					X					X					X	X	X
Functional, Cognitive, Motor and Neuropsychiatric assessments[6]	X	X															X						X	X
C-SSRS[7]	X	X	X[b]	X		X	X	X[b]	X		X	X	X[b]	X			X	X[b]	X			X	X	X
qEEG	X	X																				X	X	X
Structural MRI[8]	X																					X		X
T2 flair, T2 star, T2 FSE/TSE MRI[8]	X																							X
rsfMRI and NODDI[8, 9]	X																							X
MRI of the CSF space[8]																						X		
^{1}H-MRS[8]	X																					X		X
ECG (12-Lead)[10]	X	X		X																		X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																				Post-Treatment Period (15 Weeks)		
Study Week	**-6 to -1**	**1**				**2**	**5**				**6**	**9**				**10**	**13**				**14**	**17/ ET[2]**	**21**	**29/ ET[2]**
Study Day	**-43 to -2**	**-1**	**1**	**2**	**3**	**8**	**28**	**29**	**30**	**31**	**36**	**56**	**57**	**58**	**59**	**64**	**84**	**85**	**86**	**87**	**92**	**113**	**141**	**197**
Visit Window (days)*	**-**	*	**0**	*	*	**±2**	*	**±2**	*	*	**±2**	*	**±2**	*	*	**±2**	*	**±2**	*	*	**±2**	**±2**	**±7**	**±7**
Visit Type[1]	**cl**	**cl**	**cl**	**cl**	**ph**	**cl**	**cl**	**cl**	**cl**	**ph**	**cl**	**cl**	**cl**	**cl**	**ph**	**ph**	**cl**	**cl**	**cl**	**ph**	**ph**	**cl**	**cl**	**cl**
Chemistry Panel	X	X					X					X					X					X	X	X
Hematology	X	X					X					X					X					X	X	X
Urinalysis	X	X					X					X					X					X	X	X
Genetic Tests	X																							
HIV, Hepatitis B & C	X																							
Drug/Alcohol Screen	X																							
FSH[11]	X																							
Pregnancy Test[12]	X	X					X					X					X					X	X	X
Serum Biomarker Sample	X	X					X					X					X					X	X	X
Thyroid Panel		X					X										X						X	X
PT, INR, aPTT	X	X					X					X					X					X	X	X
Local PT, INR, aPTT and platelets[14]		X					X					X					X					X[g]	X[g]	X [h]
Plasma Sampling for PK			X[e]	X[d]				X[b]					X[b]					X[f]	X[d]			X	X	X
Archived Serum Sample[13]	X	X					X					X					X					X	X	X
CSF Sample for PK/Safety/Biomarkers			X[b]					X[b]					X[b]					X[b]				X [g]	X[g]	X [h]
Archived CSF Sample			X[b]					X[b]					X[b]					X[b]				X[g]	X[g]	X[h]
Study Drug Administration			X					X					X					X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	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	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

* Visit windows are calculated relative to Study Day 1. Note that within each block of visits associated with dose administration, the visits must occur on 4 consecutive days. There are 4 "visit blocks" in this study: (Study Days -1, 1, 2 and 3), (Study Days 28, 29, 30 and 31), (Study Days 56, 57, 58 and 59) and (Study Days 84, 85, 86 and 87).

1 cl = clinic visit; ph = phone visit

2 If the patient terminates early from the Treatment Period but is willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received, (c) proceed to the Week 17 visit approximately 4 weeks after last dose and conduct all visits in the Post-Treatment Period. If the patient terminates early from the Treatment Period and is not willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received and (c) conduct the Week 29 visit as an Early Termination Visit. If the patient terminates early from the Post-Treatment Period, conduct the Week 29 visit as an Early Termination Visit

3 On Study Day 1, the patient must stay in the clinic overnight and undergo safety monitoring follow-up as scheduled on Study Day 2. On Study Days 29, 57 and 85, the patient may either stay in the clinic overnight or be discharged (after a minimum observation period of 6 hours after Study Drug administration), provided the patient returns to the clinic on the following day (Day 30, 58 or 86) for all required assessments

4 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

5 Height is measured at Screening only

6 Functional, Cognitive, Motor and Neuropsychiatric Tests are speeded tapping, UHDRS total functional capacity scale, UHDRS independence scale, UHDRS total motor scale, HD work function scale, HD Cognitive Battery (self-paced tapping, emotion recognition, CANTAB one-touch stockings, symbol-digit modalities test, Hopkins verbal learning test – revised and trail making tests), Problems Behavior Assessment for Huntington's disease-short form, Stroop Word Reading test and Map Search test

7 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

8 For imaging during the Screening period, the scans should be conducted sufficiently early in the Screening Period to allow for repeat scanning if necessary. For imaging at post-Screening visits, efforts should be made to conduct the imaging within the visit window. If re-scanning at a post-Screening visit is necessary because the original scan is not usable, the re-scanning should be conducted within 1-week of the original scan if at all possible

9 rsfMRI and NODDI scans are conducted only in patients who have consented for these assessments

10 Measured in triplicate at the Study Day -1 visit only

11 Women who are not surgically sterile as confirmation of menopause

12 Women who are not surgically sterile. Serum test at Screen visit; dipstick at post-screen visits

13 Stored at -80º C for follow-up exploration of laboratory findings and/or adverse events (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 ISIS 443139

14 Local laboratory analysis of PT, INR, aPTT and platelets must be conducted and results reviewed prior to performing the lumbar puncture on the next day (Days -1, 28, 56, 84) or the same day (Day 113 or 141 or 197). If a lumbar puncture will not be performed, local analysis of PT, INR, aPTT and platelets is not necessary

Appendix A Schedule of Procedures *Continued*

Time (in reference to time of Study Drug administration):

a Pre-dose, 3 and 6 hours post IT injection

b Pre-dose

c Pre-dose and 3 hours post IT injection; also conduct at 6 hours post IT injection on any dosing day that the patient does not stay in the clinic overnight (overnight stays are optional on Study Days 29, 57 and 85)

d 24 hours after prior dose of Study Drug

e Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours post IT injection

f Pre-dose, 0.5, 1, 2, 3, 4 and 5 hours post IT injection

g All patients in Cohort A will have CSF collected on Study Day 113 (Week 17) and not on Study Day 141 (Week 21). For all other cohorts, CSF sampling will be conducted in approximately 50% of patients on Study Day 113 (Week 17) and in the remaining 50% of patients on Study Day 141 (Week 21), as assigned by the Sponsor according to a predetermined, randomized assignment. For each scheduled lumbar puncture, local laboratory analysis of coagulation factors (PT, INR and aPTT) and platelets must be conducted and results reviewed prior to performing the lumbar puncture. Collection for local labs may occur on the day of the lumbar puncture provided results can be obtained and reviewed prior to performing the lumbar puncture

h CSF sampling and local analysis of PT, INR, aPTT and platelets will be conducted at Study Day 197 (Week 29) in only those patients who attend the visit as an early termination visit, did not undergo CSF sampling on either Study Day 113 (Week 17) or Study Day 141 (Week 21) and will undergo CSF sampling on Study Day 197. If CSF sampling was conducted on Study Day 113 (Week 17) or Study Day 141 (Week 21), do not collect CSF or perform local analysis of PT, INR, aPTT and platelets at Study Day 197 (Week 29)

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 ISIS 443139 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 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
White blood cells
Epithelial cells
Bacteria
Casts
Crystals
Color
Appearance

Thyroid Panel
TSH
Free T4
Free T3

Coagulation
aPTT
PT
INR

Screening Tests
Hepatitis B surface antigen
Hepatitis C antibody
HIV antibody
FSH (women only)
Serum βhCG
Drug/Alcohol screen[2]

Genetics
CAG repeat length
apoE isoform genotype
BCHE-K

PK[1]
Plasma ISIS 443139 levels
CSF ISIS 443139 levels

Pregnancy
Urine hCG

CSF Safety Panel (Minimum Requirements)
Red blood cells
White blood cells
Glucose
Protein

Exploratory CSF Biomarker Panel
mu Htt
total Htt
Proenkephalin
Clusterin
FH
C3
IL-6
TNFα
IL-1β
MCP-1
YKL-40
VILIP1
ApoE
Chromogranin B
Neurogranin
SNAP25
S100B
Tau
Neurofilament light chain

Exploratory Serum/Plasma Biomarker Panel
IL-6
TNFα
24S-hydroxycholesterol

1 Any of the collected PK plasma and CSF samples from the study patients may also be used by Ionis for investigation of possible biomarkers of disease or the pharmacodynamic effects of ISIS 443139 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 ISIS 443139 with plasma and CSF 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.

2 Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates

Appendix C PK Sampling Schedule

Appendix C PK Sampling Schedule

Study Period	Treatment Evaluation Period (13 Weeks)						Post-Treatment Period or Early Termination Visit (15 Weeks)		
Study Week	**1**		**5**	**9**	**13**		**17**	**21**	**29**
Study Day	**1**	**2**	**29**	**57**	**85**	**86**	**113**	**141**	**197**
CSF Sampling	Pre-dose		Pre-dose	Pre-dose	Pre-dose		Anytime[1]		
Plasma Sampling	Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8,12 hours post IT injection	24 hours post Day 1 IT injection	Pre-dose	Pre-dose	Pre-dose, 0.5, 1, 2, 3, 4, 5 hours post IT injection	24 hours post Day 85 IT injection	Any-time	Any-time	Any-time

1 All patients in Cohort A will have CSF sampling on Study Day 113 (Week 17) and not on Study Day 141 (Week 21). For all other cohorts, CSF sampling will be conducted in approximately 50% of patients in the cohort on Study Day 113 (Week 17) and in the remaining 50% of patients in the cohort on Study Day 141 (Week 21), as assigned by the Sponsor. CSF sampling will be conducted on Study Day 197 (Week 29) in only those patients who attend the visit as an early termination visit and did not undergo CSF sampling on either Study Day 113 (Week 17) or Study Day 141 (Week 21). If CSF sampling was conducted on Study Day 113 (Week 17) or Study Day 141 (Week 21), do not collect CSF on Study Day 197 (Week 29).

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)

PROTOCOL AMENDMENTS

Protocol Number: ISIS 443139-CS1

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

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A list of changes to the protocol are below:

Amendment	Description of Change	Dates
Original Protocol	There were 2 versions of the protocol for this study. In the version for UK and Canada, fluoroscopy was permitted as an optional tool for assisting with correct spinal needle placement during lumbar puncture. In the version for Germany, fluoroscopy was not included as an optional tool because its inclusion would have required additional regulatory approvals (due to the radiation exposure) and the German investigators indicated that they would not opt to use fluoroscopy even if it were permitted.	06 Mar 2015 (UK/Canada) 19 Mar 2015 (Germany)
Amendment 1	Both versions: •Revised the DLT definition to exclude SAEs attributable to the LP procedure, other study procedure, or HD and those not of sufficient significance to be considered dose-limiting at the request of a reviewing regulatory agency; •Added referral of an event an Investigator considered to be a suspected DLT to the unblinded DSMB for determination of whether it constituted a DLT because the DSMB was in an ideal position to review accumulating study data across study centers and to judge whether an event was dose-limiting; and •Added Appendix D, a grading scale for AEs relating to laboratory abnormalities based on the CTCAE Version 4.03, to facilitate consistent grading across study centers. Germany version only: In response to a request from BfArM, the amendment added a requirement that an independent expert assist with determination of a patient's capacity to consent if the Principal Investigator was uncertain of the patient's capacity.	07 May 2015 (UK/Canada) 03 Jun 2015 (Germany)
Amendment 2	Both versions: •Added results from a supplementary toxicology study in monkeys that provided an extended safety margin for doses used in the study and increased the maximum dose that could be tested from 70 to 120 mg; •Added local assessment of coagulation and platelets on the day of or day prior to scheduled lumbar punctures to standardize testing because pre-lumbar puncture practices differed across study sites; and added routine safety laboratory testing to Study Days 56 and 113 as good clinical practice.	25 May 2016 (UK/Canada) 26 May 2016 (Germany)
Amendment 3	Both versions: •Changed the size of Cohort D from 16 to 12 participants. The Sponsor had decided to enroll a fifth cohort of patients (an optional cohort described in all prior versions of the protocol) and wanted to ensure that the fifth cohort contained enough patients to characterize the effects at that dose level. Cohort D was reduced from 16 to 12 patients to allow for sufficient enrollment	05 Apr 2017 (UK/Canada) 04 Apr 2017 (Germany)

	into the fifth cohort while remaining within the protocol-specified maximum of 48 patients. •Also, the Sponsor took the opportunity to align the dose levels indicated in the protocol with the doses that had been used during the study. Prior protocols specified dose levels of 10 mg, 30 mg, 50 mg, and 70 mg (or placebo) in Cohorts A, B, C and D, respectively, with the options of updating the levels based on accumulating PK/PD data and adding a fifth cohort if needed. The maximum permitted dose was 120 mg and, beginning with Cohort C, the dose level for a cohort was not permitted to exceed 2 times the dose tested in the prior cohort. At each dose escalation meeting, the Sponsor and the study's unblinded, independent DSMB reviewed all available safety, PK, and PD data to determine the appropriate dose for the next cohort, within the existing limitations on maximum dose and escalation. The study was executed in accordance with this design, and the dose levels utilized were 10 mg, 30 mg, 60 mg, 90 mg and 120 mg (or placebo) in Cohorts A, B, C, D, and E, respectively.	

Statistical Analysis Plan

ISIS 443139-CS1

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Date: 11/11/2015

Version: 1.0

Statistical Analysis Plan Signature Page

Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Compound Name: 443139

Protocol: CS1

Study Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Issue Date: 7 May 2015 (Amendment 1)
3 June 2015 (Amendment 1 – Germany)

Signature: PPD Date: 2015/11/11

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C

Signature: PPD Date: Nov 11, 2015

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
AUC_t	Area under the plasma concentration-time curve from time zero to time t
BP	Blood pressure
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
CRF	Case report form
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
DBS	Disease burden score
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FH	Factor H
GCP	Good Clinical Practice
HD	Huntington's disease
HDWF	Huntington's disease work function
Htt	Huntingtin protein
HR	Heart rate
HVLT-R	Hopkins verbal learning test - revised
ICH	International Conference on Harmonization
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
INR	International normalized ratio
ISIS 443139	Antisense inhibitor of Htt
IT	Intrathecal(ly)
LCR	Local cutaneous reactions
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein-1
MCV	Mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
NODDI	Neurite orientation dispersion and density imaging
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
PK	Pharmacokinetic(s)
PBA-s	Problems behavior assessment for Huntington's disease – short form
PT	Prothrombin time
qEEG	Quantitative EEG
QTcF	QT time corrected using the Friderica's method
QTcB	QT time using the Bazett's method
RR	Relative ventricular rate
S100B	S100 calcium binding protein B
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SNAP25	Synaptosomal-associated protein 25
Study Day 1	Defined as the first day Study Drug is administered to the patient
Study Drug	ISIS 443139 or placebo
SDMT	Symbol digit modalities test
TEAE	Treatment-emergent adverse event
TFC	Total functional capacity
T_{max}	Time to maximal concentration
TMS	Total motor scale
TMT-A	Trail-making test part A
TMT-B	Trail-making test part B
TNFα	Tumor necrosis factor alpha
TSE	Turbo spin echo
UHDRS	Unified Huntington's disease rating scale
VILIP1	Visinin-like protein 1
VR	Ventricular rate
WBC	White blood cell
WHO	World health organization
YKL-40	Chitinase-3-like protein 1

1.0 INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

As with any statistical analysis plan (SAP), the proposed methods and approaches to the data analysis should be viewed as flexible. The statistical analysis to some degree is iterative since the planning is based, at least in part, on statistical and other assumptions, which require verification.

1.1 Study Overview

This is a Phase 1/2a, multi-center, double-blind, randomized, placebo-controlled, dose-escalation study conducted in patients with early manifest Huntington's disease (HD). The study consists of four cohorts (n = 4-16 per cohort, randomized in a ratio of 3 active: 1 placebo). The doses planned for the study are shown below. Based on emerging safety data from this study, one or more cohorts may be expanded by enrolling additional patients. Additionally, pharmacokinetic and pharmacodynamic measures will be collected at each dose level and compared to the results that are predicted by models constructed from preclinical data. The doses utilized in remaining cohorts may be adjusted, or an additional cohort may be added, if necessary to achieve pharmacologically relevant levels. The maximum dose tested in a cohort will not exceed 70 mg.

Dose Cohorts:

Cohort A:	N = 4, 10 mg ISIS 443139 or placebo (3:1)
Cohort B:	N = 8, 30 mg ISIS 443139 or placebo (6:2)
Cohort C:	N = 8, 50 mg ISIS 443139 or placebo (6:2)
Cohort D:	N = 16, 70 mg ISIS 443139 or placebo (12:4)

Randomization in Cohort D will be stratified by early Stage 1 total functional capacity (TFC ≥ 12) or late Stage 1 (TFC = 11) disease, where Stage 1 represents the highest level of capacity of the 5 stages of manifest disease.

Patients will receive 4 intrathecal (IT) bolus doses of Study Drug at 4 week intervals during the 13-week Treatment Period (Days 1, 29, 57, 85).

Approximately 36 patients are planned to be enrolled in this study. The number of patients enrolled may be higher if some patients need to be replaced and/or if the sizes of the cohorts

are expanded to obtain further experience with particular dose levels. A maximum of 48 patients may be enrolled.

The overall study duration will be approximately 7-8 months. The study will consist of a Screening Period of up to 6 weeks, a 13-week Treatment Period and a 15-week Post-Treatment Period. The end of study is defined as last patient, last study visit. Please refer to the Schedule of Procedures in Appendix A.

1.2 Objectives

1.2.1 Primary Objectives

To evaluate the safety and tolerability of ascending dose-levels of multiple IT bolus administrations of an antisense inhibitor of Htt (ISIS 443139) to patients with HD.

1.2.2 Secondary Objectives

To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT administrations of ISIS 443139.

1.2.3 Exploratory Objectives

To explore effects of multiple doses of ISIS 443139 on potential target engagement and disease progression biomarkers and clinical endpoints relevant to HD. Plasma pharmacokinetic properties of ISIS 443139 will also be assessed. Disease progression markers are included primarily as a safety measure to document any marked worsening. A lesser objective is to gain experience with these measures in an ISIS 443139 clinical study as preparation for subsequent, longer-term clinical studies. It is not expected that the majority of biomarkers and clinical measures will be impacted significantly by the 13-week of dosing planned for this study. For the current study, select disease progression markers are considered to be key exploratory target engagement, biochemical, neuroimaging and cognitive assessments based on their potential to evidence changes in disease progression in early HD. These key exploratory endpoints are mutant Htt in CSF, neurofilament light chain in CSF, ventricular volume as assessed by structural magnetic resonance imaging (MRI) and the composite cognitive score resulting from assessment of the components of the HD Cognitive Battery, respectively.

1.3 Endpoints

1.3.1 Safety and Tolerability Endpoints

- 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
- Clinical assessments
- Volumetric and safety neuroimaging assessments

1.3.2 Pharmacokinetic Endpoints

A CSF sample will be collected at pre-dose on each injection day (Days 1, 29, 57, 85) and at one Post-Treatment Period visit for PK analyses.

Plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses.

Plasma C_{max}, AUC, elimination half-life and trough and post-distribution drug levels will be assessed, where appropriate.

1.3.3 Exploratory Endpoints

- Biochemical
  - CSF levels of mutant Htt* and total Htt
  - CSF levels of neurofilament light chain*, proenkephalin, clusterin, FH, C3, IL-6, TNFα, IL-1β, MCP-1, YKL-40, VILIP1, apolipoprotein, chromogranin B, neurogranin, SNAP25, S100B and tau
  - Plasma levels of IL-6, TNFα and 24S-hydroxycholesterol
- Neuroimaging volumes, including but not limited to:
  - Structural MRI
    - Caudate
    - Whole brain
    - Ventricular*

- Magnetic resonance spectroscopy for frontal lobe myoinositol and N-Acetylaspartic acid
- Resting state functional MRI
- NODDI

- Electrophysiological
  - qEEG
- Clinical
  - Functioning/ability to perform activities of daily living
    - UHDRS Total Functional Capacity Scale (TFC)
    - UHDRS Independence Scale
    - HD Work Function Scale
  - Cognitive and motor tests:
    - HD Cognitive Battery*
      - Self-Paced Tapping
      - Emotion Recognition
      - CANTAB One Touch Stockings
      - Symbol Digit Modalities Test
      - Hopkins Verbal Learning Test Revised
      - Trail Making Test Part B
    - UHDRS Total Motor Scale
    - Stroop Word Reading Test
    - Map Search Test
    - Speeded Tapping
  - Neuropsychiatric evaluation
    - Problems Behavior Assessment for Huntington's disease-short form (PBA-s)

* Key exploratory biochemical, neuroimaging, electrophysiological and clinical assessments

2.0 PROCEDURES

2.1 General Overview of Procedures

Isis (or designee) will review all study data including source documents, case report forms (CRFs), and laboratory reports. Study site will enter subject source data into the case report form. The CSF Safety lab data (CSF WBC, CSF RBC, CSF protein, CSF glucose) will be completed at each site's local lab and will be entered on a CRF (CSF Results CRF). Mutant Htt will be transferred electronically from CCI, total Htt will be transferred electronically from CCI. Other laboratory data will be transferred electronically from CCI. C-SSRS, UHDRS TFC, Independence Scale, UHDRS Total Motor Scale, HD Work Function Scale, PBA-s will be collected using CCI device and data provided by CCI. Neuroimaging data including structural MRI, MRS spectroscopy will be reported by CCI Resting state functional MRI and NODDI data will be generated by CCI. Self-Paced Tapping, Emotion Recognition, CANTAB One Touch Stockings, and Speeded Tapping will be collected using the CCI device and data provided by CCI. ECGs will be centrally read by CCI. EEGs will be collected by CCI Those data will be transferred electronically to Isis Pharmaceuticals, Inc.

Isis Pharmaceuticals, Inc. is responsible for the format of electronic data transfers, transfer schedule and review of the data. Those data will be stored as SAS data sets.

2.2 Randomization & Treatment Allocation

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

Eligible patients will be randomized centrally by an automated system to receive ISIS 443139 or placebo. Within each cohort, randomization will be 3:1 for ISIS 443139: placebo respectively as outlined in Section 1.1. Patients in Cohort D will be stratified by early Stage 1 (TFC ≥12) or late Stage 1 (TFC = 11) disease. Patients in Cohorts B, C, and D will also be randomly assigned to have the CSF sampling visit at Week 17 or Week 21 in a 1:1 ratio within cohort and treatment assignment. CCI will prepare the randomization list.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association

Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

Isis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Isis Pharmaceuticals, Inc. (or designee), are reviewed according to standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. For dose escalation, the progression of the study from initiation of dosing in one cohort to the next will be determined by the Sponsor and the DSMB. Isis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Isis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to all applicable study sites.

2.5 Data Management

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

2.5.1 Case Report Form Data

CCI (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Isis Pharmaceuticals, Inc. Isis Pharmaceuticals, Inc. is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. Isis Pharmaceuticals, Inc. reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data is entered, reviewed and queried the database is closed. The data is then reviewed by Isis Pharmaceuticals, Inc. and additional queries may be generated. After all queries are resolved the database is locked.

2.5.2 Laboratory Data

Isis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers and the transfer schedule. Isis Pharmaceuticals, Inc. is responsible for the review of the clinical laboratory data. This data is not stored in the EDC system. Investigator sites have access to safety laboratory data via printed lab reports sent directly from the laboratory.

2.5.3 Pharmacokinetics Data

Isis Pharmaceuticals, Inc. is responsible for the management and review of the PK data. This process involves reviewing the patient and visit identifiers with the clinical data collected in the EDC system. The PK data are not stored in the EDC system.

3.0 ANALYTICAL PLAN

3.1 General Overview of Analyses

3.1.1 Statistical Methods

All CRF data, data transfers from external vendors (e.g., laboratory, cognitive testing, ECG, qEEG), and any outcomes derived from the data will be provided in the subject data listings. Subject data listings will be presented for all subjects 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, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. Analyses may be stratified by the stratification factor and/or site if supported by data.

Since there are limited placebo-treated subjects within each dose cohort, the placebo-treated subjects will be pooled for all analyses.

For vital signs [blood pressure (BP), heart rate, respiration rate, orthostatic change and temperature], baseline will be defined as the average of the values collected prior to first dose (Screening, Study Day -1, Study Day 1, and any measurements between Screening and Day 1).

Baseline ECG will be defined as the average of the triplicate taken on Day -1, if only one or two assessments are available, the single assessment or average of the two assessments will be used.

For all other measures and parameters, baseline will be defined as the last non-missing measure prior to the first dose.

The treatment period will be defined as the period of time from the first dose administration through Day 92 visit or, if the patient does not participate in Day 92 visit, from the first dose administration through 9 days after the last dose administration.

The post-treatment assessment period will be defined as the period of time from the day after the treatment period to the end of study.

Demographic and baseline characteristics (e.g., age, sex, ethnicity, race, weight, height, BMI, Montreal Cognitive Assessment (MoCA), ISCED level, CAG repeat length, ApoE isoform genotype, BCHE-K variant, and disease burden score (DBS)) and subject disposition will be summarized using descriptive statistics by treatment group. DBS is calculated by [CAG repeat length – 35.5]*age in years. All subjects enrolled will be included in a summary of subject disposition. Protocol deviations will be listed.

Multiple results within the same visit (or timepoint for measurements collected at multiple timepoints) will be averaged for by visit analyses. Unscheduled results will not be included in the by-visit analyses except for determining baseline, but will be presented in data listings.

PK parameters will be summarized by treatment group using n, mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

3.1.2 Subject Populations Analyzed

The following analysis populations will be used for the analyses of data as described within each analysis set:

Safety Population: All patients who are randomized and receive at least one dose of Study Drug. This population will be used for safety and tolerability analyses.

Per Protocol Population: All patients who are randomized and receive all doses of the protocol-specified Study Drug (ISIS 443139 or placebo) This population will be used for pharmacodynamics, exploratory and biomarker analyses.

PK Population: All patients who are randomized to ISIS 443139 and receive at least one dose of ISIS 443139 and have sufficient sampling to permit pharmacokinetic evaluation. This population will be used for PK analyses.

In addition to the above analysis sets, it is recognized that some data displays will be provided for "All Screened", "Screening Failures" and "All Randomized" subjects but no data analysis will be executed in these populations except for the disposition table that includes all screened subjects.

3.1.3 Sample Size Consideration

While there is no statistical rationale for the sample size, it has been selected based on the prior experience with generation 2.0 ASOs given by IT injection to ensure that the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.

3.1.4 Planned Interim Analysis

Unblinded interim analyses may be performed and the results summarized by treatment group at the end of each cohort upon completion of dosing for that cohort or at any time if needed to address a safety concern. The Investigator, study staff, patients, monitors, Sponsor Medical Monitor, members of the Sponsor's clinical operations team and data management team will remain blinded throughout the study. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection.

A DSMB will be assembled to review safety, tolerability, pharmacokinetic and target engagement/pharmacodynamic (as needed) data collected on ISIS 443139 during this study. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to DSMB prior to each DSMB meeting. Based on its ongoing assessment of the safety and tolerability of ISIS 443139, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB charter.

3.1.5 Incomplete or Missing Data

Missing values will not be imputed unless otherwise specified.

3.2 Safety Analyses

3.2.1 Exposure

Treatment duration and amount of Study Drug received will be summarized by treatment group.

3.2.2 Adverse Events

An adverse event will be regarded as treatment emergent adverse event (TEAE) if it is present prior to receiving the first dose of study drug and subsequently worsened, or is not present prior to receiving the first dose of study drug but subsequently appeared.

The most conservative approach will be used to determine if the event occurs after the first dose of treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset date of an AE is a partial date with only month or year available or completely missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date or a full or partial resolution date is available that definitively demonstrates that the event ended prior to first dose of study drug.

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA^{TM}) preferred term and system organ class for:

- All treatment emergent adverse events
- Related treatment emergent adverse events. Related is defined as "Related" , "Possible" , or missing relationship to study drug
- All treatment emergent adverse events by severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. Adverse events with missing severity will be categorized as "Missing" for this summary
- Related treatment emergent adverse events by severity
- Serious treatment emergent adverse events
- Serious and related treatment emergent adverse events

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

SAEs and non-serious AEs that lead to study discontinuation or investigational drug discontinuation will be listed separately. Non-TEAEs will be flagged in the data listing.

3.2.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS collects binary responses to 11 categories: five subtypes of suicidal ideation, five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent. Specifically, the following outcomes are C-SSRS categories and have binary (Yes/No) responses. (The categories have been re-ordered from the actual scale to facilitate the definitions of the composite endpoints and to enable clarity in the presentation of the results.)

Suicidal Ideation:

Category 1 – Wish to Be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior:

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Other

Category 11 – Non-suicidal Self-injurious Behavior

In addition, a numerical score, the Suicidal Ideation Score, will be defined as the highest suicide ideation category (1–5) at which the patient responded "Yes" for the given visit. If the patient did not respond "Yes" to any of these categories, the score will be set to zero.

For each of the 11 categories above, the number and percent of patients with a "Yes" response at any time post-baseline (regardless of baseline response) will be summarized by treatment group.

In addition, emergent suicidal ideation or behavior will be summarized. The binary categories above and the Suicidal Ideation Score will be used to identify the 8 composite endpoints defined below. Note that "recent history" for these composite endpoints is defined as the 12 months prior to Screening and the Screening period. At the Screening visit, C-SSRS data is collected for the prior 12 months. Therefore, analyses that utilize data from "recent history" will include the historical 12-month data collected at Screening as well as all on-study C-SSRS data collected prior to first dose.

- **Suicidal Ideation**: A "Yes" answer at any time post-first-dose to any one of the five suicidal ideation questions (Categories 1–5), regardless of the pre-dose responses
- **Suicidal Behavior**: A "Yes" answer at any time post-first-dose to any one of the five suicidal behavior questions (Categories 6–10), regardless of the pre-dose responses
- **Suicidal Ideation or Behavior**: A "Yes" answer at any time post-first-dose to any one of the ten suicidal ideation or behavior questions (Categories 1–10), regardless of the pre-dose responses
- **Treatment-Emergent Suicidal Ideation** compared to recent history: A maximum post-first-dose suicidal ideation score that is increased from the maximum suicidal ideation score in recent history.
- **Treatment-Emergent Serious Suicidal Ideation** compared to recent history: A maximum post-first-dose suicidal ideation score of 4 or 5 when the maximum suicidal ideation score during recent history was less than 4 (i.e., scores of 0-3). Only patients with a recent history score of 0–3 will be considered evaluable for this outcome.
- **Emergence of Serious Suicidal Ideation** compared to recent history: A maximum post-first-dose suicidal ideation score of 4 or 5 when the maximum suicidal ideation score during recent history was 0. Only patients with a recent history score of 0 will be considered evaluable for this outcome.
- **Improvement in Suicidal Ideation** compared to baseline: A decrease in the suicidal ideation score at the patient's Study Day 86 C-SSRS assessment compared to the baseline score, defined as the minimum score obtained during the Screening Period (i.e., assessments collected from the Screening Visit through pre-dose on Study Day

1). The analysis will be repeated for Study Days 113, 141 and 197. Only patients with a baseline score >0 will be considered evaluable for these outcomes.

- **Emergence of Suicidal Behavior** compared to all prior history: The occurrence of suicidal behavior (a "Yes" response to one or more of Categories 6–10) post-first-dose from not having suicidal behavior prior to first dose (includes the "lifetime" score collected at the Screening Visit as well as all C-SSRS assessments collected from the Screening Visit through pre-dose on Study Day 1).

Each of the composite endpoints will be summarized by treatment group. For each treatment-emergent outcome listed, only those patients with the specified screening condition will be considered evaluable. In addition, patients who discontinue from the study with no post-first-dose C-SSRS assessment will be considered unevaluable for analyses of suicidality. Percents will be based on the number of evaluable patients for each outcome.

In addition, a shift table will be created to demonstrate the change in suicidal ideation score from recent history to treatment period and/or post-treatment period. The maximum suicidal ideation score in each period will be used to create the shift table. If a patient's recent history suicidal ideation score is missing but has a post-first-dose score, then the recent history assessment will be labeled as "unknown". Likewise, if a patient's recent history suicidal ideation score is available but has no post-first-dose score, then the scores during the treatment and post-treatment period will be labeled as "unknown".

3.2.4 Laboratory Measurements

The following is the list of lab analytes that will be measured throughout the study:

- Chemistry: Sodium, Potassium, Chloride, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Bicarbonate, Glucose, BUN, Creatinine, Total serum bilirubin, Uric acid, Alkaline phosphatase, ALT (SGOT), AST (SGPT), GGT and CPK.

- Hematology: Red blood cells, Hemoglobin, Hematocrit, Platelets, MCV, MCH, MCHC, White blood cells, and WBC differential (percentage and absolute count) (Basophils, Eosinophils, Lymphocytes, Monocytes and Neutrophils)

- Coagulation: aPTT, PT, INR

- Thyroid Panel: TSH, Free T4, and Free T3

- PK: Plasma ISIS 443139 levels, and CSF ISIS 443139 levels

- Pregnancy: Urine hCG

- CSF Safety Panel (Minimum Requirements): Red blood cells, White blood cells, Glucose and Protein

- Urinalysis: Specific gravity, pH, Protein, P/C ratio, Glucose, Ketones, Urobilinogen, Leukocyte esterase, Nitrite, Bilirubin, Blood, Red blood cells, White blood cells, Epithelial cells, Bacteria, Casts, Crystals, Color and Appearance.

In addition, the following analytes are measured at screening only: plasma hCG, FSH, hepatitis B surface antigen, hepatitis C antibody, HIV antibody, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates.

The following genetic testing is performed: CAG repeat length, ApoE isoform genotype, BCHE-K.

Missing WBC differential absolute counts and percentages will be derived:

If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophils counts and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

Laboratory tests to ensure subject safety including chemistry panel, hematology panel, coagulation, and CSF safety labs (cell counts, protein, and glucose), will be summarized by study visit for each treatment group. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

In addition, the shifts (relative to the normal range) from baseline to the minimum and maximum post-baseline values will be presented. If a subject is missing a baseline value but had a post-baseline value, then the baseline assessment is labeled as "unknown". Likewise, if a subject had a baseline value but had no post-baseline values, then the minimum and maximum are labeled as "unknown". For each parameter, the incidence of shift to low will be summarized using the minimum post-baseline values; the incidence of shift to high will be summarized using the maximum post-baseline values.

Only central laboratory data will be used for the summary tables and figures. Local laboratory data will be provided in the listings only, with the exception of local results for CSF safety tests which will be listed and summarized in tables.

All lab data will also be displayed in subject listings.

3.2.5 Vital Signs Measurements and Weight

Vital signs will include body temperature, heart rate, respiration rate, orthostatic changes, and systolic and diastolic blood pressure.

Orthostatic changes include 3 variables: change from seated systolic blood pressure to average of all available standing systolic blood pressures, change from seated diastolic blood pressure to average of all available standing diastolic blood pressure, and change from seated heart rate to average of all available standing heart rate.
Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) for vital sign values and weight as well as the change and percent change from baseline at each study visits by treatment group.

3.2.6 Neurological Examinations

Neurological examinations will be provided in patient listings.

3.2.7 12-Lead Electrocardiograms (ECG)

ECG data will be collected through a central reader.

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, QTC (recorded from ECG machine), QTcF (QT corrected using the Fridericia's formula), and QTcB (QT corrected using the Bazett's formula) as described below:

$QTcF = QT / (RR)^{1/3}$, where RR= 60/VR

$QTcB = QT / (RR)^{1/2}$, where RR= 60/VR

At Day -1, three replicates of ECG parameters will be recorded, and the mean from all replicates will be used as the subject's reportable value at Day -1. For all other time points, a single set of parameters will be recorded. QTcF and QTcB will be calculated based on the subject's reportable ECG data at each time point using the formula described above.

Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) as well as the change and percent change from baseline at each study visits by treatment group.

3.2.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug dictionary and summarized by ATC class, generic name and by treatment group.

A concomitant medication is defined as medications that were taken on or after the first study drug administration (Study Day 1). This includes medications that were started prior to the initiation of study drug if their use continued on or after the date of the first dosing. In order

to define concomitant medications with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a particular medication were missing, that medication is considered concomitant;
- if the start date of a medication was missing and the stop date of that medication fell on or after the date of dosing, that medication is considered concomitant;
- if the start date of a medication was prior to the date of first dosing and the stop date of that medication was missing, that medication is considered concomitant; or
- if the start/stop date of a medication is partial then where it is not possible to rule out that it was not taken concomitantly it will be considered concomitant.

Non concomitant medications will be flagged in the data listing.

3.3 Pharmacokinetic Analysis

CSF and Plasma samples will be collected at protocol designated times for ISIS 443139 pharmacokinetic assessments from the dose cohorts. Only concentration data from patients randomized to receive study drug (ISIS 443139) will be included in this analysis.

3.3.1 CSF Concentration Data and Pharmacokinetics

A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at one Post-Treatment Period visit for PK analyses. CSF concentrations of ISIS 443139, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, treatment group (cohort), nominal dose, and day. Differences between scheduled and actual sampling days will also be listed for all patients, as well as percent differences between actual administered dose and nominal dose.

CSF concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for CSF concentrations, all BLQ values will be set to zero. Mean CSF concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 443139 CSF concentrations will be tabulated by treatment group (cohort), nominal dose and day. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days, or large deviations between actual dose and nominal dose.

The ISIS 443139 half-life in CSF will be calculated, if possible, and summarized by treatment group (cohort), nominal dose, and nominal day.

ISIS 443139 CSF concentration versus time (actual) profiles from Day 1 to last collection (nominal Study Day 113 or 141 in Cohorts A–D), for each patient, as well as the mean (±SE)

CSF concentration versus time (scheduled) profiles for each treatment cohort, will be presented graphically on linear scale. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.3.2 Plasma Concentration Data

Plasma concentrations of ISIS 443139, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, treatment group (cohort), nominal dose, and day. Percent differences between scheduled and actual sampling times will also be listed for all patients as well as percent differences between actual administered dose and nominal dose.

Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 443139 plasma concentrations will be tabulated by treatment group (cohort), nominal dose, day, and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 443139 plasma concentration versus time (actual) profiles from Day 1 to Day 29 and Day 85 to Day 197 (Cohorts A–D), for each patient, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles for each treatment cohort, will be presented graphically on linear and semilogarithmic scales. Additionally, ISIS 443139 plasma concentration versus time (actual) profiles from 0 to 24 hours on Days 1 and 85 for all patients, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles (0 to 24 hours on Days 1 and 85) for each applicable treatment cohort will be presented graphically on linear and semilogarithmic scales. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.3.3 Plasma Pharmacokinetics

Non-compartmental pharmacokinetic analysis of ISIS 396443 will be carried out on each individual patient data set using Phoenix WinNonlin version 6.3 or higher (CCI [redacted]. Plasma pharmacokinetic parameters in each patient (when applicable) will be determined. For calculation of PK parameters, all BLQ values will be set to zero. The following plasma PK parameters will be calculated (when applicable) and based on actual sampling times:

- C_{max}: the maximum observed drug concentration in plasma.
- T_{max}: the time at which C_{max} occurs.
- AUC_{0-24h}: areas under the plasma concentration-time curve from zero time (pre-dose) to 24 hours after the intrathecal administration will be calculated using the linear trapezoidal rule after the dose administrations on Day 1 and Day 85.
- AUC_{0-28d} ($AUC_{0-\tau}$): areas under the plasma concentration-time curve from zero time (pre-dose) to 28 days after the intrathecal administration will be calculated using the linear trapezoidal rule for Days 1 and 85.
- MRT_{0-24h}: mean residence time (MRT) from time zero to 24 hours after intrathecal dose administration will be calculated from the equation, $MRT_{0-24h} = AUMC_{0-24h} / AUC_{0-24h}$, where $AUMC_{0-24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after dosing. This parameter will be calculated for Days 1 and 85. This parameter will be calculated and reported mainly as an index measure to reflect the expected initial rapid disposition of ISIS 443139 from plasma to tissues shortly after dosing.

The following PK parameters may be calculated using actual sampling times where appropriate data exists at the discretion of the pharmacokinetic scientist:

- $t_{½\lambda z}$: the plasma disposition half-life associated with the apparent terminal elimination phase may be calculated from the equation, $t_{1/2\lambda z} = 0.693/\lambda z$, on Day 85 profiles for Cohorts A to D.
- AUC_{0-inf}: AUC from zero to infinity, calculated as the sum of the AUC_{0-28d} plus the final quantifiable concentration divided by λz, for only subjects in Cohorts A to D where $t_{½\lambda z}$ can be accurately and appropriately determined and only on Day 1.
- Additional partial AUC values may be calculated depending upon the samples collected during the study.
- CL/F: Plasma clearance will be calculated from CL = Actual Dose/AUC_{0-inf}, for subjects in Cohorts A to D where $AUC_{0-\infty}$ can be accurately and appropriately determined, and from the equation CL = Actual Dose/$AUC_{0-\tau}$ for subjects in Cohorts A to D after the Day 85 dose.

Plasma pharmacokinetic parameters (if applicable) will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) treatment cohort, nominal dose, and day.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

3.4 Exploratory Pharmacokinetic-Pharmacodynamic Analysis

Potential relationships between selected pharmacodynamic (e.g., mutant Htt protein or total Htt protein) and plasma post-distribution exposure (i.e., trough and post-treatment) measures may also be explored, where deemed appropriate.

3.5 Exploratory Analyses

For the continuous exploratory variables, descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) of the results, as well as the change and percent change from baseline to each study visit, will be presented by treatment group in summary tables; for the categorical variables, counts and percentages will be provided. Where appropriate, inferential analyses will be conducted as described below.
The following exploratory endpoints will be summarized by treatment group as the above method according to their data characteristics.
These analyses will be performed on the Per Protocol Set. If deemed appropriate, these analyses may be repeated for the Safety Population or appropriate subset(s), as needed.

3.5.1 Biochemical

The results and change and percent change from baseline for CSF biomarkers and plasma biomarkers at each visit will be summarized using descriptive statistics and compared between each dose group and placebo using the ANOVA or Wilcoxon Rank Sum test, as appropriate. The normality will be assessed using the Kolmogorov-Smirnov test on the residuals.
Changes in mutant Htt in CSF and neurofilament light chain in CSF are key exploratory endpoints for the study.

Considerable between-patient variability is expected in the baseline levels of CSF and plasma biomarkers, and there may be patients with baseline levels that are comparable to a normal (i.e., not diseased) state. In this event, additional analyses will be conducted to account for differences in baseline (such as including baseline levels as covariates) and/or analyses will be repeated on the subset of the analysis population with baseline levels that are abnormal.

3.5.2 Neuroimaging Findings

Whole brain volume, intraventricular volume and caudate volume assessed using MRI as well as changes and percent changes from baseline at each visit will be summarized using descriptive statistics and compared between each dose group and placebo using the ANOVA or Wilcoxon Rank Sum test, as appropriate. The normality will be assessed using the

Kolmogorov-Smirnov test on the residuals. Change in ventricular volume is a key exploratory endpoint for the study.

The following parameters collected during MRS of a frontal white matter voxel will be summarized at each visit. Changes and percent changes from baseline at each visit will also be summarized. These parameters will be analyzed in a similar way to the brain volumes.

- tNAA (N-Acetyl-aspartate [NAA] and N-Acetyl-aspartyl-glutamate [NAAG]) concentration
- myo-inositol (mI) concentration
- tNAA / mI
- tNAA %SD
- mI %SD
- tNAA concentration corrected for the fraction of white matter in voxel
- mI concentration corrected for the fraction of white matter in voxel
- tNAA, corrected / mI, corrected

Parameters characterizing connectivity between different brain regions will be determined using rsfMRI and NODDI. These analyses will be conducted outside the scope of this SAP by subject matter experts, and an independent report will be generated to describe the results.

3.5.3 qEEG

The primary endpoints obtained using quantitative EEG methods are the anterior-posterior gradients of relative alpha and delta power, global alpha power, global delta power, theta/alpha border power and mean frequency at resting state with eyes closed. The values at each visit as well as changes and percent changes from baseline at each visit will be summarized using descriptive statistics and analyzed in a similar way to the brain volumes. Data for anterior-posterior gradients of relative alpha and delta power, global alpha power, global delta power, theta/alpha border power and mean frequency at resting state with eyes open will be provided in the data listing.

3.5.4 UHDRS Total Functional Capacity Scale (TFC)

The TFC represents the Investigator's assessment of the patient's capacity to perform a wide range of activities of daily living including occupation, finances, domestic chores, activities of daily living and care level. It is based on a brief interview with the patient and the study partner. Scores range from 0 to 13, and higher scores represent better functioning.

The TFC scores as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volumes.

3.5.5 UHDRS Independence Scale

The patient's independence scale is the Investigator's assessment of the patient's degree of independence. The scale consists of 19 discrete levels ranging from 10 to 100 (by 5) where no special care needed corresponds to a scale of 100 and tube fed and total bed care corresponds to a scale of 10. The Independence Scale as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volumes data.

3.5.6 HD Work Function (HDWF) Scale

The HDWF scale is a measure of work role limitations and effort, which are areas that may be affected by the cognitive, behavioral and motor changes associated with HD (Brossman et al. 2012). It was developed for prodromal HD, the stage prior to overt motor impairment and HD diagnosis in which structural and functional brain changes lead to subtle changes in cognition and motor function. Patients and their trial partners each complete a questionnaire consisting of 20 questions, where the response to each is based on a 7-point Likert scale ranging from "not at all like me" to "very much like me". The HDWF scores for both patient-completed questionnaire and the trial-partner-completed questionnaire are the sums of the individual question ratings, range from 20 to 140, and higher scores represent higher work function ability.

For both the patient-completed HDWF and the trial-partner-completed HDWF, the scores as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.7 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 six 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 six individual tests. The z-score for each test will be calculated as follows:

$$z = \frac{(x - \bar{x})}{s}$$

Where $\bar{x}$ is the overall baseline mean and s is the baseline standard deviation.

This composite cognitive score is a key exploratory endpoint for the study. The individual tests that comprise the battery are described below. The composite score, individual scores as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volume data.

-Self-Paced Tapping

Self-paced tapping measures cognitive and motor timing. The patient listens to a repeating tone at 3Hz and taps in time with the tone, alternating between left and right thumbs. The patient continues to tap after the tone stops, attempting to maintain the same rate of tapping. Four trials are conducted.

Scoring of each effort is based on the precision of taps, which is directly estimated, and timing precision, which is calculated as the reciprocal of the standard deviation of the intertap interval. Higher values indicate better performance, i.e., more consistent tapping rates. The paced tapping dependent measure (consistency of the intertap intervals) is computed using partial data if the participant does not complete the four trials within six minutes. The data will be summarized by visit and analyzed in a similar way to the brain volume data.

-Emotion Recognition

For this test, patients view faces depicting a neutral expression or an emotion (anger, disgust, fear, sadness, surprise, happiness). After a practice trial for each category, the patient views 70 test trials and categorizes each face by emotion. The number of correct responses for negative emotions (anger, disgust, fear, sadness), out of 24 possible, is tallied (Johnson et al. 2007). The correct response number will be summarized by visit and analyzed in a similar way to the brain volume data.

-CANTAB One Touch Stockings (OTS)

The OTS test measures executive function, spatial planning and working memory. On a computer or tablet screen, the patient is shown two stacks of colored balls, which can be perceived balls stacked in hanging socks or stockings. The patient must move the balls between the stockings to achieve a particular color pattern. Rearranging the balls to make the target pattern may take one, two, three or four moves. Then, the patient is shown two stacks of colored balls and must determine, without moving the balls, the minimum number of moves necessary to achieve the target pattern.

The outcome is the mean latency to correct response. Higher values indicated worse performance (longer time to a correct response). The mean latency will be summarized by visit and analyzed in a similar way to the brain volume data.

-Symbol Digit Modalities Test (SDMT)

The SDMT is used to assess attention, visuoperceptual processing, working memory and psychomotor speed. It has been shown to have strong reliability and validity (Smith 1982; Hinton-Bayre et al. 1999). The patient must pair abstract symbols with specific numbers according to a translation key. The test measures the number of items correctly paired (maximum of 110) in 90 seconds. The scores will be summarized by visit and analyzed in a similar way to the brain volume data.

-Hopkins Verbal Learning Test – Revised (HVLT-R)

The HVLT-R is used to assess verbal memory through tests of recall and recognition. The HVLT-R consists of a word list, containing 12 words from three taxonomic categories, which is read aloud to the patient at the rate of approximately one word every two seconds. The Immediate Recall test includes three learning trials. Delayed Recall is assessed 20 to 25 minutes after completion of the Immediate Recall test. Immediately after administration of the Delayed Recall trial, a forced-choice recognition test is administered. The recognition test includes the 12 target words, plus 12 distractors (six semantically-related and six semantically-unrelated words). Patients must recall a series of 12 words over three immediate trials (learning), free recall after a 25-minute delay and a recognition trial. The outcome measure will be calculated as the sum of words correctly recalled over four trials (three immediate and one delayed) with the maximum value of 48. The data will be summarized by visit and analyzed in a similar way to the brain volume data.

-Trail-Making Test

The Trail-Making Test Part B (TMT-B) is a test of executive functioning. Patients are presented with a picture of 25 circles, each labeled with a number (1 – 13) or a letter (A – L). The patient must draws lines to connect the circles in an ascending pattern that alternates between the numbers and letters (i.e., 1-A-2-B-3-C …). The patient is instructed to connect the circles as quickly as possible, and the time to complete the task is recorded.

The Trail-Making Test Part A (TMT-A) is also administered, but the results of the TMT-A are not considered to be part of the battery. For the TMT-A, patients are presented with 25 circles, each labeled with a number (1-25) and are asked to connect the numbers. Administration of TMT-A prior to TMT-B provides practice to aid in administering TMT-B.

Times to complete TMT-A and TMT-B, as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.8 UHDRS Total Motor Scale (TMS)

The TMS is the sum of the individual motor ratings obtained during administration of the motor assessment portion of the UHDRS, including ocular pursuit (horizontal and vertical), saccade initiation (horizontal and vertical), saccade velocity (horizontal and vertical), dysarthria, tongue protrusion, finger taps(right and left), pronate/supinate-hands (right and left), luria (fist-hand palm test), rigidity-arms(right and left), bradykinesia-body, maximal dystonia(trunk, rue, lue, rle and lle), maximal chorea (face, bol, trunk, rue, lue, rle and lle), gait, tandem walking, retropulsion pull test, and diagnosis confidence level. Scores range from 0 to 124, and higher scores represent more severe impairment.

The TMS scores will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.9 Stroop Word Reading Test

The Stroop Word Reading Test is a measure of processing and psychomotor speed. Patients are presented with a page of color names printed in black ink and are asked to read aloud as many words as possible within a given amount of time. Scoring is based on the number of correct responses in a fixed amount of time, typically within 45 seconds. Higher scores indicate better cognitive performance. The scores will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.10 Map Search Test

The Map Search Test is a test of sustained visual attention. Patients are presented with a visually cluttered map and asked to circle as many target symbols on the map as possible within a fixed period of time. Scoring is based on the number of correctly identified symbols. The scores will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.11 Speeded Tapping

The speeded tapping test is a measure of psychomotor speed and has been used as a longitudinal marker of disease severity in manifest and pre-manifest HD. For the test, the patient taps the index finger of his/her non-dominant hand as quickly as possible for a 10 second period. The task is repeated with a brief rest period held between trials. The outcome measure is the mean of the intertap intervals across taps from all trials, with higher values indicating worse performance (i.e., slower tapping).

The data as well as change and percent change at each visit will be summarized using descriptive statistics and analyzed in a similar way to the brain volume data.

3.5.12 Problems Behavior Assessment for Huntington's Disease–Short Form (PBA-s)

The PBA-s assesses common behavioral and psychiatric manifestations of HD, including affect, irritability, loss of motivation, perseverative phenomena and psychotic symptoms. The test administrator interviews the patient and trial partner and rates the patient's behavior over the prior four weeks according to the guidelines for the test. The symptoms include depressed mood, suicidal ideation, anxiety, irritability, angry or aggressive behavior, lack of initiative (apathy), perseverative, obsessive-compulsive behaviors, delusions, hallucinations and disoriented behavior. Each symptom is rated for severity, frequency and worst. Severity and frequency scores will be multiplied to produce a PBA score for each symptom.
In addition, the following composite scores will also be calculated:

- Sum of the PBA scores for depressed mood, anxiety, and suicidal ideation
- Sum of the PBA scores for irritability and angry or aggressive behaviors
- Sum of the PBA scores for delusions and hallucinations and disoriented behavior
- Sum of the PBA scores for perseveration and obsessive-compulsive behaviors

The square roots of the individual PBA scores and the composites scores will be reported and summarized by visit and analyzed in a similar way to the brain volume data.

3.5.13 Correlations between ISIS 443139 Exposure and Exploratory Endpoints

The following correlations are planned. The correlations will be evaluated using the Pearson correlation coefficients and corresponding p-values. Other correlations may be conducted based on findings in the by-visit analyses of exploratory endpoints.

- CSF mutant Htt at Day 85 and change in CSF mutant Htt (baseline to Day 85) versus concentration of ISIS 443139 in CSF at Day 85
- CSF total Htt at Day 85 and change in CSF total Htt (baseline to Day 85) versus concentration of ISIS 443139 in CSF at Day 85
- CSF NFL at Day 85 and change in CSF NFL (baseline to Day 85) versus concentration of ISIS 443139 in CSF at Day 85
- CSF tau at Day 85 and change in CSF tau (baseline to Day 85) versus concentration of ISIS 443139 in CSF at Day 85
- CSF VILIP1 at Day 85 and change in CSF VILIP1 (baseline to Day 85) versus concentration of ISIS 443139 in CSF at Day 85
- Ventricular volume at Day 113 and Day 197 and change from baseline in ventricular volume at each of these Days versus concentration of ISIS 443139 in CSF at Day 85
- Whole brain volume at Day 113 and Day 197 and change from baseline in whole brain volume at each of these Days versus concentration of ISIS 443139 in CSF at Day 85
- Metabolite concentrations (tNAA, mI, tNAA/mI) at Day 113 and Day 197 and change from baseline in metabolite concentrations at each of these Days versus concentration of ISIS 443139 in CSF at Day 85
- HD Cognitive Battery composite score at Day 84, Day 141 and Day 197 and change from baseline in HD Cognitive Battery composite score at each of these Days versus concentration of ISIS 443139 in CSF at Day 85
- qEEG changes in anterior-posterior gradients of relative alpha and delta power at Day 113, Day 141 and Day 197 and change from baseline in anterior-posterior gradients of relative alpha and delta power at each of these Days versus concentration of ISIS 443139 in CSF at Day 85
- qEEG changes in global alpha power, global delta power, theta/alpha border power and mean frequency at Day 113, Day 141 and Day 197 and change from baseline in global alpha power, global delta power, theta/alpha border power and mean frequency at each of these Days versus concentration of ISIS 443139 in CSF at Day 85
- Changes in UHDRS-TMS at Day 84, Day 141 and Day 197 and change from baseline in UHDRS-TMS at each of these Days versus concentration of ISIS 443139 in CSF at Day 85

3.5.14 Subset and Sensitivity Analyses

Patients enrolled into this study are early in the disease; therefore, for a given endpoint parameter, there may be patients with baseline levels that are essentially normal (i.e., not altered as would be expected in a diseased state). In these patients, there would be no ability to measure an improvement in that parameter, which confounds interpretation of an analysis that includes all patients. The confounding effect could be in either direction, i.e., it could lead to a false positive or a false negative. Where appropriate based on the observed baseline data, sensitivity and/or subset analyses will be conducted either to account for differences in baseline within the analysis or to utilize a subset of the analysis population with baseline levels reflective of a diseased state.

In addition, sensitivity analyses may be conducted if imbalances are detected in baseline characteristics or when particular baseline characteristics, such as DBS or TFC, are reasonably anticipated to impact the course of disease.

4.0 REFERENCE

5.0 APPENDICES

Appendix A Schedule of Procedures

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																				Post-Treatment Period (15 Weeks)		
Study Week	-6 to -1	1				2	5				6	9				10	13				14	17/ ET [2]	21	29/ ET[2]
Study Day	-43 to -2	-1	1	2	3	8	28	29	30	31	36	56	57	58	59	64	84	85	86	87	92	113	141	197
Visit Window (days) *	-	*	0	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	±2	±7	±7
Visit Type [1]	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	ph	cl	cl	cl	ph	ph	cl	cl	cl
Overnight Stay [3]			X→					X→					X→					X→						
Capacity to Consent Instrument and Informed Consent	X																							
Inclusion/Exclusion	X																							
Medical History and ISCED	X																							
MoCA	X																							
Vital Signs (BP, HR, RR, T)	X	X	X [a]				X	X[a]				X	X[a]				X	X[a]				X	X	X
Orthostasis	X		X [b]															X[b]					X	X
Physical& Neurological Exam[4]	X	X	X [c]	X[d]		X	X	X[c]	X[d]		X	X	X[c]	X[d]			X	X[c]	X[d]			X	X	X
Body Weight and Height [5]	X	X					X					X					X					X	X	X
Functional, Cognitive, Motor and Neuropsychiatric assessments [6]	X	X															X						X	X
C-SSRS [7]	X	X	X[b]	X		X	X	X[b]	X		X	X	X[b]	X			X	X[b]	X			X	X	X
qEEG	X	X																				X	X	X
Structural MRI	X																					X		X
T2 flair, T2 star, T2 FSE/TSE MRI	X																							X
MRI of the CSF space	X																							
^{1}H-MRS	X																					X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																				Post-Treatment Period (15 Weeks)		
Study Week	-6 to -1	1				2	5				6	9				10	13				14	17/ ET [2]	21	29/ ET [2]
Study Day	-43 to -2	-1	1	2	3	8	28	29	30	31	36	56	57	58	59	64	84	85	86	87	92	113	141	197
Visit Window (days) *	-	*	0	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	±2	±7	±7
Visit Type [1]	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	ph	cl	cl	cl	ph	ph	cl	cl	cl
ECG (12-Lead) [8]	X	X		X																		X		X
Chemistry Panel	X	X					X										X						X	X
Hematology	X	X					X										X						X	X
Urinalysis	X	X					X										X						X	X
Genetic Tests	X																							
HIV, Hepatitis B & C	X																							
Drug/Alcohol Screen	X																							
FSH [9]	X																							
Pregnancy Test [10]	X	X					X					X					X					X	X	X
Serum Biomarker Sample	X	X					X					X					X					X	X	X
Lipid and Thyroid Panels		X					X										X						X	X
PT, INR, aPTT	X	X					X										X						X	X
Plasma Sampling for PK			X [e]	X [d]				X [b]					X [b]					X [f]	X [d]			X	X	X
Archived Serum Sample [11]	X	X					X					X					X					X	X	X
CSF Sample for PK/Safety/Biomarkers			X [b]					X [b]					X [b]					X [b]				X [g]	X [g]	X [h]
Archived CSF Sample			X [b]					X [b]					X [b]					X [b]				X [g]	X [g]	X [h]
Study Drug Administration			X					X					X					X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	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	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

* Visit windows are calculated relative to Study Day 1. Note that within each block of visits associated with dose administration, the visits must occur on 4 consecutive days. There are four "visit blocks" in this study: (Study Days -1, 1, 2 and 3), (Study Days 28, 29, 30 and 31), (Study Days 56, 57, 58 and 59) and (Study Days 84, 85, 86 and 87).

1 cl = clinic visit; ph = phone visit

2 If the patient terminates early from the Treatment Period but is willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received, (c) proceed to the Week 17 visit approximately 4 weeks after last dose and conduct all visits in the Post-Treatment Period. If the patient terminates early from the Treatment Period and is not willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received and (c) conduct the Week 29 visit as an Early Termination Visit. If the patient terminates early from the Post-Treatment Period, conduct the Week 29 visit as an Early Termination Visit.

3 On Study Day 1, the patient must stay in the clinic overnight and undergo safety monitoring follow-up as scheduled on Study Day 2. On Study Days 29, 57 and 85, the patient may either stay in the clinic overnight or be discharged (after a minimum observation period of 6 hours after Study Drug administration), provided the patient returns to the clinic on the following day (Day 30, 58 or 86) for all required assessments.

4 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.

5 Height is measured at Screening only.

6 Functional, Cognitive, Motor and Neuropsychiatric Tests are speeded tapping, UHDRS total functional capacity scale, UHDRS independence scale, UHDRS total motor scale, HD work function scale, HD Cognitive Battery (self-paced tapping, emotion recognition, CANTAB one-touch stockings, symbol-digit modalities test, Hopkins verbal learning test – revised and trail making tests), Problems Behavior Assessment for Huntington's disease-short form, Stroop Word Reading test and Map Search test.

7 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.

8 Measured in triplicate at the Study Day -1 visit only.

9 Women who are not surgically sterile as confirmation of menopause.

10 Women who are not surgically sterile. Serum test at Screen visit; dipstick at post-screen visits.

11 Stored at -80° C for follow-up exploration of laboratory findings and/or adverse events (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 ISIS 443139.

Time (in reference to time of Study Drug administration):

a Predose, 3 and 6 hours post IT injection

b Predose

c Predose and 3 hours post IT injection; also conduct at 6 hours post IT injection on any dosing day that the patient does not stay in the clinic overnight (overnight stays are optional on Study Days 29, 57 and 85)

d 24 hours after prior dose of Study Drug

e Predose, 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours post IT injection

f Predose, 0.5, 1, 2, 3, 4 and 5 hours post IT injection

g All patients in Cohort A will have CSF collected on Study Day 113 (Week 17) and not on Study Day 141 (Week 21). For all other cohorts, CSF sampling will be conducted in approximately 50% of patients on Study Day 113 (Week 17) and in the remaining 50% of patients on Study Day 141 (Week 21), as assigned by the Sponsor according to a predetermined, randomized assignment.

h CSF sampling will be conducted at Study Day 197 (Week 29) in only those patients who attend the visit as an early termination visit and did not undergo CSF sampling on either Study Day 113 (Week 17) or Study Day 141 (Week 21). If CSF sampling was conducted on Study Day 113 (Week 17) or Study Day 141 (Week 21), do not collect CSF at Study Day 197 (Week 29)

Statistical Analysis Plan

ISIS 443139-CS1

A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Date: 03/15/2018

Version: 2.0

Statistical Analysis Plan Signature Page

Ionis Pharmaceuticals, Inc.
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Carlsbad, CA 92010

Compound Name: 443139

Protocol: CS1

Study Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

Issue Date: 5 April 2017 (Amendment 3)
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5 April 2017 (Amendment 3.1 – Canada)

Signature: PPD Date: March 15, 2018

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See Summary of Changes to Statistical Analysis Plan

CCI

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
AUC_t	Area under the plasma concentration-time curve from time zero to time t
BP	Blood pressure
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
CRF	Case report form
CSF	Cerebrospinal fluid
C-SSRS	Columbia suicide severity rating scale
DBS	Disease burden score
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FH	Factor H
GCP	Good Clinical Practice
HD	Huntington's disease
HDWF	Huntington's disease work function
Htt	Huntingtin protein
HR	Heart rate
HVLT-R	Hopkins verbal learning test - revised
ICH	International Conference on Harmonization
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
INR	International normalized ratio
ISIS 443139	Antisense inhibitor of Htt
IT	Intrathecal(ly)
LCR	Local cutaneous reactions
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP-1	Monocyte chemoattractant protein-1
MCV	Mean corpuscular volume

MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
NODDI	Neurite orientation dispersion and density imaging
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
PK	Pharmacokinetic(s)
PBA-s	Problems behavior assessment for Huntington's disease – short form
PT	Prothrombin time
qEEG	Quantitative EEG
QTcF	QT time corrected using the Friderica's method
QTcB	QT time using the Bazett's method
RR	Relative ventricular rate
S100B	S100 calcium binding protein B
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SNAP25	Synaptosomal-associated protein 25
Study Day 1	Defined as the first day Study Drug is administered to the patient
Study Drug	ISIS 443139 or placebo
SDMT	Symbol digit modalities test
TEAE	Treatment-emergent adverse event
TFC	Total functional capacity
T_{max}	Time to maximal concentration
TMS	Total motor scale
TMT-A	Trail-making test part A
TMT-B	Trail-making test part B
TNFα	Tumor necrosis factor alpha
TSE	Turbo spin echo
UHDRS	Unified Huntington's disease rating scale
VILIP1	Visinin-like protein 1
VR	Ventricular rate
WBC	White blood cell
WHO	World health organization
YKL-40	Chitinase-3-like protein 1

1.0 INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

As with any statistical analysis plan (SAP), the proposed methods and approaches to the data analysis should be viewed as flexible. The statistical analysis to some degree is iterative since the planning is based, at least in part, on statistical and other assumptions, which require verification.

1.1 Study Overview

This is a Phase 1/2a, multi-center, double-blind, randomized, placebo-controlled, dose-escalation study conducted in patients with early manifest Huntington's disease (HD). The study consists of five cohorts (n = 4-12 per cohort, randomized in a ratio of 3 active: 1 placebo). The doses planned for the study are shown below. Based on emerging safety data from this study, one or more cohorts may be expanded by enrolling additional patients. Additionally, pharmacokinetic and pharmacodynamic measures will be collected at each dose level and compared to the results that are predicted by models constructed from preclinical data. The doses utilized in remaining cohorts may be adjusted, or an additional cohort may be added, if necessary to achieve pharmacologically relevant levels. The maximum dose tested in a cohort will not exceed 120 mg.

Dose Cohorts:

Cohort A:	N = 4, 10 mg ISIS 443139 or placebo (3:1)
Cohort B:	N = 8, 30 mg ISIS 443139 or placebo (6:2)
Cohort C:	N = 8, 60 mg ISIS 443139 or placebo (6:2)
Cohort D:	N = 12, 90 mg ISIS 443139 or placebo (9:3)
Cohort E:	N = 12, 120 mg ISIS 443139 or placebo (9:3)

Randomization in Cohort D will be stratified by early Stage 1 total functional capacity (TFC $\geq$12) or late Stage 1 (TFC = 11) disease, where Stage 1 represents the highest level of capacity of the 5 stages of manifest disease.

Patients will receive 4 intrathecal (IT) bolus doses of Study Drug at 4-week intervals during the 13-week Treatment Period (Days 1, 29, 57, 85).

Approximately 44 patients are planned to be enrolled in this study. The number of patients enrolled may be higher if some patients need to be replaced and/or if the sizes of the cohorts

are expanded to obtain further experience with particular dose levels. A maximum of 48 patients may be enrolled.

The overall study duration will be approximately 7-8 months. The study will consist of a Screening Period of up to 6 weeks, a 13-week Treatment Period and a 15-week Post-Treatment Period. The end of study is defined as last patient, last study visit. Please refer to the Schedule of Procedures in Appendix A.

1.2 Objectives

1.2.1 Primary Objectives

To evaluate the safety and tolerability of ascending dose-levels of multiple IT bolus administrations of an antisense inhibitor of Htt (ISIS 443139) to patients with HD.

1.2.2 Secondary Objectives

To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT administrations of ISIS 443139.

1.2.3 Exploratory Objectives

To explore effects of multiple doses of ISIS 443139 on potential target engagement and disease progression biomarkers and clinical endpoints relevant to HD. Plasma pharmacokinetic properties of ISIS 443139 will also be assessed. Disease progression markers are included primarily as a safety measure to document any marked worsening. A lesser objective is to gain experience with these measures in an ISIS 443139 clinical study as preparation for subsequent, longer-term clinical studies. It is not expected that the majority of biomarkers and clinical measures will be impacted significantly by the 13-week of dosing planned for this study. For the current study, select disease progression markers are considered to be key exploratory target engagement, biochemical, neuroimaging and cognitive assessments based on their potential to evidence changes in disease progression in early HD. These key exploratory endpoints are mutant Htt in CSF, neurofilament light chain in CSF, ventricular volume as assessed by structural magnetic resonance imaging (MRI) and the composite cognitive score resulting from assessment of the components of the HD Cognitive Battery, respectively.

1.3 Endpoints

1.3.1 Safety and Tolerability Endpoints

- 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
- Clinical assessments
- Volumetric and safety neuroimaging assessments

1.3.2 Pharmacokinetic Endpoints

A CSF sample will be collected at pre-dose on each injection day (Days 1, 29, 57, 85) and at one Post-Treatment Period visit for PK analyses.

Plasma samples will be collected on study Days 1, 2, 29, 57, 85 and 86 and at each Post-Treatment Period visit for PK analyses.

Plasma C_{max}, AUC, elimination half-life and trough and post-distribution drug levels will be assessed, where appropriate.

1.3.3 Exploratory Endpoints

- Biochemical
  - CSF levels of mutant Htt*
  - CSF levels of neurofilament light chain*, YKL-40, , neurogranin, and tau
  - Plasma levels of IL-6, TNFα and 24S-hydroxycholesterol
- Neuroimaging volumes, including but not limited to:
  - Structural MRI
    - Caudate
    - Whole brain
    - Ventricular*
  - Resting state functional MRI
  - NODDI

- Electrophysiological
  - qEEG
- Clinical
  - Functioning/ability to perform activities of daily living
    - UHDRS Total Functional Capacity Scale (TFC)
    - UHDRS Independence Scale
    - HD Work Function Scale
  - Cognitive and motor tests:
    - HD Cognitive Battery*
      - Self-Paced Tapping
      - Emotion Recognition
      - CANTAB One Touch Stockings
      - Symbol Digit Modalities Test
      - Hopkins Verbal Learning Test Revised
      - Trail Making Test Part B
    - UHDRS Total Motor Scale
    - Stroop Word Reading Test
    - Map Search Test
    - Speeded Tapping
  - Neuropsychiatric evaluation
    - Problems Behavior Assessment for Huntington's disease-short form (PBA-s)

* Key exploratory biochemical, neuroimaging, electrophysiological and clinical assessments

2.0 PROCEDURES

2.1 General Overview of Procedures

Ionis (or designee) will review all study data including source documents, case report forms (CRFs), and laboratory reports. Study site will enter subject source data into the case report form. The CSF Safety lab data (CSF WBC, CSF RBC, CSF protein, CSF glucose) will be completed at each site's local lab and will be entered on a CRF (CSF Results CRF). Mutant Htt will be transferred electronically from CCI Other laboratory data will be transferred electronically from C . C-SSRS, UHDRS TFC, Independence Scale, UHDRS Total Motor Scale, HD Work Function Scale, PBA-s will be collected using CCI device and data provided by CCI . Neuroimaging data including structural MRI, MRS spectroscopy will be reported by CCI Resting state functional MRI and NODDI data will be generated by CCI Self-Paced Tapping, Emotion Recognition, CANTAB One Touch Stockings, and Speeded Tapping will be collected using the CCI device and data provided by CCI . ECGs will be centrally read by CCI . EEGs will be collected by CCI Those data will be transferred electronically to Ionis Pharmaceuticals, Inc.

Ionis Pharmaceuticals, Inc. is responsible for the format of electronic data transfers, transfer schedule and review of the data. Those data will be stored as SAS data sets.

2.2 Randomization & Treatment Allocation

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

Eligible patients will be randomized centrally by an automated system to receive ISIS 443139 or placebo. Within each cohort, randomization will be 3:1 for ISIS 443139: placebo respectively as outlined in Section 1.1. Patients in Cohort D will be stratified by early Stage 1 (TFC ≥12) or late Stage 1 (TFC = 11) disease. Patients in Cohorts B, C, D, and E will also be randomly assigned to have the CSF sampling visit at Week 17 or Week 21 in a 1:1 ratio within cohort and treatment assignment. CCI will prepare the randomization list.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), are reviewed according to standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. For dose escalation, the progression of the study from initiation of dosing in one cohort to the next will be determined by the Sponsor and the DSMB. Ionis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to all applicable study sites.

2.5 Data Management

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

2.5.1 Case Report Form Data

CCI (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Ionis Pharmaceuticals, Inc. is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. Ionis Pharmaceuticals, Inc. reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data is entered, reviewed and queried the database is closed. The data is then reviewed by Ionis Pharmaceuticals, Inc. and additional queries may be generated. After all queries are resolved the database is locked.

2.5.2 Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers and the transfer schedule. Ionis Pharmaceuticals, Inc. is responsible for the review of the clinical laboratory data. This data is not stored in the EDC system. Investigator sites have access to safety laboratory data via printed lab reports sent directly from the laboratory.

2.5.3 Pharmacokinetics Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the PK data. This process involves reviewing the patient and visit identifiers with the clinical data collected in the EDC system. The PK data are not stored in the EDC system.

3.0 ANALYTICAL PLAN

3.1 General Overview of Analyses

3.1.1 Statistical Methods

All CRF data, data transfers from external vendors (e.g., laboratory, cognitive testing, ECG, qEEG), and any outcomes derived from the data will be provided in the subject data listings. Subject data listings will be presented for all subjects 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, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. Analyses may be stratified by the stratification factor and/or site if supported by data.

Since there are limited placebo-treated subjects within each dose cohort, the placebo-treated subjects will be pooled for all analyses.

For vital signs [blood pressure (BP), heart rate, respiration rate, orthostatic change and temperature], baseline will be defined as the average of the values collected prior to first dose (Screening, Study Day -1, Study Day 1, and any measurements between Screening and Day 1).

Baseline ECG will be defined as the average of the triplicate taken on Day -1, if only one or two assessments are available, the single assessment or average of the two assessments will be used.

For all other measures and parameters, baseline will be defined as the last non-missing measure prior to the first dose.

The treatment period will be defined as the period of time from the first dose administration through Day 92 visit or, if the patient does not participate in Day 92 visit, from the first dose administration through 9 days after the last dose administration.

The post-treatment assessment period will be defined as the period of time from the day after the treatment period to the end of study.

Demographic and baseline characteristics (e.g., age, sex, ethnicity, race, weight, height, BMI, Montreal Cognitive Assessment (MoCA), ISCED level, CAG repeat length, ApoE isoform genotype, BCHE-K variant, and disease burden score (DBS)) and subject disposition will be summarized using descriptive statistics by treatment group. DBS is calculated by [CAG repeat length – 35.5]*age in years. All subjects enrolled will be included in a summary of subject disposition. Protocol deviations will be listed.

Multiple results within the same visit (or timepoint for measurements collected at multiple timepoints) will be averaged for by visit analyses. Unscheduled results will not be included in the by-visit analyses except for determining baseline, but will be presented in data listings.

PK parameters will be summarized by treatment group using n, mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

3.1.2 Subject Populations Analyzed

The following analysis populations will be used for the analyses of data as described within each analysis set:

Safety Population: All patients who are randomized and receive at least one dose of Study Drug. This population will be used for safety and tolerability analyses.

Per Protocol Population: All patients who are randomized and receive all doses of the protocol-specified Study Drug (ISIS 443139 or placebo). This population will be used for pharmacodynamics, exploratory and biomarker analyses.

PK Population: All patients who are randomized to ISIS 443139 and receive at least one dose of ISIS 443139 and have sufficient sampling to permit pharmacokinetic evaluation. This population will be used for PK analyses.

In addition to the above analysis sets, it is recognized that some data displays will be provided for "All Screened", "Screening Failures" and "All Randomized" subjects but no data analysis will be executed in these populations except for the disposition table that includes all screened subjects.

3.1.3 Sample Size Consideration

While there is no statistical rationale for the sample size, it has been selected based on the prior experience with generation 2.0 ASOs given by IT injection to ensure that the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.

3.1.4 Planned Interim Analysis

Unblinded interim analyses may be performed and the results summarized by treatment group at the end of each cohort upon completion of dosing for that cohort or at any time if needed to address a safety concern. The Investigator, study staff, patients, monitors, Sponsor Medical Monitor, members of the Sponsor's clinical operations team and data management team will remain blinded throughout the study. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection.

A DSMB will be assembled to review safety, tolerability, pharmacokinetic and target engagement/pharmacodynamic (as needed) data collected on ISIS 443139 during this study. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to DSMB prior to each DSMB meeting. Based on its ongoing assessment of the safety and tolerability of ISIS 443139, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB charter.

3.1.5 Incomplete or Missing Data

Missing values will not be imputed unless otherwise specified.

3.2 Safety Analyses

3.2.1 Exposure

Treatment duration and amount of Study Drug received will be summarized by treatment group.

3.2.2 Adverse Events

An adverse event will be regarded as treatment emergent adverse event (TEAE) if it is present prior to receiving the first dose of study drug and subsequently worsened, or is not present prior to receiving the first dose of study drug but subsequently appeared.

The most conservative approach will be used to determine if the event occurs after the first dose of treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset date of an AE is a partial date with only month or year available or completely missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date or a full or partial resolution date is available that definitively demonstrates that the event ended prior to first dose of study drug.

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™) preferred term and system organ class for:

- All treatment emergent adverse events
- Related treatment emergent adverse events. Related is defined as "Related", "Possible", or missing relationship to study drug
- All treatment emergent adverse events by severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. Adverse events with missing severity will be categorized as "Missing" for this summary
- Related treatment emergent adverse events by severity
- Serious treatment emergent adverse events
- Serious and related treatment emergent adverse events

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

SAEs and non-serious AEs that lead to study discontinuation or investigational drug discontinuation will be listed separately. Non-TEAEs will be flagged in the data listing.

3.2.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS collects binary responses to 11 categories: five subtypes of suicidal ideation, five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent. Specifically, the following outcomes are C-SSRS categories and have binary (Yes/No) responses. (The categories have been re-ordered from the actual scale to facilitate the definitions of the composite endpoints and to enable clarity in the presentation of the results.)

Suicidal Ideation:

Category 1 – Wish to Be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior:

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Other

Category 11 – Non-suicidal Self-injurious Behavior

In addition, a numerical score, the Suicidal Ideation Score, will be defined as the highest suicide ideation category (1–5) at which the patient responded "Yes" for the given visit. If the patient did not respond "Yes" to any of these categories, the score will be set to zero.

For each of the 11 categories above, the number and percent of patients with a "Yes" response at any time post-baseline (regardless of baseline response) will be summarized by treatment group.

In addition, emergent suicidal ideation or behavior will be summarized. The binary categories above and the Suicidal Ideation Score will be used to identify the 8 composite endpoints defined below. Note that "recent history" for these composite endpoints is defined as the 12 months prior to Screening and the Screening period. At the Screening visit, C-SSRS data is collected for the prior 12 months. Therefore, analyses that utilize data from "recent history" will include the historical 12-month data collected at Screening as well as all on-study C-SSRS data collected prior to first dose.

- **Suicidal Ideation**: A "Yes" answer at any time post-first-dose to any one of the five suicidal ideation questions (Categories 1–5), regardless of the pre-dose responses
- **Suicidal Behavior**: A "Yes" answer at any time post-first-dose to any one of the five suicidal behavior questions (Categories 6–10), regardless of the pre-dose responses
- **Suicidal Ideation or Behavior**: A "Yes" answer at any time post-first-dose to any one of the ten suicidal ideation or behavior questions (Categories 1–10), regardless of the pre-dose responses
- **Treatment-Emergent Suicidal Ideation** compared to recent history: A maximum post-first-dose suicidal ideation score that is increased from the maximum suicidal ideation score in recent history.
- **Treatment-Emergent Serious Suicidal Ideation** compared to recent history: A maximum post-first-dose suicidal ideation score of 4 or 5 when the maximum suicidal ideation score during recent history was less than 4 (i.e., scores of 0-3). Only patients with a recent history score of 0–3 will be considered evaluable for this outcome.
- **Emergence of Serious Suicidal Ideation** compared to recent history: A maximum post-first-dose suicidal ideation score of 4 or 5 when the maximum suicidal ideation score during recent history was 0. Only patients with a recent history score of 0 will be considered evaluable for this outcome.
- **Improvement in Suicidal Ideation** compared to baseline: A decrease in the suicidal ideation score at the patient's Study Day 86 C-SSRS assessment compared to the baseline score, defined as the minimum score obtained during the Screening Period (i.e., assessments collected from the Screening Visit through pre-dose on Study Day

1). The analysis will be repeated for Study Days 113, 141 and 197. Only patients with a baseline score >0 will be considered evaluable for these outcomes.

- **Emergence of Suicidal Behavior** compared to all prior history: The occurrence of suicidal behavior (a "Yes" response to one or more of Categories 6–10) post-first-dose from not having suicidal behavior prior to first dose (includes the "lifetime" score collected at the Screening Visit as well as all C-SSRS assessments collected from the Screening Visit through pre-dose on Study Day 1).

Each of the composite endpoints will be summarized by treatment group. For each treatment-emergent outcome listed, only those patients with the specified screening condition will be considered evaluable. In addition, patients who discontinue from the study with no post-first-dose C-SSRS assessment will be considered unevaluable for analyses of suicidality. Percents will be based on the number of evaluable patients for each outcome.

In addition, a shift table will be created to demonstrate the change in suicidal ideation score from recent history to treatment period and/or post-treatment period. The maximum suicidal ideation score in each period will be used to create the shift table. If a patient's recent history suicidal ideation score is missing but has a post-first-dose score, then the recent history assessment will be labeled as "unknown". Likewise, if a patient's recent history suicidal ideation score is available but has no post-first-dose score, then the scores during the treatment and post-treatment period will be labeled as "unknown".

3.2.4 Laboratory Measurements

The following is the list of lab analytes that will be measured throughout the study:

- Chemistry: Sodium, Potassium, Chloride, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Bicarbonate, Glucose, BUN, Creatinine, Total serum bilirubin, Uric acid, Alkaline phosphatase, ALT (SGOT), AST (SGPT), GGT and CPK.

- Hematology: Red blood cells, Hemoglobin, Hematocrit, Platelets, MCV, MCH, MCHC, White blood cells, and WBC differential (percentage and absolute count) (Basophils, Eosinophils, Lymphocytes, Monocytes and Neutrophils)

- Coagulation: aPTT, PT, INR

- Thyroid Panel: TSH, Free T4, and Free T3

- PK: Plasma ISIS 443139 levels, and CSF ISIS 443139 levels

- Pregnancy: Urine hCG

- CSF Safety Panel (Minimum Requirements): Red blood cells, White blood cells, Glucose and Protein

- Urinalysis: Specific gravity, pH, Protein, P/C ratio, Glucose, Ketones, Urobilinogen, Leukocyte esterase, Nitrite, Bilirubin, Blood, Red blood cells, White blood cells, Epithelial cells, Bacteria, Casts, Crystals, Color and Appearance.

In addition, the following analytes are measured at screening only: plasma hCG, FSH, hepatitis B surface antigen, hepatitis C antibody, HIV antibody, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates.

The following genetic testing is performed: CAG repeat length, ApoE isoform genotype, BCHE-K.

Missing WBC differential absolute counts and percentages will be derived:

If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophils counts and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

Laboratory tests to ensure subject safety including chemistry panel, hematology panel, coagulation, and CSF safety labs (cell counts, protein, and glucose), will be summarized by study visit for each treatment group. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

In addition, the shifts (relative to the normal range) from baseline to the minimum and maximum post-baseline values will be presented. If a subject is missing a baseline value but had a post-baseline value, then the baseline assessment is labeled as "unknown". Likewise, if a subject had a baseline value but had no post-baseline values, then the minimum and maximum are labeled as "unknown". For each parameter, the incidence of shift to low will be summarized using the minimum post-baseline values; the incidence of shift to high will be summarized using the maximum post-baseline values.

Only central laboratory data will be used for the summary tables and figures. Local laboratory data will be provided in the listings only, with the exception of local results for CSF safety tests which will be listed and summarized in tables.

All lab data will also be displayed in subject listings.

3.2.5 Vital Signs Measurements and Weight

Vital signs will include body temperature, heart rate, respiration rate, orthostatic changes, and systolic and diastolic blood pressure.

Orthostatic changes include 3 variables: change from seated systolic blood pressure to average of all available standing systolic blood pressures, change from seated diastolic blood pressure to average of all available standing diastolic blood pressure, and change from seated heart rate to average of all available standing heart rate.
Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) for vital sign values and weight as well as the change and percent change from baseline at each study visits by treatment group.

3.2.6 Neurological Examinations

Neurological examinations will be provided in patient listings.

3.2.7 12-Lead Electrocardiograms (ECG)

ECG data will be collected through a central reader.

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, QTC (recorded from ECG machine), QTcF (QT corrected using the Fridericia's formula), and QTcB (QT corrected using the Bazett's formula) as described below:

$QTcF = QT / (RR)^{1/3}$, where RR= 60/VR

$QTcB = QT / (RR)^{1/2}$, where RR= 60/VR

At Day -1, three replicates of ECG parameters will be recorded, and the mean from all replicates will be used as the subject's reportable value at Day -1. For all other time points, a single set of parameters will be recorded. QTcF and QTcB will be calculated based on the subject's reportable ECG data at each time point using the formula described above.

Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) as well as the change and percent change from baseline at each study visits by treatment group.

3.2.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug dictionary and summarized by ATC class, generic name and by treatment group.

A concomitant medication is defined as medications that were taken on or after the first study drug administration (Study Day 1). This includes medications that were started prior to the initiation of study drug if their use continued on or after the date of the first dosing. In order

to define concomitant medications with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a particular medication were missing, that medication is considered concomitant;
- if the start date of a medication was missing and the stop date of that medication fell on or after the date of dosing, that medication is considered concomitant;
- if the start date of a medication was prior to the date of first dosing and the stop date of that medication was missing, that medication is considered concomitant; or
- if the start/stop date of a medication is partial then where it is not possible to rule out that it was not taken concomitantly it will be considered concomitant.

Non concomitant medications will be flagged in the data listing.

3.3 Pharmacokinetic Analysis

CSF and Plasma samples will be collected at protocol designated times for ISIS 443139 pharmacokinetic assessments from the dose cohorts. Only concentration data from patients randomized to receive study drug (ISIS 443139) will be included in this analysis.

3.3.1 CSF Concentration Data and Pharmacokinetics

A CSF sample will be collected pre-dose on each injection day (Days 1, 29, 57, 85) and at one Post-Treatment Period visit for PK analyses. CSF concentrations of ISIS 443139, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, treatment group (cohort), nominal dose, and day. Differences between scheduled and actual sampling days will also be listed for all patients, as well as percent differences between actual administered dose and nominal dose.

CSF concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for CSF concentrations, all BLQ values will be set to zero. Mean CSF concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 443139 CSF concentrations will be tabulated by treatment group (cohort), nominal dose and day. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days, or large deviations between actual dose and nominal dose.

The ISIS 443139 half-life in CSF will be calculated, if possible, and summarized by treatment group (cohort), nominal dose, and nominal day.

ISIS 443139 CSF concentration versus time (actual) profiles from Day 1 to last collection (nominal Study Day 113 or 141 in Cohorts A–D), for each patient, as well as the mean (±SE)

CSF concentration versus time (scheduled) profiles for each treatment cohort, will be presented graphically on linear scale. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.3.2 Plasma Concentration Data

Plasma concentrations of ISIS 443139, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, treatment group (cohort), nominal dose, and day. Percent differences between scheduled and actual sampling times will also be listed for all patients as well as percent differences between actual administered dose and nominal dose.

Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 443139 plasma concentrations will be tabulated by treatment group (cohort), nominal dose, day, and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 443139 plasma concentration versus time (actual) profiles from Day 1 to Day 29 and Day 85 to Day 197 (Cohorts A–D), for each patient, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles for each treatment cohort, will be presented graphically on linear and semilogarithmic scales. Additionally, ISIS 443139 plasma concentration versus time (actual) profiles from 0 to 24 hours on Days 1 and 85 for all patients, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles (0 to 24 hours on Days 1 and 85) for each applicable treatment cohort will be presented graphically on linear and semilogarithmic scales. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.3.3 Plasma Pharmacokinetics

Non-compartmental pharmacokinetic analysis of ISIS 443139 will be carried out on each individual patient data set using Phoenix WinNonlin version 6.3 or higher CCI . Plasma pharmacokinetic parameters in each patient (when applicable) will be determined. For calculation of PK parameters, all BLQ values will be set to zero. The following plasma PK parameters will be calculated (when applicable) and based on actual sampling times:

- C_{max}: the maximum observed drug concentration in plasma.
- T_{max}: the time at which C_{max} occurs.
- $AUC_{0\text{-}24h}$: areas under the plasma concentration-time curve from zero time (pre-dose) to 24 hours after the intrathecal administration will be calculated using the linear trapezoidal rule after the dose administrations on Day 1 and Day 85.
- $AUC_{0\text{-}28d}$ ($AUC_{0\text{-}\tau}$): areas under the plasma concentration-time curve from zero time (pre-dose) to 28 days after the intrathecal administration will be calculated using the linear trapezoidal rule for Days 1 and 85.
- $MRT_{0\text{-}24h}$: mean residence time (MRT) from time zero to 24 hours after intrathecal dose administration will be calculated from the equation, $MRT_{0\text{-}24h} = AUMC_{0\text{-}24h} / AUC_{0\text{-}24h}$, where $AUMC_{0\text{-}24h}$ is the area under the moment plasma concentration-time curve from time zero to 24 hours after dosing. This parameter will be calculated for Days 1 and 85. This parameter will be calculated and reported mainly as an index measure to reflect the expected initial rapid disposition of ISIS 443139 from plasma to tissues shortly after dosing.

The following PK parameters may be calculated using actual sampling times where appropriate data exists at the discretion of the pharmacokinetic scientist:

- $t_{½\lambda z}$: the plasma disposition half-life associated with the apparent terminal elimination phase may be calculated from the equation, $t_{1/2\lambda z} = 0.693/\lambda z$, on Day 85 profiles for Cohorts A to D.
- $AUC_{0\text{-}inf}$: AUC from zero to infinity, calculated as the sum of the $AUC_{0\text{-}28d}$ plus the final quantifiable concentration divided by λz, for only subjects in Cohorts A to D where $t_{½\lambda z}$ can be accurately and appropriately determined and only on Day 1.
- Additional partial AUC values may be calculated depending upon the samples collected during the study.
- CL/F: Plasma clearance will be calculated from CL = Actual Dose/$AUC_{0\text{-}inf}$, for subjects in Cohorts A to D where $AUC_{0\text{-}\infty}$ can be accurately and appropriately determined, and from the equation CL = Actual Dose/$AUC_{0\text{-}\tau}$ for subjects in Cohorts A to D after the Day 85 dose.

Plasma pharmacokinetic parameters (if applicable) will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) treatment cohort, nominal dose, and day.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

3.4 Exploratory Pharmacokinetic-Pharmacodynamic Analysis

Potential relationships between selected pharmacodynamic (e.g., mutant Htt protein) and plasma post-distribution exposure (i.e., trough and post-treatment) measures may also be explored, where deemed appropriate.

3.5 Exploratory Analyses

For the continuous exploratory variables, descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) of the results, as well as the change and percent change from baseline to each study visit, will be presented by treatment group in summary tables; for the categorical variables, counts and percentages will be provided. Where appropriate, inferential analyses will be conducted as described below.
The following exploratory endpoints will be summarized by treatment group as the above method according to their data characteristics.
These analyses will be performed on the Per Protocol Set. If deemed appropriate, these analyses may be repeated for the Safety Population or appropriate subset(s), as needed.

3.5.1 Biochemical

The results and change and percent change from baseline for CSF biomarkers and plasma biomarkers at each visit will be summarized using descriptive statistics and compared between each dose group and placebo using the ANOVA or Wilcoxon Rank Sum test, as appropriate. The normality will be assessed using the Kolmogorov-Smirnov test on the residuals.
Changes in mutant Htt in CSF and neurofilament light chain in CSF are key exploratory endpoints for the study.

Considerable between-patient variability is expected in the baseline levels of CSF and plasma biomarkers, and there may be patients with baseline levels that are comparable to a normal (i.e., not diseased) state. In this event, additional analyses will be conducted to account for differences in baseline (such as including baseline levels as covariates) and/or analyses will be repeated on the subset of the analysis population with baseline levels that are abnormal.

3.5.2 Neuroimaging Findings

Whole brain volume, intraventricular volume and caudate volume assessed using MRI as well as changes and percent changes from baseline at each visit will be summarized using descriptive statistics and compared between each dose group and placebo using the ANOVA or Wilcoxon Rank Sum test, as appropriate. The normality will be assessed using the

Kolmogorov-Smirnov test on the residuals. Change in ventricular volume is a key exploratory endpoint for the study.

Parameters characterizing connectivity between different brain regions will be determined using rsfMRI and NODDI. These analyses will be conducted outside the scope of this SAP by subject matter experts, and an independent report will be generated to describe the results.

3.5.3 qEEG

The primary endpoints obtained using quantitative EEG methods are the anterior-posterior gradients of relative alpha and delta power, global alpha power, global delta power, theta/alpha border power and mean frequency at resting state with eyes closed. The values at each visit as well as changes and percent changes from baseline at each visit will be summarized using descriptive statistics and analyzed in a similar way to the brain volumes. Data for anterior-posterior gradients of relative alpha and delta power, global alpha power, global delta power, theta/alpha border power and mean frequency at resting state with eyes open will be provided in the data listing.

3.5.4 UHDRS Total Functional Capacity Scale (TFC)

The TFC represents the Investigator's assessment of the patient's capacity to perform a wide range of activities of daily living including occupation, finances, domestic chores, activities of daily living and care level. It is based on a brief interview with the patient and the study partner. Scores range from 0 to 13, and higher scores represent better functioning.

The TFC scores as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volumes.

3.5.5 UHDRS Independence Scale

The patient's independence scale is the Investigator's assessment of the patient's degree of independence. The scale consists of 19 discrete levels ranging from 10 to 100 (by 5) where no special care needed corresponds to a scale of 100 and tube fed and total bed care corresponds to a scale of 10. The Independence Scale as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volumes data.

3.5.6 HD Work Function (HDWF) Scale

The HDWF scale is a measure of work role limitations and effort, which are areas that may be affected by the cognitive, behavioral and motor changes associated with HD (Brossman et al. 2012). It was developed for prodromal HD, the stage prior to overt motor impairment and HD diagnosis in which structural and functional brain changes lead to subtle changes in cognition and motor function. Patients and their trial partners each complete a questionnaire consisting of 20 questions, where the response to each is based on a 7-point Likert scale ranging from "not at all like me" to "very much like me". The HDWF scores for both patient-

completed questionnaire and the trial-partner-completed questionnaire are the sums of the individual question ratings, range from 20 to 140, and higher scores represent higher work function ability.

For both the patient-completed HDWF and the trial-partner-completed HDWF, the scores as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.7 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 six 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 six individual tests. The z-score for each test will be calculated as follows:

$$z = \frac{(x - \bar{x})}{s}$$

Where $\bar{x}$ is the overall baseline mean and s is the baseline standard deviation.

This composite cognitive score is a key exploratory endpoint for the study. The individual tests that comprise the battery are described below. The composite score, individual scores as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volume data.

-Self-Paced Tapping

Self-paced tapping measures cognitive and motor timing. The patient listens to a repeating tone at 3Hz and taps in time with the tone, alternating between left and right thumbs. The patient continues to tap after the tone stops, attempting to maintain the same rate of tapping. Four trials are conducted.

Scoring of each effort is based on the precision of taps, which is directly estimated, and timing precision, which is calculated as the reciprocal of the standard deviation of the intertap interval. Higher values indicate better performance, i.e., more consistent tapping rates. The paced tapping dependent measure (consistency of the intertap intervals) is computed using partial data if the participant does not complete the four trials within six minutes. The data will be summarized by visit and analyzed in a similar way to the brain volume data.

-Emotion Recognition

For this test, patients view faces depicting a neutral expression or an emotion (anger, disgust, fear, sadness, surprise, happiness). After a practice trial for each category, the patient views 70 test trials and categorizes each face by emotion. The number of correct responses for

negative emotions (anger, disgust, fear, sadness), out of 24 possible, is tallied (Johnson et al. 2007). The correct response number will be summarized by visit and analyzed in a similar way to the brain volume data.

-CANTAB One Touch Stockings (OTS)

The OTS test measures executive function, spatial planning and working memory. On a computer or tablet screen, the patient is shown two stacks of colored balls, which can be perceived balls stacked in hanging socks or stockings. The patient must move the balls between the stockings to achieve a particular color pattern. Rearranging the balls to make the target pattern may take one, two, three or four moves. Then, the patient is shown two stacks of colored balls and must determine, without moving the balls, the minimum number of moves necessary to achieve the target pattern.

The outcome is the mean latency to correct response. Higher values indicated worse performance (longer time to a correct response). The mean latency will be summarized by visit and analyzed in a similar way to the brain volume data.

-Symbol Digit Modalities Test (SDMT)

The SDMT is used to assess attention, visuoperceptual processing, working memory and psychomotor speed. It has been shown to have strong reliability and validity (Smith 1982; Hinton-Bayre et al. 1999). The patient must pair abstract symbols with specific numbers according to a translation key. The test measures the number of items correctly paired (maximum of 110) in 90 seconds. The scores will be summarized by visit and analyzed in a similar way to the brain volume data.

-Hopkins Verbal Learning Test – Revised (HVLT-R)

The HVLT-R is used to assess verbal memory through tests of recall and recognition. The HVLT-R consists of a word list, containing 12 words from three taxonomic categories, which is read aloud to the patient at the rate of approximately one word every two seconds. The Immediate Recall test includes three learning trials. Delayed Recall is assessed 20 to 25 minutes after completion of the Immediate Recall test. Immediately after administration of the Delayed Recall trial, a forced-choice recognition test is administered. The recognition test includes the 12 target words, plus 12 distractors (six semantically-related and six semantically-unrelated words). Patients must recall a series of 12 words over three immediate trials (learning), free recall after a 25-minute delay and a recognition trial. The outcome measure will be calculated as the sum of words correctly recalled over four trials (three immediate and one delayed) with the maximum value of 48. The data will be summarized by visit and analyzed in a similar way to the brain volume data.

-Trail-Making Test

The Trail-Making Test Part B (TMT-B) is a test of executive functioning. Patients are presented with a picture of 25 circles, each labeled with a number (1 – 13) or a letter (A – L).

The patient must draws lines to connect the circles in an ascending pattern that alternates between the numbers and letters (i.e., 1-A-2-B-3-C …). The patient is instructed to connect the circles as quickly as possible, and the time to complete the task is recorded.

The Trail-Making Test Part A (TMT-A) is also administered, but the results of the TMT-A are not considered to be part of the battery. For the TMT-A, patients are presented with 25 circles, each labeled with a number (1-25) and are asked to connect the numbers. Administration of TMT-A prior to TMT-B provides practice to aid in administering TMT-B.

Times to complete TMT-A and TMT-B, as well as changes and percent changes from baseline will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.8 UHDRS Total Motor Scale (TMS)

The TMS is the sum of the individual motor ratings obtained during administration of the motor assessment portion of the UHDRS, including ocular pursuit (horizontal and vertical), saccade initiation (horizontal and vertical), saccade velocity (horizontal and vertical), dysarthria, tongue protrusion, finger taps(right and left), pronate/supinate-hands (right and left), luria (fist-hand palm test), rigidity-arms(right and left), bradykinesia-body, maximal dystonia(trunk, rue, lue, rle and lle), maximal chorea (face, bol, trunk, rue, lue, rle and lle), gait, tandem walking, and retropulsion pull test. Scores range from 0 to 124, and higher scores represent more severe impairment.

The TMS scores will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.9 Stroop Word Reading Test

The Stroop Word Reading Test is a measure of processing and psychomotor speed. Patients are presented with a page of color names printed in black ink and are asked to read aloud as many words as possible within a given amount of time. Scoring is based on the number of correct responses in a fixed amount of time, typically within 45 seconds. Higher scores indicate better cognitive performance. The scores will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.10 Map Search Test

The Map Search Test is a test of sustained visual attention. Patients are presented with a visually cluttered map and asked to circle as many target symbols on the map as possible within a fixed period of time. Scoring is based on the number of correctly identified symbols. The scores will be summarized by visit and analyzed in a similar way to the brain volume data.

3.5.11 Speeded Tapping

The speeded tapping test is a measure of psychomotor speed and has been used as a longitudinal marker of disease severity in manifest and pre-manifest HD. For the test, the

patient taps the index finger of his/her non-dominant hand as quickly as possible for a 10 second period. The task is repeated with a brief rest period held between trials. The outcome measure is the mean of the intertap intervals across taps from all trials, with higher values indicating worse performance (i.e., slower tapping).

The data as well as change and percent change at each visit will be summarized using descriptive statistics and analyzed in a similar way to the brain volume data.

3.5.12 Problems Behavior Assessment for Huntington's Disease–Short Form (PBA-s)

The PBA-s assesses common behavioral and psychiatric manifestations of HD, including affect, irritability, loss of motivation, perseverative phenomena and psychotic symptoms. The test administrator interviews the patient and trial partner and rates the patient's behavior over the prior four weeks according to the guidelines for the test. The symptoms include depressed mood, suicidal ideation, anxiety, irritability, angry or aggressive behavior, lack of initiative (apathy), perseverative, obsessive-compulsive behaviors, delusions, hallucinations and disoriented behavior. Each symptom is rated for severity, frequency and worst. Severity and frequency scores will be multiplied to produce a PBA score for each symptom.
In addition, the following composite scores will also be calculated:

- Sum of the PBA scores for depressed mood, anxiety, and suicidal ideation
- Sum of the PBA scores for irritability and angry or aggressive behaviors
- Sum of the PBA scores for delusions and hallucinations and disoriented behavior
- Sum of the PBA scores for perseveration and obsessive-compulsive behaviors

The square roots of the individual PBA scores and the composites scores will be reported and summarized by visit and analyzed in a similar way to the brain volume data.

3.5.13 Correlations between ISIS 443139 Exposure and Exploratory Endpoints

The following correlations are planned. The correlations will be evaluated using the Pearson correlation coefficients and corresponding p-values. Other correlations may be conducted based on findings in the by-visit analyses of exploratory endpoints.

- CSF mutant Htt at latest from Day 85 or Day 113 and change in CSF mutant Htt (baseline to latest from Day 85 or Day 113) versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113
- CSF NFL at latest from Day 85 or Day 113 and change in CSF NFL (baseline to latest from Day 85 or Day 113) versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113
- CSF tau at latest from Day 85 or Day 113 and change in CSF tau (baseline to latest from Day 85 or Day 113) versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113

- Ventricular volume at Day 113 and Day 197 and change from baseline in ventricular volume at each of these Days versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113
- Whole brain volume at Day 113 and Day 197 and change from baseline in whole brain volume at each of these Days versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113
- HD Cognitive Battery composite score at Day 84, Day 141 and Day 197 and change from baseline in HD Cognitive Battery composite score at each of these Days versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113
- qEEG changes in anterior-posterior gradients of relative alpha and delta power at Day 113, Day 141 and Day 197 and change from baseline in anterior-posterior gradients of relative alpha and delta power at each of these Days versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113
- qEEG changes in global alpha power, global delta power, theta/alpha border power and mean frequency at Day 113, Day 141 and Day 197 and change from baseline in global alpha power, global delta power, theta/alpha border power and mean frequency at each of these Days versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113
- Changes in UHDRS-TMS at Day 84, Day 141 and Day 197 and change from baseline in UHDRS-TMS at each of these Days versus concentration of ISIS 443139 in CSF at latest from Day 85 or Day 113

3.5.14 Subset and Sensitivity Analyses

Patients enrolled into this study are early in the disease; therefore, for a given endpoint parameter, there may be patients with baseline levels that are essentially normal (i.e., not altered as would be expected in a diseased state). In these patients, there would be no ability to measure an improvement in that parameter, which confounds interpretation of an analysis that includes all patients. The confounding effect could be in either direction, i.e., it could lead to a false positive or a false negative. Where appropriate based on the observed baseline data, sensitivity and/or subset analyses will be conducted either to account for differences in baseline within the analysis or to utilize a subset of the analysis population with baseline levels reflective of a diseased state.

In addition, sensitivity analyses may be conducted if imbalances are detected in baseline characteristics or when particular baseline characteristics, such as DBS or TFC, are reasonably anticipated to impact the course of disease.

4.0 REFERENCE

5.0 APPENDICES

Appendix A Schedule of Procedures

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																				Post-Treatment Period (15 Weeks)		
Study Week	-6 to -1	1				2	5				6	9				10	13				14	17/ ET [2]	21	29/ ET [2]
Study Day	-43 to -2	-1	1	2	3	8	28	29	30	31	36	56	57	58	59	64	84	85	86	87	92	113	141	197
Visit Window (days) *	-	*	0	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	±2	±7	±7
Visit Type [1]	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	ph	cl	cl	cl	ph	ph	cl	cl	cl
Overnight Stay [3]			X→					X→					X→					X→						
Capacity to Consent Instrument and Informed Consent	X																							
Inclusion/Exclusion	X																							
Medical History and ISCED	X																							
MoCA	X																							
Vital Signs (BP, HR, RR, T)	X	X	X [a]				X	X[a]				X	X[a]				X	X[a]				X	X	X
Orthostasis	X		X [b]															X[b]					X	X
Physical& Neurological Exam[4]	X	X	X [c]	X[d]		X	X	X[c]	X[d]		X	X	X[c]	X[d]			X	X[c]	X[d]			X	X	X
Body Weight and Height [5]	X	X					X					X					X					X	X	X
Functional, Cognitive, Motor and Neuropsychiatric assessments [6]	X	X															X						X	X
C-SSRS [7]	X	X	X[b]	X		X	X	X[b]	X		X	X	X[b]	X			X	X[b]	X			X	X	X
qEEG	X	X																				X	X	X
Structural MRI	X																					X		X
T2 flair, T2 star, T2 FSE/TSE MRI	X																							X
MRI of the CSF space	X																							
^{1}H-MRS	X																					X		X

Appendix A Schedule of Procedures *Continued*

Study Period	Screen	Treatment Evaluation Period (13 Weeks)																Post-Treatment Period (15 Weeks)		
Study Week	-6 to -1	1				2	5				6	9				10	13				14	17/ ET [2]	21	29/ ET [2]
Study Day	-43 to -2	-1	1	2	3	8	28	29	30	31	36	56	57	58	59	64	84	85	86	87	92	113	141	197
Visit Window (days) *	-	*	0	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	*	±2	*	*	±2	±2	±7	±7
Visit Type [1]	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	cl	cl	cl	cl	ph	ph	cl	cl	cl	ph	ph	cl	cl	cl
ECG (12-Lead) [8]	X	X		X																		X		X
Chemistry Panel	X	X					X										X						X	X
Hematology	X	X					X										X						X	X
Urinalysis	X	X					X										X						X	X
Genetic Tests	X																							
HIV, Hepatitis B & C	X																							
Drug/Alcohol Screen	X																							
FSH [9]	X																							
Pregnancy Test [10]	X	X					X					X					X					X	X	X
Serum Biomarker Sample	X	X					X					X					X					X	X	X
Lipid and Thyroid Panels		X					X										X						X	X
PT, INR, aPTT	X	X					X										X						X	X
Plasma Sampling for PK			X [e]	X[d]				X[b]					X[b]					X [f]	X[d]			X	X	X
Archived Serum Sample [11]	X	X					X					X					X					X	X	X
CSF Sample for PK/Safety/Biomarkers			X[b]					X[b]					X[b]					X[b]				X [g]	X[g]	X [h]
Archived CSF Sample			X[b]					X[b]					X[b]					X[b]				X[g]	X[g]	X[h]
Study Drug Administration			X					X					X					X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	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	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

* Visit windows are calculated relative to Study Day 1. Note that within each block of visits associated with dose administration, the visits must occur on 4 consecutive days. There are four "visit blocks" in this study: (Study Days -1, 1, 2 and 3), (Study Days 28, 29, 30 and 31), (Study Days 56, 57, 58 and 59) and (Study Days 84, 85, 86 and 87).

1 cl = clinic visit; ph = phone visit

2 If the patient terminates early from the Treatment Period but is willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received, (c) proceed to the Week 17 visit approximately 4 weeks after last dose and conduct all visits in the Post-Treatment Period. If the patient terminates early from the Treatment Period and is not willing to participate in the Post-Treatment Period, (a) conduct the full block of visits associated with the last dose received (see asterisk above), (b) conduct the visit scheduled for 7 days after the last dose received and (c) conduct the Week 29 visit as an Early Termination Visit. If the patient terminates early from the Post-Treatment Period, conduct the Week 29 visit as an Early Termination Visit.

3 On Study Day 1, the patient must stay in the clinic overnight and undergo safety monitoring follow-up as scheduled on Study Day 2. On Study Days 29, 57 and 85, the patient may either stay in the clinic overnight or be discharged (after a minimum observation period of 6 hours after Study Drug administration), provided the patient returns to the clinic on the following day (Day 30, 58 or 86) for all required assessments.

4 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.

5 Height is measured at Screening only.

6 Functional, Cognitive, Motor and Neuropsychiatric Tests are speeded tapping, UHDRS total functional capacity scale, UHDRS independence scale, UHDRS total motor scale, HD work function scale, HD Cognitive Battery (self-paced tapping, emotion recognition, CANTAB one-touch stockings, symbol-digit modalities test, Hopkins verbal learning test – revised and trail making tests), Problems Behavior Assessment for Huntington's disease-short form, Stroop Word Reading test and Map Search test.

7 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.

8 Measured in triplicate at the Study Day -1 visit only.

9 Women who are not surgically sterile as confirmation of menopause.

10 Women who are not surgically sterile. Serum test at Screen visit; dipstick at post-screen visits.

11 Stored at -80° C for follow-up exploration of laboratory findings and/or adverse events (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 ISIS 443139.

Time (in reference to time of Study Drug administration):

a Predose, 3 and 6 hours post IT injection

b Predose

c Predose and 3 hours post IT injection; also conduct at 6 hours post IT injection on any dosing day that the patient does not stay in the clinic overnight (overnight stays are optional on Study Days 29, 57 and 85)

d 24 hours after prior dose of Study Drug

e Predose, 0.5, 1, 2, 3, 4, 5, 6, 8 and 12 hours post IT injection

f Predose, 0.5, 1, 2, 3, 4 and 5 hours post IT injection

g All patients in Cohort A will have CSF collected on Study Day 113 (Week 17) and not on Study Day 141 (Week 21). For all other cohorts, CSF sampling will be conducted in approximately 50% of patients on Study Day 113 (Week 17) and in the remaining 50% of patients on Study Day 141 (Week 21), as assigned by the Sponsor according to a predetermined, randomized assignment.

h CSF sampling will be conducted at Study Day 197 (Week 29) in only those patients who attend the visit as an early termination visit and did not undergo CSF sampling on either Study Day 113 (Week 17) or Study Day 141 (Week 21). If CSF sampling was conducted on Study Day 113 (Week 17) or Study Day 141 (Week 21), do not collect CSF at Study Day 197 (Week 29)

STATISTICAL ANALYSIS PLAN VERSIONS

Protocol Number: ISIS 443139-CS1

Protocol Title: A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 443139 in Patients with Early Manifest Huntington's Disease

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A list of changes to the statistical analysis plan are below:

Version	Description of Change	Dates
Original SAP	No Changes	11 Nov 2015
Version 2	•Updated study description to align with final protocol •Updated select exploratory correlation analyses from utilizing exploratory endpoint values at Day 85 to utilizing exploratory endpoint values at the latter available of Day 85 and Day 113 because Day 113, though not available in all patients due to study design, is 28 days after the last dose of study drug and therefore serves as the best possible estimate of trough steady-state. Summary tables of raw and change data are planned for individual study days (e.g., Day 85 and Day 113) as well as for this defined endpoint (i.e., latter available of Day 85 and Day 113) •Removed planned summaries of data that were ultimately entirely or largely missing due to unavailability of reliable laboratory assays, CSF volume limitations or data quality control failure •Corrected formula for calculation of TMS	15 Mar 2018