Clinical Study Protocol

A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-120101 Administered Intrathecally in Patients with Huntington's Disease

WVE-HDSNP1-001

Drug Development Phase:	Phase 1b/2a
Investigational Product:	WVE-120101
Indication:	Huntington's disease
EudraCT Number	2016-005095-10
Sponsor:	Wave Life Sciences UK Limited Hays Galleria 1 Hays Lane London, SE1 2RD United Kingdom
Amendment	2.0
Date:	21 January 2020

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and local regulatory requirements as applicable.

[redacted]

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: WAVE LIFE SCIENCES

I have read and understand the contents of this clinical protocol for Study No. WVE-HDSNP1-001 dated 21 January 2020 and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this study.

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. WVE-HDSNP1-001 dated 21 January 2020 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current International Conference on Harmonization guidelines governing Good Clinical Practices, applicable Food and Drug Administration (FDA) regulations, and other local regulatory requirements:

Name of Principal Investigator:

Title:
Institution:
Address:
Phone:
Fax:

Signature	**Date**

PROTOCOL SYNOPSIS

Sponsor: Wave Life Sciences	**Investigational Product:** WVE-120101	**Phase:** 1b/2a	**EudraCT Number:** 2016-005095-10

Title of Study: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-120101 Administered Intrathecally in Patients with Huntington's Disease

Protocol Number: WVE-HDSNP1-001

Study Center(s): Approximately 25 study sites worldwide

Indication: Huntington's disease (HD)

Objectives:

Primary objective:

- Evaluate the safety and tolerability of WVE-120101 in patients with early manifest HD.

Secondary objectives:

- Characterize the pharmacokinetics (PK) of WVE-120101 in plasma.
- Characterize the exposure of WVE-120101 in cerebrospinal fluid (CSF).
- Assess the pharmacodynamic (PD) effect of WVE-120101 on levels of mutant huntingtin protein (mHTT) in CSF.
- Assess the effect of WVE-120101 on signs and symptoms of HD, as measured by the Total Functional Capacity (TFC), administered as part of the Unified Huntington's Disease Rating Scale (UHDRS).

Exploratory Objectives:

- Characterize changes in magnetic resonance imaging (MRI) of the brain in patients receiving WVE-120101.
- Assess the effect of WVE-120101 on signs and symptoms of HD, as measured by the motor, cognitive, independence, and functional assessments, administered as part of the UHDRS.
- Assess the effect of WVE-120101 on signs and symptoms of HD, as measured by the Short Problem Behaviors Assessment (PBA-s).

Methodology: This is a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of intrathecal (IT) WVE-120101 in adult patients with early manifest HD who carry a targeted single nucleotide polymorphism (SNP) rs362307 (SNP1).

This study will evaluate a single dose of WVE-120101 followed by multiple doses in eligible patients with early manifest HD. To participate in the study, patients must have documented heterozygosity for SNP1 with the thymine (T) variant on the same allele as the cytosine-adenine-guanine (CAG) triplet expansion. Patients who have not previously undergone SNP analysis will be required to be prescreened to determine heterozygosity for SNP1. The prescreening assessment will have a separate informed consent form (ICF).

Patients may participate in the complete study, in which they will receive all 4 doses. In order to allow for evaluation of a full multi-dose cohort (N=12), new patients may be enrolled

directly in the multiple-dose portion to account for those patients who do not roll over from the single-dose portion to the multi-dose portion. These patients will receive 3 doses. Five dose cohorts will be evaluated (2, 4, 8, 16, and 32 mg).

Single Dose Portion

In each cohort, 12 patients (9 active and 3 placebo) will receive a single dose of WVE-120101 or placebo. Dosing will be initiated in a staggered manner, in which 2 sentinel patients (1 placebo and 1 active) will be dosed and observed for 48 hours in the clinic. If neither patient experiences a serious adverse event (SAE) during that period, the remaining 10 patients (2 placebo and 8 WVE-120101) will be dosed sequentially. Patients in the 2, 4, 8, and 16 mg dose cohorts will be assessed for safety, PK, PD, and clinical effects through the 8-week washout period after the first dose. Patients in the 32 mg cohort will be assessed for safety, PK, PD, and clinical effects through 4 weeks after the first dose.

Multiple Dose Portion

Following a safety review of the single-dose data from all the patients in a dose cohort, the cohort will proceed to multiple dosing. Patients will receive 3 doses of WVE-120101 in the multiple-dose portion, administered once every 4 weeks for a period of 8 weeks. Patients in the 2, 4, 8, and 16 mg dose cohorts will be assessed for safety, PK, PD, and clinical effects through Week 30 (14 weeks after the last dose). Patients in the 32 mg cohort will be assessed for safety, PK, PD, and clinical effects through Week 26 (14 weeks after the last dose).

Patients who drop out may be replaced.

Following completion of this study, all patients may be eligible to participate in an open-label extension study regardless of whether they participated in only the single dose portion, multiple dose portion, or both parts of the study.

Dose Escalation Committee Review

The decision regarding escalation to each subsequent dose and whether a single dose can proceed to multiple dosing will be made by the Dose Escalation Committee. The Dose Escalation Committee will be blinded to treatment assignment throughout the study. All recommendations of this committee will be reviewed by the Safety Monitoring Committee (SMC) and endorsed by the chairperson.

Safety Monitoring Committee Review: Throughout the study, unblinded aggregate safety data will be reviewed periodically and on an ad hoc basis by the SMC. The SMC will review any SAEs that occur in sentinel patients in order to determine if the cohort should continue or if a lower dose should be selected. In addition, if treatment-emergent adverse events (TEAEs) occur that meet the Stopping Criteria, the SMC will review the unblinded safety data and determine whether it is safe to proceed with the cohort.

Stopping Criteria: During the single-dose, dose escalation phase, dosing will be suspended:

1. If a single patient experiences an SAE assessed as related to study drug;
2. If ≥2 patients experience a TEAE of ≥Grade 3 (using National Cancer Institute Common Terminology Criteria for AE [NCI CTCAE] grading) that is assessed as related to study drug; or

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3. If ≥4 patients experience a non-serious TEAE of ≥Grade 2 within the Medical Dictionary for Regulatory Activities (MedDRA) High Level Group Term (HLGT) *Spinal cord and nerve root disorders*, assessed as related to study drug.

Adverse event (AE) terms related to lumbar puncture and administration (eg, procedural pain, traumatic lumbar puncture, or post-lumbar puncture syndrome) will be exempted from the assessment of Stopping Criteria. A full list of AE terms exempt from the Stopping Criteria is provided in Table 4 in Section 4.3.4.1.

If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations prior to restarting treatment.

During the multiple-dose phase, dosing will be stopped for an individual patient if:

1. Patient experiences a serious or intolerable adverse event (AE), that in the Investigator's opinion requires study drug discontinuation.
2. Patient experiences the same related TEAE ≥Grade 3 twice (excepting exempt TEAEs noted in Table 4).

If a patient meets the individual stopping criteria in the multiple-dose phase, that patient will not receive any more doses of WVE-120101. The patient will be followed up for safety per protocol.

Number of Patients: Approximately 60 patients will be enrolled.

Study Population: Patients must satisfy all of the inclusion and none of the exclusion criteria to be eligible for the study. If the patient does not have documented heterozygosity at SNP1, the patient must undergo Prescreening.

Inclusion Criteria:

1. Documented ability to understand the written study ICF(s), and has provided signed written informed consent prior to any study procedures.
2. Ambulatory male or female.
3. Age ≥25 to ≤65 years old.
4. Body mass index (BMI) ≤32 kg/m^2.
5. Documented CAG triplet repeats ≥36 in the *Huntingtin* gene.
6. Documented heterozygosity for SNP1.
7. Documented presence of the T variant of SNP1 on the same allele as the pathogenic CAG expansion
8. Clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4.
9. Stage I or Stage II HD, defined as UHDRS TFC scores ≥7 and ≤13.
10. In the opinion of the Investigator, the patient is able to tolerate all study procedures, and is willing to comply with all other protocol requirements.

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11. Willingness to practice highly effective contraception for the duration of the study if patients or their partners are of childbearing potential. Non-childbearing potential and highly effective methods of contraception are defined in the protocol (Section 5.2.1).

Exclusion Criteria:

1. Malignancy or received treatment for malignancy, other than treated basal cell or squamous cell carcinoma of the skin, within the previous 5 years.
2. Positive for Hepatitis B virus (HBV) or Hepatitis C virus (HCV).
3. Known to be positive for human immunodeficiency virus (HIV).
4. Clinically significant medical finding on the physical examination other than HD that, in the judgment of the Investigator, will make the patient unsuitable for participation in and/or completion of the study procedures.
5. Received an investigational drug, including an investigational oligonucleotide, within the past 1 year or 5 half-lives of the drug, whichever is longer.
6. Implantable central nervous system (CNS) device that may interfere with ability to administer study drug via lumbar puncture or undergo MRI scan.
7. Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) diagnosis at the Screening Visit of active alcohol, cannabinoid, or other substance use disorder (except nicotine) within 6 months prior to the Screening Visit.
8. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit.
9. Started or changed dose for concomitant medication for the treatment of HD symptoms or psychiatric disorders within 30 days prior to the Screening Visit (concomitant medications that have been administered on a stable regimen for ≥30 days are permitted).
10. Pregnant (as determined by a serum pregnancy test) or breast feeding at the Screening Visit, or plans to become pregnant during the course of the study.
11. Clinically significant laboratory abnormality at Screening, including, but not limited to:
    a Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values at Screening or Baseline >3 times the upper limit of normal (ULN).
    b Renal insufficiency, defined as either serum creatinine >1.8 mg/dL or creatinine clearance <40 mL/min.
12. Clinically significant abnormality at Screening electrocardiogram (ECG), including but not necessarily limited to a confirmed QT interval corrected for heart rate (QTc) ≥450 msec for males or ≥470 msec for females.
13. Clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal, neurologic, malignant, metabolic, psychiatric, or other condition that, in the opinion of the Investigator, precludes the patient's safe participation in the study or would interfere with the study assessments.
14. Bone, spine, bleeding, or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture.
15. Inability to undergo brain MRI (with or without sedation).

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16. Deemed to be at significant risk for suicidal behavior based on:
    a The opinion of the Investigator; or
    b Answers "yes" to Actual Suicide Attempts or Suicidal Behaviors in the Suicidal Behaviors section of the Columbia-Suicide Severity Rating Scale (C-SSRS) with reference to a 2-year period prior to the Screening Visit; or
    c Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to the Screening Visit; or
    d Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS at the Baseline Visit since the last visit (Screening Visit).
17. Involved directly or indirectly in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study.

Test Product, Dose and Mode of Administration:

The starting dose will be 2 mg. Planned dose cohorts are 2, 4, 8,16, and 32 mg. The dosage form will be a lyophilized powder for reconstitution for solution for injection. The route of administration of the reconstituted study drug in solution will be IT injection by direct lumbar puncture.

Reference Therapy, Dose, and Mode of Administration:

Placebo will be 0.9% Sodium Chloride Injection, sterile, preservative-free solution. Placebo will be visually identical in appearance to the WVE-120101 injection solution and administered intrathecally in order to maintain the blind.

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Study Duration:

Doses for the 2, 4, 8, and 16 mg dose cohorts will be administered on Days 1, 56, 84, and 112, with an additional 14-week follow-up. Doses for the 32 mg cohort will be administered on Days 1, 28, 56, and 84, with an additional 14-week follow-up.

Criteria for Evaluation:

Safety:

Adverse events, concomitant medications, physical examinations including detailed neurological examination, vital signs, 12-lead ECGs, clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis), CSF evaluations (total protein, glucose, and white blood cell counts with differential), MRI of the brain, and C-SSRS.

Pharmacokinetics

- Pharmacokinetic parameters of WVE-120101 in plasma at predefined time points.
- Exposure of WVE-120101 in CSF at predefined time points.

Pharmacodynamics

- Concentration of mHTT protein in CSF predose (baseline value) and at the last measured time point.

Clinical Effects

- Change from baseline (baseline value to the last measured time point) and difference from placebo in the TFC, administered as part of the UHDRS.
- Change from baseline (baseline value to the last measured time point) and difference from placebo in the motor, cognitive, independence, and functional assessments administered as part of the UHDRS.
- Change from baseline (baseline value to the last measured time point) and difference from placebo in the PBA-s.
- Changes from baseline MRI of the brain (Screening to last measured time point).

Statistical Methods: In general, summary statistics (n, mean, standard deviation [SD], median, minimum and maximum values for continuous variables, and number [%] of patients in each category for categorical variables) will be provided by dose cohort and visit. Patient-level data will be presented in data listings.

Analyses will be primarily descriptive; confidence intervals will be presented where appropriate.

The sample size was not calculated on the basis of statistical hypothesis testing. However, based on the results of Wild et al.[1], for each of the active doses, 9 patients per active dose will yield a two-sided 90% confidence interval width for mHTT in CSF of approximately ±110 fM.

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Abbreviation	Definition
3T	3 Tesla
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-\tau}$	area under the plasma concentration-time curve over the dosing interval
BMI	body mass index
CAG	cytosine-adenine-guanine
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed concentration
CNS	central nervous system
CRO	contract research organization
CSR	clinical study report
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EHDN	European Huntington's Disease Network
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HD	Huntington's disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	human equivalent dose
HLGT	High Level Group Term
HIV	human immunodeficiency virus

Abbreviation	Definition
HTT, HTT	*Huntingtin* gene or huntingtin protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
INN	International Nonproprietary Name
IRB	Institutional Review Board
IT	intrathecal
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IXRS	interactive voice/web response system
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mHTT, mHTT	mutant huntingtin gene or protein
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NOEL	no-observed-effect level
PBA-HD	Problem Behaviors Assessment for HD
PBA-s	Short Problem Behaviors Assessment
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic
PS	phosphorothioate
PT	preferred term
PVG	pharmacovigilance
QTc	QT interval corrected for heart rate
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDMT	Symbol Digit Modalities Test
SMC	Safety Monitoring Committee
SNP	single nucleotide polymorphism
SNP1	single nucleotide polymorphism rs362307
SOC	system organ class
SOP	Standard Operating Procedure

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
T	thymine
TEAE	treatment-emergent adverse event
TFC	Total Functional Capacity
t_{max}	time of occurrence of C_{max}
tx	treatment
U	uracil
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of normal
USP	United States Pharmacopoeia
WHO	World Health Organization
wtHTT	wild-type huntingtin
λ_z	terminal elimination rate constant

1 INTRODUCTION

WVE-120101 is intended as a disease-modifying agent for the treatment of patients with Huntington's disease (HD). It is a stereopure antisense oligonucleotide (ASO) intended to selectively target the mutant form of the *huntingtin* (*mHTT*) gene transcript.

1.1 HUNTINGTON'S DISEASE

Huntington's disease is a rare, progressive neurological disease that results in motor, cognitive, and psychiatric disability and is invariably fatal[2]. Because it is a genetic, hereditary disease, it can affect multiple family members across generations[3]. Although cognitive and psychiatric symptoms may develop first, the clinical diagnosis of HD is usually based on the presence of chorea, one of the most visually prominent symptoms of this disease. Chorea is an abnormal involuntary movement disorder, which occurs in 90% of patients and is moderate to severe in approximately 70% of these patients. These physical symptoms can appear at any age, but typically appear between the ages of 30 and 50[2]. A physical examination, sometimes combined with a neurological examination, can determine whether the onset of the disease has begun. Life expectancy after symptom onset is reduced to around 15 to 20 years[2,3]. Prevalence in Europe, North America, and Australia is approximately 6 per 100,000[4]. In the United States alone, approximately 30,000 people have diagnosed HD[5,6] and another 200,000 or more Americans carry the gene and are at risk of developing the disease[6]. Currently, no treatments exist that can cure, slow, or reverse the course of HD. Some of the symptoms of HD can be managed with medication and therapies such as antipsychotics and drugs affecting the dopamine pathways, which modulate the movement disorder[3].

Huntington's disease is caused by known mutations on a single gene, characterized by an expansion of a cytosine-adenine-guanine (CAG) triplet repeat in the *Huntingtin* (*HTT*) gene[7]. Wild-type HTT (wtHTT) protein is critical for neuronal development[8]. Although the purpose of wtHTT in adults is not completely understood, some studies have shown that it may play an important role in neuronal functions[8-11]. However, expansion in the CAG triplet repeat in the *HTT* gene results in production of the mHTT protein. Accumulation of this protein leads to progressive loss of neurons in the brain[3]. In nonclinical studies, lowering the level of mHTT protein as measured in the cerebrospinal fluid (CSF) has been demonstrated to be therapeutic[12,13]. Therefore, a drug that can silence the *mHTT* gene transcript, while leaving the wild-type allele intact, may be able to slow down, stop, or even reverse the course of HD[14].

1.2 INVESTIGATIONAL PRODUCT WVE-120101

WVE-120101 is an oligonucleotide, a type of nucleic acid that includes innovative drugs that are assembled from chemically modified, short-length ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) strands. The potential therapeutic uses of oligonucleotides include modulating the function of target RNAs to affect the production of disease-associated proteins. The mechanism of action used by many oligonucleotides, including ASOs, is to promote degradation of the target RNA. Phosphorothioate (PS) modification was one of the earliest and remains one of the most common backbone modifications used in oligonucleotide synthesis. These modifications improve the stability, biodistribution, and cellular uptake of oligonucleotides. The use of PS modification in oligonucleotide synthesis creates a chiral center at the phosphorus at each PS, each of which has either an "*S*p" or "*R*p" configuration at random. A conventional, fully PS-

modified oligonucleotide (20 nucleotides in length, 19 PS modifications) is a mixture of over 500,000 stereoisomers (2^{19}), each having the same nucleotide sequence but differing in the stereochemistry along its backbone, resulting in heterogenous and uncontrolled pharmacological properties.

The Sponsor has developed a proprietary technology that enables the synthesis of PS-modified nucleic acid therapeutics in which stereochemistry at each PS position is precisely controlled. This degree of control enables rational design and synthesis of optimized, or stereopure, oligonucleotides with improved pharmacological and toxicological properties.

WVE-120101 is a stereopure ASO being developed to selectively target mHTT, leaving wtHTT relatively unaffected. WVE-120101 specifically targets the mHTT messenger ribonucleic acid (mRNA) transcript, at the uracil (U) variant of single nucleotide polymorphism (SNP) rs362307 (SNP1). A SNP is a single variation in the DNA that can be associated with a mutated gene. One of the most frequent SNPs in the *mHTT* gene is SNP1, which has been shown to be present in approximately 50% of patients with HD[14-17].

1.3 NONCLINICAL DATA

The nonclinical program evaluating WVE-120101 to date encompasses in vitro studies of primary and secondary pharmacology, preliminary in vitro assessments of drug metabolism, standard Good Laboratory Practice (GLP)-compliant in vitro and in vivo genetic toxicology, in vivo safety pharmacology, and toxicity studies.

In vitro pharmacology studies confirm that WVE-120101 demonstrates selective knockdown of the mHTT mRNA and protein through cleavage of the mRNA transcript of the mutant allele with the targeted SNP (SNP1) versus the wild type allele without the targeted SNP (SNP1). This selective knockdown results in greater reduction of the mHTT protein over wtHTT protein produced by this RNA and thus, limits the unintended, potentially deleterious effects of decreasing wtHTT[8-11]. Preliminary in vivo tissue distribution studies demonstrate that upon intrathecal (IT) administration, WVE-120101 distributes to the brain, the intended target tissue, where it may be able to produce sustained and effective target suppression. However, in the absence of an animal model with the disease phenotype and the SNP (ie, SNP1) specifically targeted by WVE-120101, no in vivo data are available regarding the required dose or the duration of knockdown. The optimal dose and dosing frequency for efficacy in humans will be explored during clinical development.

WVE-120101 exhibits the expected distribution to the brain and spinal cord upon IT administration to animals. In rats and monkeys, WVE-120101 distributed rapidly into the plasma and transferred into peripheral tissues, such as the kidney and liver, but it was also broadly distributed via cerebrospinal fluid (CSF) circulation to the tissues of the brain. At the end of the 8-week recovery period in the repeat-dose study in monkeys, mean WVE-120101 levels decreased to below the lower limit of quantitation (LLOQ; 5 ng/mL in the CSF and 0.195 µg/g in the brain tissue) in the 4- and 6-mg groups. In vitro, WVE-120101 is stable in plasma and CSF for 24 and 48 hours, respectively, and is highly protein-bound in rat, monkey, and human plasma (>99%).

In single- and repeat-dose toxicity studies conducted in rats and monkeys, IT administration of WVE-120101 was associated with the test-article related, non-adverse finding of transient limb dysfunction in both species. In the single-dose GLP rat study, related findings (splayed limbs, righting reflex impaired, ataxia, or low carriage) were reported at doses of 0.1, 0.25, and 0.4 mg, during the immediate postdose observation period, but resolved completely within 72 hours. The incidence of limb dysfunction increased with increasing dose (15/20 animals in the 0.1 mg group, 31/40 animals in the 0.25 mg group, and 35/40 animals in the 0.4 mg group); however, it was not clear if the findings related to dose or increasing test-article concentration in the CNS. There was a marked decrease in the observation of limb dysfunction or similar neurological findings at the 0.05 mg dose in the repeat-dose study (5/20 animals had transient ataxia after the first dose only; no events of limb dysfunction were reported) and progression of the neurological findings were not observed with repeat dosing. Findings of limb dysfunction were also observed in single- and repeat-dose studies in monkeys. In these monkey studies, limb dysfunction was not observed at the lowest dose (2 mg), and was observed infrequently at the mid-dose (4 mg); the highest incidence was observed in the 6-mg (high dose) group. No other related findings were observed in monkeys. In both species, events of limb dysfunction appeared to be dose- and test article-related, although the transience of the observation and full recovery of animals led to its assessment as a non-adverse finding. The apparent difference in the dose response between rats and monkeys may be due to a higher test article concentration at the local injection site in the rat. The higher range of dose concentrations administered to rats (2, 4, 10, and 16 mg/mL) versus monkeys (2, 4, and 6 mg/mL) combined with the lower CSF volume in rats[18] may have contributed to the increased test-article related findings in rats. Further, given the technical challenges of IT injection in rats, it is possible that the increased incidence of neurologic findings may be, at least in part, due to the procedure rather than the test article alone[18-20]. Therefore, in consideration of these data and its relevance to the human when considering CSF volume, the monkey is considered the more relevant model for determining toxicities. The only other toxicity observed in monkeys was the observation of decreased activity, which may have been indicative of stress and/or general malaise associated with the anesthesia and dosing procedure. This occurred in 2/8 animals at the 2-mg dose in the repeat-dose study after the second dose only. All other findings of decreased activity occurred at the 4 and 6 mg doses. Transient neurologic effects in monkeys and rats were both monitorable and reversible. Overall, these findings suggest that the nonclinical studies conducted to date have adequately characterized the safety profile of WVE-120101 to initiate the Phase 1b/2a study.

In the repeat-dose toxicity studies in rats and monkeys, minimal to mild histologic changes at the injection site included the presence of cellular infiltrates, and microgliosis. These findings were focal and localized to the injection site and were generally attributed to the presence of a large molecular weight test article in the IT space[21,22]. Histological observations described as degeneration of the spinal nerve root were observed, which were considered test article-related in the rat only. In rats, at doses ≥0.05 mg, these findings were minimal to mild in severity and occurred with similar incidence and severity to control animals. A slight increase was observed following a single IT dose of 0.4 mg (HED 224 mg) or repeat doses of 0.1 and 0.25 mg (HED of 56 and 140 mg, respectively). Given the incidence of these findings in the WVE-120101 IV dose group, in which WVE-120101 was not expected to distribute appreciably to the spinal cord[23], and in which IT injection was not performed, this is considered a background/incidental finding[19,24] with potential exacerbation by the IT procedure, dose, or dose concentration of the test article. In monkeys, observations described as minimal to mild degeneration of the spinal

nerve root were also observed sporadically in a few animals (≤2 animals in any dose group) across all doses, including controls, in the single and repeat-dose studies, without a clear dose-response relationship. This finding was not observed after a single, 2-mg dose in monkeys, or in repeated doses of up to 6 mg/month for 13-weeks or 4 mg/month for 9 months. Given that this finding was only observed at an increased incidence/severity compared to control following a single dose at the dose level of 0.4 mg in rats (HED 224 mg), this is not considered a risk for Protocol WVE-HDSNP1-001 at the planned dose ranges (2 to 32 mg).

In the 3- and 9-month repeat-dose toxicity studies in monkeys, the only treatment-related histological finding was an increase in mononuclear cell infiltrates of the CNS, predominantly at the meninges/epineurium bordering the spinal cord. The incidence and/or severity of these findings was not clearly dose-related, lacked associated degeneration and necrosis, and were nearly completely resolved at the end of the post-dose recovery period (8-weeks for the 13-week study and 26-weeks for the 39-week study). The no-adverse-effect-levels (NOAELs) from these studies were 6 mg/dose (13-week study) and 4 mg/dose (39-week study), the highest doses evaluated.

Systemic effects after IT administration were limited to non-adverse findings of transient suppression of erythropoiesis (0.4 mg in rats) and the presence of vacuolated mononuclear cells in the CSF of monkeys treated at the high dose-level of 6 mg/dose. Intravenous administration of WVE-120101 for 3 months at these dose levels revealed no substantial additional or increased toxicity in either rats or monkeys despite higher circulating plasma levels than those observed following IT administration in male rats (2-fold) and male and female monkeys (7-fold). This result suggests a reduced concern for C_{max}-related toxicities and supports the hypothesis that histological effects observed after IT administration are related to procedural trauma and high local drug concentrations.

WVE-120101 demonstrated minimal potential for the recognized toxicities of phosphorothioate oligonucleotides, such as pro-inflammatory effects, activated partial thromboplastin time (aPTT) prolongation, hepatotoxicity, or nephrotoxicitiy[25,26]. In addition, WVE-120101 was not associated with any other toxicities, including mutagenicity or effects on cardiovascular or respiratory function, and exhibited minimal potential for off-target effects via hybridization to the human genome.

1.4 CLINICAL EXPERIENCE

This is the first clinical study conducted with WVE-120101. For the most up-to-date clinical experience information refer to the Investigator's Brochure (IB).

2 RATIONALE FOR THE STUDY

Huntington's disease is an invariably fatal disorder with no known cure. The accumulation of mHTT produced in patients with an abnormal *Huntingtin* allele leads to a progressive loss of neurons in the brain. Therefore, several therapeutic approaches for HD have focused on reduced production or removal of mHTT. However, at the present time, there are no clinical research studies in HD evaluating investigational agents that specifically target mHTT. Instead, some studies target both mutant and wtHTT, with the intent of reducing both forms of the protein to levels that will hopefully improve symptoms without leading to the deleterious effects that may

result from a reduction in wtHTT[8-11]. Alternate splicing has been proposed as a mechanism for the generation of mHTT; however, ASOs should suppress this as they act on pre-mRNA[2].

WVE-120101 is intended to selectively target mHTT, leaving wtHTT relatively unaffected, by targeting the SNP1 variant associated with the pathogenic CAG expansion (≥36 repeats). This should result in selective reduction of the level of mHTT protein.

2.1 RATIONALE FOR THE DOSES AND THE DOSING REGIMEN

The target for WVE-120101 is the mutant HTT (mHTT) mRNA, acting at the U variant of SNP1. Since no appropriate animal models that recapitulated the mutation observed in this subpopulation of HD patients were available to the Sponsor before initiation of the human studies, the proposed therapeutic dose range of 2 to 32 mg is based on the totality of the in vitro pharmacology data, which defined the concentration range needed to achieve mHTT depletion; the in vivo toxicology studies, which defined the tolerable dose range; and the clinical safety data available. The clinical starting dose was selected in consideration of the data from both single- and 13-week repeat-dose toxicology studies. Escalation to subsequent doses (approximately 4, 8, 16, and 32 mg) will be based on safety assessments from prior cohorts.

In vitro pharmacology studies demonstrated selective knockdown of mHTT mRNA and protein through preferential cleavage of the mutant allele compared with the wild-type allele. In a study conducted in patient fibroblasts that were heterozygous (U/C) for SNP1, treatment with 5 µM (33 µg/mL) WVE-120101 resulted in mRNA knockdown and protein reduction for mHTT but no meaningful mRNA change or protein reduction for wtHTT. The range of theoretical peak CSF concentrations in patients over the proposed dose range of 2 to 32 mg corresponds to 14 to 230 µg/mL. Based on the concentration found to have activity in fibroblasts, the CSF concentrations that correspond to the proposed clinical dose range are expected to adequately yield knockdown of mHTT mRNA and protein.

In the single- and repeat-dose toxicity studies of WVE-120101, dose-related observations on limb dysfunction were observed in both rats and monkeys. Additional neurologic findings related to limb dysfunction were also observed in the rat which were likely related to high local concentration of test-article within a small CNS space as compared to the monkey. Furthermore, the technical complexities of IT administration to small animal models may contribute to the findings in the rat. In monkeys no findings of limb dysfunction were reported at the lowest dose (2 mg) evaluated in either the single-dose or repeat-dose studies Application of a 10-fold safety margin to the human equivalent dose (HED), based on CSF volume, at the 2-mg dose in monkeys suggests a clinical starting dose of 2 mg. The clinical starting dose of 2 mg is also 1/13 the HED of the 0.05-mg dose in rats. Findings at this dose in rats were limited to transient, minimal clinical observations of ataxia (2 males and 3 females) after the first dose only. In addition, the dose concentration of 0.2 mg/mL that will be administered to humans is 1/10 the dose concentration administered to rats at the 0.05-mg dose (HED 28 mg) and monkeys at the 2-mg dose (HED 22.4 mg) in the repeat-dose toxicity studies.

The proposed high dose of 32 mg is expected to produce CSF exposures that are within the range of those tested and found to be well-tolerated in animals. In the 13-week monkey study, estimated peak CSF concentration at the 6 mg NOAEL dose (HED 67.2 mg) was approximately 0.48 mg/mL (based on an estimated CSF volume of 12.5 mL). In the rat, the NOAEL dose of

0.25 mg (HED 140 mg) produced an estimated peak CSF concentration of 1 mg/mL (based on an estimated CSF volume of 0.25 mL). The 32 mg dose is expected to produce a peak CSF concentration of 0.23 mg/mL, which is approximately 2-fold and 4-fold lower than those achieved in the monkey and rat, respectively, at the NOAEL-dose levels. To date, data from this study indicate that the drug has been well tolerated in patients at all dose levels evaluated. Doses of 4 mg (HED 44.8 mg) were also well-tolerated in monkeys when administered by once monthly intrathecal injection for 9 months (10 doses).

The study design is based on the need to assess the safety and tolerability of WVE-120101 by gradual exposure of a small number of patients with early manifest HD to low single doses of the study drug. If a single dose in a cohort is shown to be safe and well tolerated, that dose level will proceed to multiple dosing, and a higher dose will be administered to a subsequent cohort.

The use of a placebo in the control group is appropriate because there are currently no disease-modifying treatments for HD. The placebo group will provide a robust reference for safety and tolerability of the study drug. In particular, the placebo will help determine whether adverse events noted are related to WVE-120101 itself or to the study procedures (lumbar puncture and IT injection).

After the first dose of WVE-120101 on Day 1, the 32 mg cohort will have a 4-week follow-up period instead of an 8-week washout period. The amount of time between the first dose and the second dose was reduced because current clinical data suggest that most TEAEs occur within the first 28 days after the first dose.

Follow-up will continue for 14 weeks after the last dose, i.e., to Week 30 for participants in the 2, 4, 8, and 16 mg cohorts and to Week 26 for patients in the 32 mg cohort. The 8-week washout period was selected based on the distribution of WVE-120101 in the repeat dose (13-week) monkey study. At the end of the 8-week recovery period in the repeat-dose study in monkeys, mean WVE-120101 levels in the brain and CSF decreased to below the limit of quantitation in the brain tissue, spinal cord, and CSF in the 4- and 6-mg groups, with the exception of a few spinal cord sections that had detectable drug (0.11 µg/gm at the 4 mg dose and 0.03 µg/gm at the 6 mg dose). The concentration of WVE-120101 at 14 weeks postdose would be anticipated to be less than the lower limit of quantification (LLOQ) in all matrices (brain tissue [LLOQ 0.162µg/gm], spinal cord [LLOQ 0.162µg/gm], and CSF [LLOQ 5 ng/mL])

Patients have the option to leave the study and be treated per standard care at any time.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of WVE-120101 in patients with early manifest HD.

Secondary objectives

Secondary objectives of this study include:

- Characterize the pharmacokinetics (PK) of WVE-120101 in plasma.
- Characterize the exposure of WVE-120101 in CSF.
- Assess the pharmacodynamic (PD) effect of WVE-120101 on levels of mHTT in CSF.
- Assess the effect of WVE-120101 on signs and symptoms of HD, as measured by the Total Functional Capacity (TFC), administered as part of the Unified Huntington's Disease Rating Scale (UHDRS).

Exploratory Objectives:

Exploratory objectives of this study include:

- Assess the effect of WVE-120101 on signs and symptoms of HD, as measured by the motor, cognitive, independence, and functional assessments, administered as part of the UHDRS.
- Assess the effect of WVE-120101 on signs and symptoms of HD, as measured by the Short Problem Behaviors Assessment (PBA-s).
- Characterize changes in magnetic resonance imaging (MRI) of the brain in patients receiving WVE-120101.

3.2 STUDY ENDPOINTS

Primary Endpoint

The primary endpoint is the safety and tolerability of WVE-120101, as compared with placebo, as assessed by the number of patients with adverse events (AEs), severity of AEs, number of patients with serious AEs (SAEs), and the number of patients who withdraw due to AEs.

Secondary Endpoint(s)

Secondary endpoints include:

Pharmacokinetics

- Pharmacokinetic parameters of WVE-120101 in plasma at predefined time points.
- Exposure of WVE-120101 in CSF at predefined time points.

Pharmacodynamics

- Concentration of mHTT protein in CSF predose (baseline value) and at the last measured time point.

Clinical Effects

- Change from baseline (baseline value to the last measured time point) and difference from placebo in the TFC, administered as part of the UHDRS.

Exploratory Endpoints

- Change from baseline (baseline value to the last measured time point) and difference from placebo in the motor, cognitive, independence, and functional assessments administered as part of the UHDRS.
- Change from baseline (baseline value to the last measured time point) and difference from placebo in the PBA-s.
- Changes from baseline MRI of the brain (Screening to last measured time point).

4 STUDY DESIGN

4.1 STUDY DESIGN OVERVIEW

This is a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of IT WVE-120101 in adult patients with early manifest HD who carry a targeted single nucleotide polymorphism, SNP1.

This study will evaluate a single dose of WVE-120101 followed by multiple doses in eligible patients with early manifest HD. To participate in the study, patients must have documented heterozygosity for SNP1 with the thymine (T) variant on the same allele as the CAG triplet expansion. Patients who have not previously undergone SNP analysis will be required to be prescreened to determine heterozygosity for SNP1. The prescreening assessment will have a separate informed consent form (ICF).

Patients may participate in the complete study, in which they will receive all 4 doses. In order to allow for evaluation of a full multi-dose cohort (N=12), new patients may be enrolled directly in the multiple-dose portion to account for those patients who do not roll over from the single-dose portion to the multi-dose portion. These patients will receive 3 doses. Five dose cohorts will be evaluated (2, 4, 8, 16, and 32 mg).

Single Dose Portion

In each cohort, 12 patients (9 active and 3 placebo) will receive a single dose of WVE-120101 or placebo. Dosing will be initiated in a staggered manner, in which 2 sentinel patients (1 placebo and 1 active) will be dosed and observed for 48 hours in the clinic. If neither patient experiences an SAE during that period, the remaining 10 patients (2 placebo and 8 WVE-120101) will be dosed sequentially and observed in the hospital for 24 hours. Patients in the 2, 4, 8, and 16 mg dose cohorts will be assessed for safety, PK, PD, and clinical effects through the 8-week washout period after the first dose. Patients in the 32 mg cohort will be assessed for safety, PK, PD, and clinical effects through 4 weeks after the first dose.

Multiple Dose Portion

Following a safety review of the single-dose data from all the patients in a dose cohort by the Dose Escalation Committee (Section 4.3.3), the cohort will proceed to multiple dosing. Patients will receive 3 doses of WVE-120101 in the multiple dose portion, administered once every 4 weeks (for the 2, 4, 8, and 16 mg cohorts: Day 56, Day 84, and Day 112; for the 32 mg cohort: Day 28, Day 56, and Day 84). Patients in the 2, 4, 8, and 16 mg cohorts will be assessed for

safety, PK, PD, and clinical effects until Week 30 (14 weeks after the last dose). Patients in the 32 mg cohort will be assessed for safety, PK, PD, and clinical effects through Week 26 (14 weeks after the last dose).

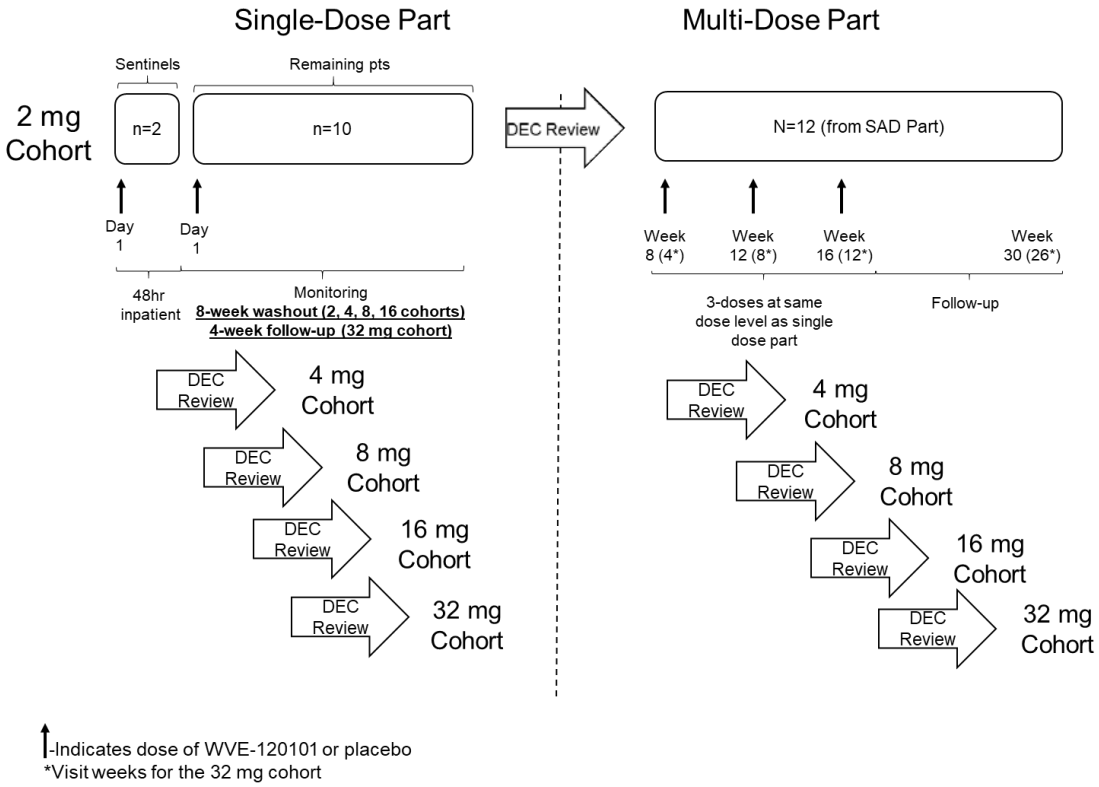
The Dose Escalation Committee will also confirm the dose for the next single-dose cohort (Section 4.3.3). Recommendations will be reviewed by the unblinded, independent Safety Monitoring Committee (SMC) and endorsed by the chairperson.

Patients who drop out may be replaced.

Following completion of this study, all patients may be eligible to participate in an open-label extension study regardless of whether they participated in only the single dose portion, multiple dose portion, or both parts of the study.

A schematic of the overall study design and timing is provided in Figure 1.

Figure 1 Schematic of Study Design



Abbreviations: DEC = Dose Escalation Committee; hr = hour; SAD = single ascending dose; SD = single dose.

4.1.1 Prescreening Phase

If documentation of heterozygosity and the presence of SNP1 is not available, patients must undergo Prescreening. The prescreening period is intended to identify patients who carry the targeted SNP.

Patients will sign a prescreening ICF specific to the assessments performed to determine whether they meet the eligibility criteria for heterozygosity of the targeted SNP, CAG triplet repeats (≥36), and presence of the T variant of SNP1 on the same allele as the pathogenic CAG expansion (Section 8.1). This testing process is expected to take at least 6 weeks. Prescreening can happen any time before Screening. If patients meet these criteria, they will continue to the Screening Phase (Visit 2).

4.1.2 Screening Phase

The screening period is intended to allow determination of patient eligibility for the study. It will begin when the study informed consent is signed. The ability of the patient to understand the consent form will be documented in the study ICF.

The Screening period will last up to 4 weeks. The required screening evaluations are outlined in the Schedule of Assessments (Table 1, Table 2, and Table 3). Screening assessments can occur on multiple days, provided they are within the Screening period. The Investigator will determine whether patients meet eligibility criteria and will collect the demographic and medical data permitting full characterization of the patient.

4.1.3 Single-Dose Phase

Eligible patients will be randomized in a 3:1 ratio to either active or placebo treatment at the Baseline visit. Patients will receive a single IT treatment. Within 1 week prior to performing the lumbar puncture, a blood sample will be tested locally for platelet count and prothrombin time to confirm that it is safe to proceed with the lumbar puncture (Section 8.2.6). Other predose assessments may also be performed up to 1 week prior to dosing as specifically listed in Table 1.

Cohorts will be dosed sequentially, following a safety review by the Dose Escalation Committee:

- 2 mg Cohort (N=12): WVE-120101 or placebo single-dose IT injection.
- 4 mg Cohort (N=12): WVE-120101 or placebo single-dose IT injection.
- 8 mg Cohort (N=12): WVE-120101 or placebo single-dose IT injection.
- 16 mg Cohort (N=12): WVE-120101 or placebo single-dose IT injection.
- 32 mg Cohort (N=12): WVE-120101 or placebo single-dose IT injection.

Dosing to all cohorts will be initiated in a staggered manner as noted in Figure 1.

Two sentinel patients in each cohort (1 placebo and 1 WVE-120101) will be dosed and will then remain in the clinic for approximately 48 hours postdose. If either sentinel patient experiences an SAE during that period, the safety data will be reviewed by the SMC to determine the next steps (Section 4.3.2). If the sentinel patients do not experience an SAE during that period, the remaining 10 patients (2 placebo and 8 WVE-120101) may be dosed in a sequential fashion.

Immediately after study drug administration, all patients should be ambulatory and active for approximately 30 minutes postdose. The Investigator should note any subtle weakness or fatigue during this period. Formal physical examinations targeting the neurological system will be

performed at the time points noted in the Schedule of Assessments (Table 1). Any postdose SAEs will be monitored until resolution.

Sentinel patients will remain in the clinic and undergo assessments throughout the 48-hour postdose period. Day 3 procedures will be performed prior to discharge. Non-sentinel patients will remain in the clinic for a minimum of 24 hours postdose for assessments (Table 1). For patients in the 2, 4, 8, and 16 mg cohorts, additional assessments of safety, PK, PD, and clinical effects will be performed through the 8-week postdose washout period for all patients. For patients in the 32 mg cohort, additional assessments of safety, PK, PD, and clinical effects will be performed through 4 weeks after the first dose.

The decision regarding escalation to the next planned dose, intermediate dose, extension of the current dose level, selection of a higher dose, and if a cohort can proceed to multiple dosing will be made by an appointed Dose Escalation Committee, with endorsement from the chairperson of the SMC (Section 4.3.3). Treatment-emergent AEs that meet the Stopping Criteria will be reviewed by the unblinded SMC (Section 4.3.4). In addition, the SMC will review unblinded, aggregate safety data (Section 4.3.1).

4.1.4 Multiple-Dose Phase

The Dose Escalation Committee will determine if a dose cohort can proceed to multiple dosing.

Patients who participated in the single-dose portion of the study must complete the 8-week washout period (2, 4, 8, and 16 mg cohorts) or 4-week follow-up period before receiving additional doses. Patients will visit the clinic on Day 56 (2, 4, 8, and 16 mg cohorts) or Day 28 (32 mg cohort only) for the first of 3 monthly IT doses (Days 56, 84, and 112 or Days 28, 56, and 84) (Table 1 and Table 2).

Patients who are enrolled into the multiple-dose portion of the study only will undergo the Prescreening (Visit 1) and Screening (Visit 2) visits. Patients in the 2, 4, 8, and 16 mg cohorts will not participate in Visits 3 through 7, and will receive their first dose on Visit 8. Patients will return for 2 additional doses (Visit 9 and Visit 10) and for all follow-up visits (Table 3). Patients in the 32 mg cohort will not participate in Visits 3 through 6 and will receive their first dose on Visit 7. Patients will return for two additional doses (Visit 8 and Visit 9) and for all follow-up visits (Table 3).

Within 1 week prior to each lumbar puncture, a blood sample will be tested locally for platelet count and prothrombin time to confirm that it is safe to proceed with the lumbar puncture (Section 8.2.6). Other predose assessments may also be performed up to 1 week prior to dosing, as specifically listed in Table 1, Table 2, and Table 3.

Immediately after study drug administration, all patients should be ambulatory and active for approximately 30 minutes postdose. The Investigator should note any subtle weakness or fatigue during this period. Formal physical examinations targeting the neurological system, will be performed at the time points noted in the Schedule of Assessments (Table 1, Table 2, and Table 3). Any postdose SAEs will be monitored until resolution.

Following each dose, patients will remain in the clinic for a minimum of 4 hours postdose for safety monitoring. In addition, patients will be assessed for safety, PK, PD, and clinical effects.

The SMC will periodically review unblinded, aggregate safety data (Section 4.3.1).

4.1.5 Follow-up Phase

All patients are required to complete follow-up assessments, including evaluations of safety, PD, PK, clinical effects, and MRI. Patients will be followed-up for 14 weeks after the last dose (Week 30 for the 2, 4, 8, and 16 mg cohorts and Week 26 for the 32 mg cohort). An early termination (ET) visit will be required in the event of early withdrawal.

4.2 SCHEDULE OF ASSESSMENTS

The schedule of assessments for patients participating in the single and multiple dose portions of the study is presented in Table 1 (2, 4, 8, and 16 mg cohorts) and Table 2 (32 mg cohort). The Schedule of Assessments for patients participating in the multiple-dose portion of the study only is presented in Table 3.

At each relevant time point, the UHDRS, PBA-s, and Columbia-Suicide Severity Rating Scale (C-SSRS) should be performed prior to other assessments.

Table 1 Schedule of Assessments for Patients Participating in Both the Single and Multiple Dose Portions of the Study (2, 4, 8, and 16 mg cohorts)

	Pre-Screen-ing[a]	Screen-ing[b]	Double-Blind Treatment (Single Dose)		Sentinel Patient Follow-up	Follow-up		Double-Blind Treatment (Multiple Dose)			Follow-up		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[c]**	**9**	**10**	**11 or ET**	**12**	**13**
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**28**	**30**
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day -6 to Day 1 (Baseline)**	**Day 2 (24 ± 4h postdose)**	**Day 3 (48 ± 4h postdose)**	**Day 14 (±2)**	**Day 28 (±3)**	**Day 56 (±3)**	**Day 84 (±3)**	**Day 112 (±3)**	**Day 140 or ET (±5)**	**Day 196 (±5)**	**Day 210[d] (EOS) (±5)**
Predose/Non-dosing Days													
Patient informed consent form (ICF) Signed	X	X											
Inclusion/exclusion criteria		X	X					X					
Medical history and demographics		X											
Physical examination[e]		X	X	X	X	X	X	X	X	X	X	X	
C-SSRS[f]		X	X*			X	X	X*	X*	X	X*		
UHDRS		X	X			X	X	X	X	X	X		
PBA-s		X	X			X	X	X	X	X	X		
Drug screen[g]		X											
Urine pregnancy test[h]			X*					X*	X*	X*			
Adverse event monitoring		X	X*	X[q]	X[q]	X	X	X*	X*	X*	X	X	X
Prior and concomitant medications		X	X*	X[q]	X[q]	X	X	X*	X*	X*	X	X	X
3T MRI of the brain (without contrast)		X					X				X		
Vital signs[i]		X	X*	X	X	X	X	X*	X*	X*	X	X	
12-lead ECG[j]		X					X						
Serum pregnancy test[h]		X											
Clinical laboratory tests[k]		X	X	X	X	X	X	X	X	X	X	X	
Hepatitis (HBsAg, HCV)		X											
Blood sample for Prescreening assays[l]	X												
Blood sample for PK[m]			X	X	X	X	X	X	X	X	X		
Blood sample for immunogenicity[n]			X				X	X	X	X	X	X	
CSF sample for safety, exposure, and PD[o]			X*				X	X*	X*	X*	X[r]	X	
Randomization			X										

	Pre-Screen-ing[a]	Screen-ing[b]	Double-Blind Treatment (Single Dose)		Sentinel Patient Follow-up	Follow-up		Double-Blind Treatment (Multiple Dose)			Follow-up		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[c]**	**9**	**10**	**11 or ET**	**12**	**13**
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**28**	**30**
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day -6 to Day 1 (Baseline)**	**Day 2 (24 ± 4h postdose)**	**Day 3 (48 ± 4h postdose)**	**Day 14 (±2)**	**Day 28 (±3)**	**Day 56 (±3)**	**Day 84 (±3)**	**Day 112 (±3)**	**Day 140 or ET (±5)**	**Day 196 (±5)**	**Day 210[d] (EOS) (±5)**
Study drug administration via IT injection[p]			**X**					**X**	**X**	**X**			
Postdose on Dosing Days	**-**												
Physical examination[e]			**X**					**X**	**X**	**X**			
Adverse event monitoring			**X[q]**					**X**	**X**	**X**			
Clinical laboratory tests[k]			**X**					**X**	**X**	**X**			
Concomitant medications			**X**					**X**	**X**	**X**			
Vital signs[i]			**X**					**X**	**X**	**X**			
Blood samples for PK[m]			**X**							**X**			
Study completion													**X**

Abbreviations: AE = adverse event; CAG = cytosine-adenine-guanine; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; h = hour; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IT = intrathecal; MRI = magnetic resonance imaging; PBA-s = Short Problem Behaviors Assessment; PD = pharmacodynamics; PK = pharmacokinetics; SNP= single nucleotide polymorphism; SNP1 = SNP rs362307 T= thymine; UHDRS = Unified Huntington's Disease Rating Scale.

Note: The UHDRS, PBA-s, and C-SSRS should be completed prior to any other assessments. Assessments completed predose on Day 1 are considered Baseline.

***For each dosing visit (Day 1/Visit 3 [single dose phase]; Day 56/Visit 8; Day 84/Visit 9; and Day 112/Visit 10 [multiple dose phase]), these predose procedures must be performed predose on the day of dosing. All other predose assessments (inclusion/exclusion criteria [Day 1/Visit 3 and Day 56/Visit 8 only], physical examination, UHDRS, PBA-S, clinical laboratory tests [including a blood sample to confirm platelet count and prothrombin clotting time], blood sample for PK, and blood sample for immunogenicity) may be performed up to a week prior to dosing.**

a Prescreening is only required for patients who do not have documented heterozygosity for SNP rs362307 (SNP1) with the T variant on the same allele as the cytosine-adenine-guanine (CAG) triplet expansion. Prescreening can happen anytime before Screening. It is anticipated that it will take at least 6 weeks to process the results of this testing.

b Screening assessments can occur on multiple days, provided they are within the 4-week Screening period.

c There is a minimum washout period of 8 weeks between the first dose and the start of multiple dosing. However, due to the timing of Dose Escalation Committee review to determine if the multiple dose phase can proceed for a dose cohort, the duration between the Week 4 visit and Week 8 visit may be longer than 4 weeks. Investigators will be notified when the Visit 8/Week 8 visit can occur. During this time, a telephone contact for safety follow-up should be performed monthly, at a minimum.

d Follow-up Day 210 Visit for AE monitoring can be a telephone call.

e At Screening, physical examination will include (but is not limited to) an examination of skin; head, eyes, ears, nose, throat; respiratory; cardiovascular; gastrointestinal; endocrine, metabolic; blood, lymphatic; musculoskeletal, psychiatric, and neurologic systems. Predose and on Visits 6 (Day 14), 7 (Day 28), 11 (Day 140), and 12 (196) the physical exam must include (at a minimum) head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic systems. Other systems should be evaluated as appropriate. After study drug administration, a targeted physical exam, including the neurologic system (with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation),

will be performed 30 minutes (±5 minutes), 1, 2, 3, and 4 hours (±15 minutes) postdose, with an additional exam 24 hours (±4 hours) after the first dose. The sentinel patients in each cohort will also repeat this exam at 8 hours (±30 minutes), 12 hours (±2 hours), 24, and 48 hours (±4 hours).

f C-SSRS baseline/screening version will be performed at the Screening Visit, and the 'since last visit' version will be performed at all other noted visits.

g Urine drug screen for selected drugs of abuse.

h For female patients of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit. On dosing days, a negative urine pregnancy test must be documented predose.

i Vital signs include blood pressure, pulse, temperature, weight, and height. On dosing days blood pressure and pulse will be measured at the following time points: ≤30 minutes predose and 1, 2, and 4 hours (±15 minutes) postdose. Sentinel patients will also have blood pressure and pulse measured 12 hours (±2 hours), 24 and 48 hours (±4 hours) postdose. Weight and temperature will only be measured predose on dosing days. Height will be measured at baseline only. Blood pressure (systolic and diastolic), temperature, and pulse should be measured after patient has been resting quietly for ≥3 minutes.

j Electrocardiogram recordings will be obtained in triplicate in the supine position after the patient has rested comfortably for ≥5 minutes.

k Clinical laboratory safety testing, including clinical chemistry, hematology, and urinalysis. Within 1 week prior to lumbar puncture, a blood sample will be tested to confirm platelet count and prothrombin clotting time. Clinical laboratory safety testing will be performed predose on all dosing days. On Day 1 only, samples for clinical chemistry and hematology measures (CBC, complement, and fibrinogen only) will also be collected at 1 and 4 hours (±15 minutes), and 24 hours (±4 hours) postdose, and for sentinel patients only, 48 hours (±4 hours). On all non-dosing days, clinical laboratory safety testing will be performed just once. On Day 196, only platelet count and prothrombin clotting time need to be assessed (prior to CSF sample). Urinalysis will be performed predose on all dosing days, and once on all other days noted.

l Blood samples for the Prescreening assays to determine eligibility.

m On Day 1, sentinel patients will have blood samples for PK analysis collected predose, 30 minutes (±5 minutes), 1, 2, 4 hours (±15 minutes), 12 hours (±2 hours), 24 hours and 48 hours (±4 hours) postdose. All other patients will have blood samples for PK analysis collected predose and 30 minutes (±5 minutes), 1, 2, 4 hours (±15 minutes), 12 hours (±2 hours), and 24 hours (±4 hours) postdose on Day 1. On Day 112, all patients will have blood samples collected for PK analysis predose and 1, 2, and 4 hours (±15 minutes) postdose. On all other dosing days, PK samples will be collected predose only. On non-dosing days noted, PK will be collected once.

n Blood sample for assessment of antibodies to WVE-120101 will be obtained predose (within 1 week prior to injection) or on non-dosing days, as indicated.

o On dosing days, CSF sample will be collected ≤15 minutes prior to study drug administration. No more than 10 mL of CSF total should be collected. CSF samples must be tested locally for safety for the following parameters: total protein, glucose and cell counts (white blood cell counts with differential) on all noted visits.

p Immediately after study drug administration, patients should be active for approximately 30 minutes postdose.

q All patients will remain in the clinic and have AEs and concomitant medications recorded through 24 hours postdose. In addition, 2 sentinel patients will remain in the clinic and have AEs and concomitant medications recorded throughout the 48-hour postdose period.

r This lumbar puncture is optional for patients who terminate early.

Table 2 Schedule of Assessments for Patients Participating in Both the single and Multiple Dose Portions of the Study (32 mg Cohort)

	Pre-Screening[a]	Screening[b]	Double-Blind Treatment (Single Dose)		Sentinel Patient Follow-up	Follow-up	Double-Blind Treatment (Multiple Dose)			Follow-up		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7[c]**	**8**	**9**	**10 or ET**	**11**	**12**
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**24**	**26**
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day -6 to Day 1 (Baseline)**	**Day 2 (24 ± 4h postdose)**	**Day 3 (48 ± 4h postdose)**	**Day 14 (±2)**	**Day 28 (±3)**	**Day 56 (±3)**	**Day 84 (±3)**	**Day 112 or ET (±5)**	**Day 168 (±5)**	**Day 182(EOS) (±5)[d]**
Predose/Non-dosing Days												
Patient informed consent form (ICF) Signed	X	X										
Inclusion/exclusion criteria		X	X				X					
Medical history and demographics		X										
Physical examination[e]		X	X	X	X	X	X	X	X	X	X	
C-SSRS[f,]		X	X*			X	X*	X*	X*	X		
UHDRS		X	X			X	X	X	X	X		
PBA-s		X	X			X	X	X	X	X		
Drug screen[g]		X										
Urine pregnancy test[h]			X*				X*	X*	X*			
Adverse event monitoring		X	X*	X[q]	X[q]	X	X*	X*	X*	X	X	X
Prior and concomitant medications		X	X*	X[q]	X[q]	X	X*	X*	X*	X	X	X
3T MRI of the brain (without contrast)		X					X			X		
Vital signs[i]		X	X*	X	X	X	X*	X*	X*	X	X	
12-lead ECG[j]		X	X	X		X						
Serum pregnancy test[h]		X										
Clinical laboratory tests[k]		X	X	X	X	X	X	X	X	X	X	
Hepatitis (HBsAg, HCV)		X										
Blood sample for Prescreening assays[l]	X											
Blood sample for PK[m]			X	X	X	X	X	X	X	X		
Blood sample for immunogenicity[n]			X				X	X	X	X	X	
CSF sample for safety, exposure, and PD[o]			X*				X*	X*	X*	X[r]	X	
Randomization			X									
Study drug administration via IT injection[p]			X				X	X	X			

	Pre-Screen-ing[a]	Screen-ing[b]	Double-Blind Treatment (Single Dose)		Sentinel Patient Follow-up	Follow-up	Double-Blind Treatment (Multiple Dose)			Follow-up		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7[c]**	**8**	**9**	**10 or ET**	**11**	**12**
Week		**-4 to 0**	**0**	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**24**	**26**
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day -6 to Day 1 (Baseline)**	**Day 2 (24 ± 4h postdose)**	**Day 3 (48 ± 4h postdose)**	**Day 14 (±2)**	**Day 28 (±3)**	**Day 56 (±3)**	**Day 84 (±3)**	**Day 112 or ET (±5)**	**Day 168 (±5)**	**Day 182(EOS) (±5)[d]**
Postdose on Dosing Days												
Physical examination[e]			**X**				**X**	**X**	**X**			
Adverse event monitoring			**X[q]**				**X**	**X**	**X**			
12-lead ECG[j]			**X**									
Clinical laboratory tests[k]			**X**				**X**	**X**	**X**			
Concomitant medications			**X**				**X**	**X**	**X**			
Vital signs[i]			**X**				**X**	**X**	**X**			
Blood samples for PK[m]			**X**						**X**			
24 hour Urine sample for PK assessments[s]			**X**									
Study completion												**X**

Abbreviations: AE = adverse event; CAG = cytosine-adenine-guanine; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; h = hour; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IT = intrathecal; MRI = magnetic resonance imaging; PBA-s = Short Problem Behaviors Assessment; PD = pharmacodynamics; PK = pharmacokinetics; SNP= single nucleotide polymorphism; SNP1 = SNP rs362307; T= thymine; UHDRS = Unified Huntington's Disease Rating Scale.

Note: The UHDRS, PBA-s, and C-SSRS should be completed prior to any other assessments. Assessments completed predose on Day 1 are considered Baseline.

***For each dosing visit (Day 1/Visit 3 [single dose phase]; Day 28/Visit 7; Day 56/Visit 8; and Day 84/Visit 9 [multiple dose phase]), these predose procedures must be performed predose on the day of dosing. All other predose assessments (inclusion/exclusion criteria [Day 1/Visit 3 and Day 28/Visit 7 only], physical examination, UHDRS, PBA-S, clinical laboratory tests [including a blood sample to confirm platelet count and prothrombin clotting time], blood sample for PK, and blood sample for immunogenicity) may be performed up to a week prior to dosing.**

a Prescreening is only required for patients who do not have documented heterozygosity for SNP rs362307 (SNP1) with the T variant on the same allele as the cytosine-adenine-guanine (CAG) triplet expansion. Prescreening can happen anytime before Screening. It is anticipated that it will take at least 6 weeks to process the results of this testing.

b Screening assessments can occur on multiple days, provided they are within the 4-week Screening period.

c There is a minimum follow-up period of 4 weeks between the first dose and the start of multiple dosing. However, due to the timing of Dose Escalation Committee review to determine if the multiple dose phase can proceed for a dose cohort, the duration between the Week 4 visit and Week 7 visit may be longer than 4 weeks. Investigators will be notified when the Visit 7/Week 4 visit can occur. During this time, a telephone contact for safety follow-up should be performed monthly, at a minimum.

d Follow-up Day 182 Visit for AE monitoring can be a telephone call.

e At Screening, physical examination will include (but is not limited to) an examination of skin; head, eyes, ears, nose, throat; respiratory; cardiovascular; gastrointestinal; endocrine, metabolic; blood, lymphatic; musculoskeletal, psychiatric, and neurologic systems. Predose and on Visits 6 (Day 14), 10 (Day 112), and 11 (168) the physical exam must include (at a minimum) head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic systems. Other systems should be evaluated as appropriate. After study drug administration, a targeted physical exam, including the neurologic system (with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation), will be performed 30 minutes (±5 minutes), 1, 2, 3, and 4 hours (±15 minutes) postdose, with an additional exam 24 hours (±4 hours) after the first dose. The sentinel patients in each cohort will also repeat this exam at 8 hours (±30 minutes), 12 hours (±2 hours), 24, and 48 hours (±4 hours).

f C-SSRS baseline/screening version will be performed at the Screening Visit, and the 'since last visit' version will be performed at all other noted visits.

g Urine drug screen for selected drugs of abuse.

h For female patients of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit. On dosing days, a negative urine pregnancy test must be documented predose.

i Vital signs include blood pressure, pulse, temperature, weight, and height. On dosing days blood pressure and pulse will be measured at the following time points: ≤30 minutes predose and 1, 2, and 4 hours (±15 minutes) postdose. Sentinel patients will also have blood pressure and pulse measured 12 hours (±2 hours), 24 and 48 hours (±4 hours) postdose. Weight and temperature will only be measured predose on dosing days. Height will be measured at baseline only. Blood pressure (systolic and diastolic), temperature, and pulse should be measured after patient has been resting quietly for ≥3 minutes.

j Electrocardiogram recordings will be obtained in triplicate in the supine position after the patient has rested comfortably for ≥5 minutes. Within 24 hours predose on Day 1, 12-lead ECGs will be performed (3 measurements within 1 hour). Postdose, 12-lead ECGs (triplicate) will be performed 1, 2, 4, and 24 hours (±15 mins) after dose administration. ECGs should be performed prior to blood draws, vital signs, or functional assessments.

k Clinical laboratory safety testing, including clinical chemistry, hematology, and urinalysis. Within 1 week prior to lumbar puncture, a blood sample will be tested to confirm platelet count and prothrombin clotting time. Clinical laboratory safety testing will be performed predose on all dosing days. On Day 1 only, samples for clinical chemistry and hematology measures (CBC, complement, and fibrinogen only) will also be collected at 1 and 4 hours (±15 minutes), and 24 hours (±4 hours) postdose, and for sentinel patients only, 48 hours (±4 hours). On all non-dosing days, clinical laboratory safety testing will be performed just once. On Day 168, only platelet count and prothrombin clotting time need to be assessed (prior to CSF sample). Urinalysis will be performed predose on all dosing days, and once on all other days noted

l Blood samples for the Prescreening assays to determine eligibility.

m On Day 1, sentinel patients will have blood samples for PK analysis collected predose, 30 minutes (±5 minutes), 1, 2, 4 hours (±15 minutes), 12 hours (±2 hours), 24 hours and 48 hours (±4 hours) postdose. All other patients will have blood samples for PK analysis collected predose, and 30 minutes (±5 minutes), 1, 2, 4 hours (±15 minutes), 12 hours (±2 hours) and 24 hours (±4 hours) postdose on Day 1. On Day 84, all patients will have blood samples collected for PK analysis predose and 1, 2, and 4 hours (±15 minutes) postdose. On all other dosing days, PK samples will be collected predose only. On non-dosing days noted, PK will be collected once.

n Blood sample for assessment of antibodies to WVE-120101 will be obtained predose (within 1 week prior to injection) or on non-dosing days, as indicated.

o On dosing days, CSF sample will be collected ≤15 minutes prior to study drug administration. No more than 10 mL of CSF total should be collected. CSF samples must be tested locally for safety for the following parameters: total protein, glucose and cell counts (white blood cell counts with differential) on all noted visits.

p Immediately after study drug administration, patients should be active for approximately 30 minutes postdose.

q All patients will remain in the clinic and have AEs and concomitant medications recorded through 24 hours postdose. In addition, 2 sentinel patients will remain in the clinic and have AEs and concomitant medications recorded throughout the 48-hour postdose period.

r This lumbar puncture is optional for patients who terminate early.

s On Day 1, all patients will have urine samples for PK analysis collected at 0 to 4 hours, 4 to 8 hours, and 8 to 24 hours postdose.

Table 3 Schedule of Assessments for Treatment-Naïve Patients in the Multiple-Dose Portion of the Study

	Pre-Screen-ing[a]	Screening[b]	Double-Blind Treatment (Multiple Dose)			Follow-up		
Visit	**1**	**2**	**8 (7[q])**	**9 (8[q])**	**10 (9[q])**	**11 (10[q]) or ET**	**12 (11[q])**	**13 (12[q])**
Week		**-4 to 0**	**8 (4[q])**	**12 (8[q])**	**16 (12[q])**	**20 (16[q])**	**28 (24[q])**	**30 (26[q])**
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day 56 (28[q]) (±3) (Baseline)**	**Day 84 (56[q]) (±3)**	**Day 112 (84[q]) (±3)**	**Day 140 (112[q]) or ET (±5)**	**Day 196 (168[q]) (±5)**	**Day 210[c] (182[q]) (EOS) (±5)**
Predose/Non-dosing Days								
Patient informed consent form (ICF) Signed	X	X						
Inclusion/exclusion criteria		X	X					
Medical history and demographics		X						
Physical examination[d]		X	X	X	X	X	X	
C-SSRS[e]		X	X*	X*	X	X*		
UHDRS		X	X	X	X	X		
PBA-s		X	X	X	X	X		
Drug screen[f]		X						
Urine pregnancy test[g]			X*	X*	X*			
Adverse event monitoring		X	X*	X*	X*	X	X	X
Prior and concomitant medications		X	X*	X*	X*	X	X	X
3T MRI of the brain (without contrast)		X				X		
Vital signs[h]		X	X*	X*	X*	X	X	
12-lead ECG[i]		X						
Serum pregnancy test[g]		X						
Clinical laboratory tests[j]		X	X	X	X	X	X	
Hepatitis (HBsAg, HCV)		X						
Blood sample for Prescreening assays[k]	X							
Blood sample for PK[l]			X	X	X	X		
Blood sample for immunogenicity[m]			X	X	X	X	X	
CSF sample for safety, exposure, and PD[n]			X*	X*	X*	X[p]	X	
Treatment Assignment			X					
Study drug administration via IT injection[o]			X	X	X			
Postdose on Dosing Days	-							
Physical examination[d]			X	X	X			
Adverse event monitoring			X	X	X			

	Pre-Screening[a]	Screening[b]	Double-Blind Treatment (Multiple Dose)			Follow-up		
Visit	**1**	**2**	**8 (7[q])**	**9 (8[q])**	**10 (9[q])**	**11 (10[q]) or ET**	**12 (11[q])**	**13 (12[q])**
Week		**-4 to 0**	**8 (4[q])**	**12 (8[q])**	**16 (12[q])**	**20 (16[q])**	**28 (24[q])**	**30 (26[q])**
Study Day (Visit Window, if applicable) Event/Assessment		**Day -28 to -1**	**Day 56 (28[q]) (±3) (Baseline)**	**Day 84 (56[q]) (±3)**	**Day 112 (84[q]) (±3)**	**Day 140 (112[q]) or ET (±5)**	**Day 196 (168[q]) (±5)**	**Day 210[c] (182[q]) (EOS) (±5)**
Clinical laboratory tests[j]			**X**	**X**	**X**			
Concomitant medications			**X**	**X**	**X**			
Vital signs[h]			**X**	**X**	**X**			
Blood samples for PK[l]					**X**			
Study completion								**X**

Abbreviations: AE = adverse event; CAG = cytosine-adenine-guanine; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; h = hour; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IT = intrathecal; MRI = magnetic resonance imaging; PBA-s = Short Problem Behaviors Assessment; PD = pharmacodynamics; PK = pharmacokinetics; SNP= single nucleotide polymorphism; SNP1 = SNP rs362307; T= thymine; UHDRS = Unified Huntington's Disease Rating Scale.

Note: The UHDRS, PBA-s, and C-SSRS should be completed prior to any other assessments. Assessments completed predose on Day 56 (Day 28 for the 32 mg cohort) are considered Baseline. Patients who are treatment-naïve for the multiple-dose portion of the study will undergo Prescreening and Screening, and then receive their first dose on Day 56 (Visit 56).

***For each dosing visit during the multiple dose phase, these predose procedures must be performed predose on the day of dosing. All other predose assessments (inclusion/exclusion criteria [Day 56/Visit 8 for 2, 4, 8, and 16 mg cohorts or Day 28/Visit 7 for 32 mg cohort], physical examination, UHDRS, PBA-S, clinical laboratory tests [including a blood sample to confirm platelet count and prothrombin clotting time], blood sample for PK, and blood sample for immunogenicity) may be performed up to a week prior to dosing.**

a Prescreening is only required for patients who do not have documented heterozygosity for SNP rs362307 (SNP1) with the T variant on the same allele as the cytosine-adenine-guanine (CAG) triplet expansion. Prescreening can happen anytime before Screening. It is anticipated that it will take at least 6 weeks to process the results of this testing.

b Screening assessments can occur on multiple days, provided they are within the 4-week Screening period.

c Follow-up Day 210 Visit (Day 182 Visit for the 32 mg cohort) for AE monitoring can be a telephone call.

d At Screening, physical examination will include (but is not limited to) an examination of skin; head, eyes, ears, nose, throat; respiratory; cardiovascular; gastrointestinal; endocrine, metabolic; blood, lymphatic; musculoskeletal, psychiatric, and neurologic systems. Predose and on Visit 11/Day 140 and Visit 12/Day 196 for the 2, 4, 8, and 16 mg cohorts and Visit 10/Day 112 and Visit 11/Day 168 for the 32 mg cohort, the physical exam must include (at a minimum) head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic systems. Other systems should be evaluated as appropriate. After study drug administration, a targeted physical exam, including the neurologic system (with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation), will be performed 30 minutes (±5 minutes), 1, 2, 3, and 4 hours (±15 minutes) postdose.

e C-SSRS baseline/screening version will be performed at the Screening Visit, and the 'since last visit' version will be performed at all other noted visits.

f Urine drug screen for selected drugs of abuse.

g For female patients of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit. On dosing days, a negative urine pregnancy test must be documented predose.

h Vital signs include blood pressure, pulse, temperature, weight, and height. On dosing days blood pressure and pulse will be measured at the following time points: ≤30 minutes predose and 1, 2, and 4 hours (±15 minutes) postdose. Weight and temperature will only be measured predose on dosing days. Height will be measured at baseline only. Blood pressure (systolic and diastolic), temperature, and pulse should be measured after patient has been resting quietly for ≥3 minutes.

i Electrocardiogram recordings will be obtained in triplicate in the supine position after the patient has rested comfortably for ≥5 minutes.

j Clinical laboratory safety testing, including clinical chemistry, hematology, and urinalysis. Within 1 week prior to lumbar puncture, a blood sample will be tested to confirm platelet count and prothrombin clotting time. Clinical laboratory safety testing will be performed predose on all dosing days. On Day 56 (Day 28 for 32 mg cohort) only, samples for clinical chemistry and hematology measures (CBC, complement, and fibrinogen only) will also be collected at 1 and 4 hours (±15 minutes) postdose. On all non-dosing days, clinical laboratory safety testing will be performed just

once. On Day 196 (Day 168 for 32 mg cohort), only platelet count and prothrombin clotting time need to be assessed (prior to CSF sample). Urinalysis will be performed predose on all dosing days, and once on all other days noted.

k Blood samples for the Prescreening assays to determine eligibility.

l On Day 56 (Day 28 for 32 mg cohort), all patients will have blood samples collected for PK analysis predose and 30 minutes (±5 minutes), 1, 2, 4 hours (±15 minutes) postdose. On Day 112 (Day 84 for the 32 mg cohort), all patients will have blood samples collected for PK analysis predose and 1, 2, and 4 hours (±15 minutes) postdose. On all other dosing days, PK samples will be collected predose only. On non-dosing days noted, PK will be collected once.

m Blood sample for assessment of antibodies to WVE-120101 will be obtained predose (within 1 week prior to injection) or on non-dosing days, as indicated.

n On dosing days, CSF sample will be collected ≤15 minutes prior to study drug administration. No more than 10 mL of CSF total should be collected. CSF samples must be tested locally for safety for the following parameters: total protein, glucose and cell counts (white blood cell counts with differential) on all noted visits.

o Immediately after study drug administration, patients should be active for approximately 30 minutes postdose.

p This lumbar puncture is optional for patients who terminate early.

q Visit, week, and day for the 32 mg cohort.

4.3 SAFETY REVIEWS, STOPPING CRITERIA, AND COMMUNICATION PLAN

Periodic safety reviews, including reviews of treatment-emergent AEs (TEAEs) that meet the Stopping Criteria, will be performed by the unblinded, independent SMC (Section 13.1) throughout the study, as specified below. The study can be terminated at any time based on the findings of any safety reviews.

4.3.1 Safety Monitoring Committee Reviews

The independent SMC will review unblinded, aggregate safety data periodically and will review SAE reports in real time. Recommendations based on these reviews will be provided to the Sponsor.

The SMC will also review SAEs that occur in the sentinel patients (Section 4.3.2) and TEAEs that meet the Stopping Criteria (Section 4.3.4). In addition, the SMC will review the Dose Escalation Committee's decisions regarding dose escalation and continuation to multiple dosing, and the chairperson will endorse the decision. Neither escalation to the next dose level nor continuation to multiple dosing may proceed without review of unblinded data by the SMC and subsequent endorsement by the committee Chair.

Based on any of the safety reviews performed by the SMC, the SMC may recommend stopping the study at any time.

4.3.2 Safety Review After Sentinel Patients

The SMC will perform reviews of any SAEs that occur in the sentinel patients. If either of the sentinel patients in a cohort experiences an SAE within 48 hours postdose, all pertinent safety data will be provided to the SMC. No further patients in the cohort will be dosed pending this data review. The SMC will determine if it is safe to proceed with the cohort, or, in conjunction with the Dose Escalation Committee, whether an intermediate dose should be selected for the remaining patients in that cohort.

4.3.3 Dose Escalation and Continuation to Multiple Dosing

The Dose Escalation Committee will review blinded data to make the decision regarding escalation to each subsequent dose and whether a single dose cohort can proceed to multiple dosing. After all patients in the 2, 4, 8, and 16 mg cohorts complete the Day 28 Visit and all patients in the 32 mg cohort complete the Day 14 Visit, the Dose Escalation Committee will review:

- Safety data from all patients in the current cohort through the Day 28 visit (2, 4, 8, and 16 mg cohorts) or Day 14 (32 mg cohort).
- Any available safety data from patients in the current cohort through the Day 56 visit (2, 4, 8, and 16 mg cohorts) or Day 28 visit (32 mg cohort).
- Any available safety data from all other cohorts, including those that have proceeded to multiple dosing (for the 4, 8,16, and 32 mg dose cohorts, a minimum of 50% of patients in the previous cohort must have received at least 2 doses in the multiple dose phase, and all

data from the single-dose phase must be reviewed for the current cohort to proceed to multiple doses).

- Treatment-emergent adverse events (TEAEs) that resulted in stopping criteria review (Section 4.3.4).

The Dose Escalation Committee may decide to enroll a larger number of patients in a cohort if further information is needed regarding single administration at that dose, provided no suspected unexpected serious adverse reactions (SUSARs) have occurred at that dose. For the next cohort, the Dose Escalation Committee may decide to select an intermediate dose, extend the current dose level, or select a higher dose. The high dose of 32 mg will not be exceeded; if the Sponsor decides that doses >32 mg should be explored, this will be addressed in a protocol amendment.

If the Dose Escalation Committee determines that the cohort should not continue to multiple dosing, that cohort will end. Patients will be monitored for safety through 8 weeks postdose. The Dose Escalation Committee may identify a lower dose for the subsequent cohort.

All recommendations will be reviewed by the SMC and endorsed by the chairperson. Neither escalation to the next dose level nor continuation to multiple dosing may proceed without review of unblinded data by the SMC and subsequent endorsement by the committee Chair. Sites will be notified rapidly of any decisions made.

4.3.4 Stopping Criteria

4.3.4.1 Single-dose Phase

During the single-dose, dose escalation phase, dosing will be suspended:

1. If a single patient experiences an SAE assessed as related to study drug;
2. If ≥2 patients experience a TEAE of ≥Grade 3 (using National Cancer Institute Common Terminology Criteria for AE [NCI CTCAE] grading) that is assessed as related to study drug; or
3. If ≥4 patients experience a non-serious TEAE of ≥Grade 2 within the Medical Dictionary for Regulatory Activities (MedDRA) High Level Group Term (HLGT) *Spinal cord and nerve root disorders*, assessed as related to study drug.

Objective stopping criterion (#3) was developed to assess any potential events of neurological toxicity that were not otherwise captured via surveillance of serious and severe TEAEs as outlined in criteria 1 and 2. Certain adverse events may be due to the IT administration and are therefore exempt from the stopping criteria (discussed below).

If the stopping criteria are met, the unblinded safety data will be reviewed in a timely manner by the SMC to determine if it is safe to proceed with the cohort or if an intermediate dose should be selected for the remaining patients in that cohort. If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations (eg, amendment) prior to restarting treatment.

Any SUSARs that occur will be reported to regulatory authorities as required. If a decision is made to terminate dosing in a cohort, all Investigators will be informed immediately, as detailed in Section 4.3.5.

Adverse Events That are Exempt from Stopping Criteria

Intrathecal administration of drugs is known to result in untoward effects such as post-lumbar puncture headache, pain, etc[28,29]. Given the common occurrence of such side-effects following lumbar puncture, it is anticipated that patients may experience AEs temporal to the IT administration procedure which are not attributable to study drug[28,29]. Therefore, the AE terms listed in Table 4 will be exempted from the assessment of Stopping Criteria:

Table 4 Adverse Event Preferred Terms Exempted From Stopping Criteria

Preferred Terms Exempt From Stopping Criteria	
Administration site bruise	Instillation site bruise
Catheter site bruise	Post-lumbar puncture syndrome
Infusion site bruising	Post-procedural discomfort
Infusion site discomfort	Post-procedural contusion
Infusion site pain	Procedural headache
Injection site bruising	Procedural pain
Injection site discomfort	Traumatic lumbar puncture
Injection site pain	

Note: AEs exempted from the Stopping Criteria include the MedDRA PTs listed above and their associated verbatim terms.

While these procedural events are exempt from Stopping Criteria review, they will be recorded as AEs as described in Section 9. In addition, as part of their ongoing review of unblinded safety data, the SMC will carefully review the above-referenced, exempted AE terms to ensure there are no meaningful imbalances between treatment groups.

4.3.4.2 Multiple-dose Phase Stopping Criteria for an Individual Patient

Dosing will be stopped for an individual patient if:

1. Patient experiences a serious or intolerable AE that, in the Investigator's opinion, requires study drug discontinuation.
2. Patient experiences the same related TEAE ≥Grade 3 twice (excepting exempt TEAEs noted in Table 4).

If a patient meets the individual stopping criteria in the multiple-dose phase, that patient will not receive any more doses of WVE-120101. The patient will be followed up for safety per protocol.

4.3.5 Communication of Emergent Safety Concerns

Enrollment to the study will be closely monitored by the Sponsor. If the stopping criteria are met at any point in the study, enrollment and dosing will be suspended for all cohorts until the data are reviewed. Similarly, if an SAE occurs in the sentinel patients in a cohort, no additional patients will be dosed in that cohort until the safety data are reviewed.

All sites will be informed by fax and email if enrollment and/or dosing is suspended. In addition, if enrollment is suspended, the interactive voice/web response system (IXRS) will be adjusted such that no patients can be randomized to treatment or receive additional doses of study drug until the safety review has been completed and a decision has been made to resume enrollment/dosing.

5 PATIENT SELECTION AND WITHDRAWAL CRITERIA

Approximately 60 patients will be enrolled. Patients will be assigned to study treatment only if they satisfy all of the inclusion and none of the exclusion criteria. If the patient does not have documented heterozygosity at SNP1, the patient must undergo Prescreening.

At Prescreening, patients will be assessed for eligibility for heterozygosity of the targeted SNP, CAG triplet repeats (≥36), and presence of the T variant of SNP1 on the same allele as the pathogenic CAG expansion. Patients who do not meet these criteria will be considered Prescreen failures. These results should be recorded for all patients, including those who fail Prescreening.

At Screening, patients who do not meet all remaining inclusion/exclusion criteria will be considered screen failures. The following information should be recorded for all patients who fail screening: demographics, UHDRS Diagnostic Confidence Score, UHDRS TFC score, and reason for screen failure.

5.1 INCLUSION CRITERIA

1. Documented ability to understand the written study ICF(s), and has provided signed written informed consent prior to any study procedures.
2. Ambulatory male or female.
3. Age ≥25 to ≤65 years old.
4. Body mass index (BMI) ≤32 kg/m^2.
5. Documented CAG triplet repeats ≥36 in the *Huntingtin* gene.
6. Documented heterozygosity for SNP1.
7. Documented presence of the T variant of SNP1 on the same allele as the pathogenic CAG expansion
8. Clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Score = 4.
9. Stage I or Stage II HD, defined as UHDRS TFC scores ≥7 and ≤13.
10. In the opinion of the Investigator, the patient is able to tolerate all study procedures, and is willing to comply with all other protocol requirements.

11. Willingness to practice highly effective contraception for the duration of the study if patients or their partners are of childbearing potential. Non-childbearing potential and highly effective methods of contraception are defined in the protocol (Section 5.2.1).

5.2 EXCLUSION CRITERIA

1. Malignancy or received treatment for malignancy, other than treated basal cell or squamous cell carcinoma of the skin, within the previous 5 years.
2. Positive for Hepatitis B virus (HBV) or Hepatitis C virus (HCV).
3. Known to be positive for human immunodeficiency virus (HIV).
4. Clinically significant medical finding on the physical examination other than HD that, in the judgment of the Investigator, will make the patient unsuitable for participation in and/or completion of the study procedures.
5. Received an investigational drug, including an investigational oligonucleotide, within the past 1 year or 5 half-lives of the drug, whichever is longer.
6. Implantable central nervous system (CNS) device that may interfere with ability to administer study drug via lumbar puncture or undergo MRI scan.
7. Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) diagnosis at the Screening Visit of active alcohol, cannabinoid, or other substance use disorder (except nicotine) within 6 months prior to the Screening Visit.
8. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit.
9. Started or changed dose for concomitant medication for the treatment of HD symptoms or psychiatric disorders within 30 days prior to the Screening Visit (concomitant medications that have been administered on a stable regimen for ≥30 days are permitted).
10. Pregnant (as determined by a serum pregnancy test) or breast feeding at the Screening Visit, or plans to become pregnant during the course of the study.
11. Clinically significant laboratory abnormality at Screening, including, but not limited to:
    a Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values at Screening or Baseline >3 times the upper limit of normal (ULN).
    b Renal insufficiency, defined as either serum creatinine >1.8 mg/dL or creatinine clearance <40 mL/min.
12. Clinically significant abnormality at Screening electrocardiogram (ECG), including but not necessarily limited to a confirmed QT interval corrected for heart rate (QTc) ≥450 msec for males or ≥470 msec for females.
13. Clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal, neurologic, malignant, metabolic, psychiatric, or other condition that, in the opinion of the Investigator, precludes the patient's safe participation in the study or would interfere with the study assessments.
14. Bone, spine, bleeding, or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture.
15. Inability to undergo brain MRI (with or without sedation).
16. Deemed to be at significant risk for suicidal behavior based on:

a The opinion of the Investigator; or

b Answers "yes" to Actual Suicide Attempts or Suicidal Behaviors in the Suicidal Behaviors section of the Columbia-Suicide Severity Rating Scale (C-SSRS) with reference to a 2-year period prior to the Screening Visit; or

c Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS with reference to a 6-month period prior to the Screening Visit; or

d Answers "yes" on any items in the Suicidal Ideation section of the C-SSRS at the Baseline Visit since the last visit (Screening Visit).

17. Involved directly or indirectly in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study.

5.2.1 Additional Study Restrictions

As noted in the inclusion criteria, patients or their partners of childbearing potential must practice true abstinence or use highly effective methods of contraception. True abstinence is defined as refraining from heterosexual intercourse for the duration of the trial. Non-childbearing potential and highly effective methods of contraception are defined in Section 5.2.1.1 and Section 5.2.1.2.

5.2.1.1 Non-Childbearing Potential

Non-childbearing potential is defined as a female who meets either of the following criteria:

- Postmenopausal state defined as no menses for 12 months without an alternative medical cause, or
- Documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

5.2.1.2 Highly Effective Methods of Contraception

Contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods are defined as 1 of the following:

- True abstinence, defined as refraining from heterosexual intercourse for the duration of the trial, when in line with the preferred and usual lifestyle of the subject.
- Vasectomized partner (if that vasectomized partner is the sole sexual partner and has received medical assessment of the surgical success of the vasectomy).
- An intrauterine hormone-releasing system (IUS).
- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal combined).
- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable).
- An intrauterine device (IUD).

Note that periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea are not acceptable methods of contraception.

5.3 Withdrawal Criteria

5.3.1 Reasons for Withdrawal/Discontinuation

The duration of the study is defined for each patient as the date a signed written informed consent is provided through the last scheduled follow-up visit or early termination. Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. The reasons for patients not completing the study will be recorded. A patient may be withdrawn from the study for any of the following reasons:

- Serious or intolerable AE that in the Investigator's opinion requires discontinuation of treatment. Patient will be encouraged to remain in the study for safety follow-up.
- A change in the patient's medical condition not consistent with the protocol requirements or that justifies withdrawal.
- Lost to follow-up.
- Pregnancy (refer to Section 9.5).
- The patient withdraws consent or the Investigator or Sponsor decides to withdraw the from the study.
- Termination of the study by the Sponsor.

Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor. If a patient is discontinued from the study drug because of an AE, the event will be followed until resolution or until the Investigator and the Sponsor agree that further follow-up is not required.

5.3.2 Handling of Withdrawals

Patients are free to withdraw from the study or study treatment at any time upon request. Patient participation in the study may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor, as described in Section 5.3.1.

Patients who discontinue study treatment or active participation in the study will no longer receive study drug but are encouraged to remain in the study for safety follow-up. When a patient withdraws from the study, the reason(s) for withdrawal will be recorded by the Investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all patients who discontinue study treatment, or withdraw from the study prematurely, will undergo an early termination visit (Table 1, Table 2, and Table 3). Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. At a minimum, 3 documented telephone calls should be made on different days over the course of 2 weeks. If the patient is unreachable by telephone, a registered letter will be sent to the patient requesting him or her to contact the study center. As part of the informed consent, patients will be asked if they are willing to be contacted at the follow-up time point if they have discontinued from study drug or withdrawn from the study.

It is vital to obtain follow-up data on any patient who discontinues study drug or withdraws because of an AE or SAE. In every case, efforts must be made to undertake safety and follow-up procedures as specified by the protocol. All patients who withdraw from the study with an ongoing AE or SAE must be followed until resolution or until the Investigator and the Sponsor agree that further follow-up is not required.

All patients who withdraw from the study due to pregnancy must be followed to record the outcome of the pregnancy.

5.3.3 Replacements

Patients who drop out before Day 28 (2, 4, 8, and 16 mg cohorts) or Day 14 (32 mg cohort) in the single-dose phase will be replaced in accordance with the requirements for dose escalation. Patients who drop out after this point may be replaced with patients directly entering the multidose part of the study.

6 STUDY TREATMENTS

6.1 METHOD OF ASSIGNING PATIENTS TO STUDY DRUG

Patients who meet all of the inclusion criteria and none of exclusion criteria will be randomized into the study on Day 1 to receive either active study drug or placebo, both administered intrathecally. Patients will receive WVE-120101 (9 patients in each cohort) or placebo (3 patients in each cohort).

In order to allow for evaluation of a full multidose cohort (N=12), new patients may be enrolled directly in the multiple-dose portion to account for those patients who do not roll over from the single-dose portion to the multi-dose portion. Treatment assignment will be performed such that these treatment-naïve patients will receive the same treatment as the patient who completed the single-dose portion.

6.2 DOSE AND STUDY DRUG ADMINISTRATION

6.2.1 Identity of Study Drug

6.2.1.1 WVE-120101

WVE-120101 will be provided as a lyophilized powder in a clear glass vial for reconstitution for solution for injection. Directions on reconstitution are provided in the Pharmacy Manual.

Laboratory Code: WVE-120101

Chemistry: WVE-120101 drug substance is the fully neutralized sodium salt of a mixed 2′-*O*-methyl ribonucleic acid/deoxyribonucleic acid oligonucleotide 20-mer containing a prescribed combination of 3′-*O* to 5′-*O* linked phosphodiester and phosphorothioate linkages, the latter of which consist of a prescribed combination of stereodefined *R*p and *S*p linkages.

International Nonproprietary Name (INN): None

Molecular Formula: The empirical formula is: $C_{202}H_{259}N_{82}O_{111}P_{19}S_{13}$

Molecular weight: 6617.05 g/mol (Average)

6.2.1.2 Placebo

Placebo will be 0.9% Sodium Chloride Injection sterile, preservative-free solution administered alone via the IT route. It will be provided in commercially available single-use vials or plastic ampoules. Placebo, as prepared by an unblinded study pharmacist in a dosing solution for injection, will be visually identical in appearance to the WVE-120101 injection solution.

6.2.2 Administration of Study Drug and Collection of CSF

Study drug (WVE-120101 or placebo) will be administered as a single dose followed by multiple doses (3 doses at 4-week intervals). The route of administration will be IT by direct lumbar injection, and the total volume of the injection will be 10 mL. The lumbar puncture will be performed by an appropriately trained individual. Within 1 week prior to the lumbar puncture, a blood sample will be tested locally for platelet count and prothrombin time to confirm that it is safe to proceed with the lumbar puncture (Section 8.2.6). Patients should not be sedated during administration of study drug. Detailed instructions on the procedure to be used for lumbar puncture are provided in the Study Operations Manual.

Within ≤15 minutes prior to administration of study drug, CSF samples will be collected for safety assessments (Section 8.2.7), exposure (Section 8.3), and PD (Section 8.4), per the Schedule of Assessments (Table 1, Table 2, and Table 3). Additional CSF collected will be stored and used for research purposes. No more than 10 mL of CSF total should be collected.

Immediately after each administration of study drug, all patients should be ambulatory and active for approximately 30 minutes postdose. The Investigator should note any subtle weakness or fatigue during this period. In addition, formal physical examinations targeting the neurological system, will be performed at the time points noted in the Schedule of Assessments (Table 1, Table 2, and Table 3). Any postdose SAEs will be monitored until resolution.

Cerebrospinal fluid samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for HD and will be stored for a maximum of 10 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

6.3 TREATMENT COMPLIANCE

Provided that a patient attends the clinic visits, treatment non-compliance is not expected to be an issue. Thus, every attempt will be made to ensure regular visits by the patient to the clinic per the study schedule. Investigative staff will make every effort to contact patients who miss visits in order to obtain as much follow-up information as possible.

6.4 MANAGEMENT OF CLINICAL SUPPLIES

6.4.1 Study Drug Packaging and Storage

WVE-120101 will be supplied by the Sponsor as a lyophilized powder in clear glass vials. Sterile saline (placebo) will be supplied in commercially available single-use vials or plastic ampoules.

All study drugs will be transported, received, stored, and handled in accordance with the container or product label, the instructions supplied to the pharmacy, relevant institution's Standard Operating Procedures (SOPs), and applicable regulations. Appropriate storage and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug.

Study drugs will be stored at 2ºC to 8ºC in a locked area accessible only to the pharmacy personnel until reconstitution. WVE-120101 reconstituted and diluted solution for injection contains no preservatives and should be administered without delay or within 4 hours of reconstitution.

Partially used, unused, or damaged vials should be disposed according to Sponsor instructions.

Details on reconstitution and administration are provided in the Pharmacy Manual and Investigator's Brochure (IB).

6.4.2 Study Drug Accountability

The Investigator will maintain accurate records of receipt of drug supplies, including dates of receipt. In addition, accurate records will be kept regarding when each treatment is administered, which patients received treatment, and the name of the personnel administering the treatment. Reasons for departure from the expected treatment regimen must also be recorded. Only trained site staff are permitted to treat study patients. A study monitor will review the accountability records onsite.

6.5 OTHER SUPPLIES

The study sites will be provided with the IB, Study Operations Manual, Pharmacy Manual, Imaging Manual, Laboratory Manual, laboratory kits, and other materials, as appropriate.

7 BLINDING

7.1 BLINDING AND RANDOMIZATION

This is a double-blind and placebo-controlled randomized study. The treatment blind will not be broken until the end of the study, except in the case of emergency (Section 7.2). The Sponsor and contract research organization (CRO) staff directly responsible for the conduct of data collection for the study, the Investigator, and study center staff will be blinded to treatment for the duration of the study until such time that all discrepancies in the clinical database are resolved (ie, at the time of the database lock).

The randomization scheme will be assigned by an IXRS, which will send notifications of the treatment assignment to the designated pharmacy personnel.

The pharmacy personnel will be unblinded to prepare doses of WVE-120101 or placebo to ensure that the clinical site staff responsible for administering study drug and conducting assessments per the protocol, and the patient, remain blinded to study treatment. In addition, a clinical research associate will be unblinded to perform drug vial accountability and oversee the shipping and inventory of study drug.

7.2 BREAKING THE BLIND

A patient's treatment assignment will not be broken until the end of the study except in the event that medical treatment of the patient depends on knowing the study treatment the patient received. If the Investigator feels they need to break the blind in the case of medical emergency, they can do so via the IXRS system.

In addition, certain Sponsor or CRO staff members may be unblinded to the applicable patient's treatment code as required for regulatory reporting of SUSARs.

Reasons for treatment unblinding must be explained clearly and justified in the eCRF. The date on which the code was broken, together with the identity of the person responsible for breaking the blind, must also be documented in the patient's source documents. The unblinded treatment information will not be disclosed to anyone who does not need to know the information. In consultation with the medical monitor and the Sponsor, the patient may be withdrawn from the study if the blind is broken.

8 METHODS OF ASSESSMENT AND ENDPOINTS

8.1 PRESCREENING ASSESSMENTS

WVE-120101 is specifically designed to treat HD patients who carry the U isoform of the intended SNP on the same allele as the pathogenic CAG expansion (≥36 repeats). If documentation of heterozygosity at SNP1 is not available, patients must have a blood sample taken at a Prescreening Visit to enable patient eligibility assessment based on these criteria using 3 separate methods:

The number of CAG repeats will be confirmed via polymerase chain reaction (PCR). Subsequently, Sanger sequencing will be performed to determine heterozygosity at the targeted SNP.

Only samples for which heterozygosity and required CAG repeats have been confirmed will undergo further testing using a long-read sequence analysis to determine whether the T isoform of SNP1 is present on the same allele as the pathogenic CAG expansion. Long-read sequencing technology will be performed by a central laboratory using a CE-marked genetic sequencer (Pacific Biosciences RS II System).

Patients confirmed to carry the T isoform of SNP1 on the same allele as the pathogenic CAG expansion will be qualified to undergo further screening for confirmation of eligibility.

Investigators and patients will be advised only as to whether the patient meets the prescreening criteria and will not be provided with specific genetic test results (eg, number of CAG repeats).

All blood samples will be sent to central laboratories for processing, analysis, and verification. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Study Operations Manual.

8.2 SAFETY ASSESSMENTS

The safety assessments will include the following:

- Adverse events (Section 9)
- Medical history and demographics
- Prior and concomitant medications
- Physical examinations (including neurological and psychiatric)
- Vital signs
- 12-lead ECGs
- Clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis)
- Magnetic resonance imaging (Section 8.6)
- Cerebrospinal fluid sample evaluations (cell count and total protein)
- Suicidality assessment
- Pregnancy testing

Any abnormal laboratory test results (hematology, clinical chemistry, or urine) or other safety assessments (eg, vital sign measurements, C-SSRS), including those that worsen from Screening (Visit 2), that are felt to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

8.2.1 Medical History and Demographics

A general medical history will be obtained at the Screening Visit. Investigator assessment of past medical history at Screening will include information regarding any significant medical, surgical, psychiatric, and/or neurological conditions and treatments.

Whether the patient is diagnosed with Stage 1 or Stage 2 HD, treatments received, and other details about this condition will be recorded.

Demographic data will include date of birth, sex, ethnic categorization, and race.

8.2.2 Prior and Concomitant Medications

Use of all concomitant medications from 6 weeks before the Screening Visit to the end of the patient's participation in the study will be recorded in the patient's eCRF. The minimum requirement is that the drug name, dose, indication, and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

8.2.3 Physical Examination

A physical examination will be performed at the time points noted in the Schedule of Assessments (Table 1, Table 2, and Table 3).

At Screening, the full physical examination will include (but is not limited to) an examination of skin; head, eyes, ears, nose, throat; respiratory; cardiovascular; gastrointestinal; endocrine, metabolic; blood, lymphatic; musculoskeletal, psychiatric, and neurologic (including mental status, cranial nerves, motor system, reflexes, coordination and gait, and sensory system) systems.

Through 4 hours postdose (and up to 24/48 hours postdose following administration on Day 1), a targeted physical exam to assess potential motor effects will be performed. This exam will include a neurologic examination with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation.

At all other time points, the physical exam must include (at a minimum) head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic). Other systems should be evaluated as appropriate.

Physical findings will be recorded in the eCRF and source documents.

8.2.4 Vital Signs

Blood pressure (systolic and diastolic), temperature, and pulse will be measured by medically qualified personnel at the time points described in the Schedule of Assessments (Table 1, Table 2, and Table 3), and recorded in the eCRF and source documents. Vital signs measurements will be taken as per standard site practice, after the patient has been resting quietly (either lying flat or sitting, whichever is most appropriate for the condition of the patient) for a period of at least 3 minutes. As feasible, the same position (either sitting or lying) should be used for all subsequent vital sign measurements during the study for an individual patient. If the initial reading is high, the measurements will be repeated twice and the average of the 3 readings will be used.

The patient's height and weight will be measured at the time points described in the Schedule of Assessments (Table 1, Table 2, and Table 3), and recorded in the eCRF and source documents.

8.2.5 12-Lead ECG

Computerized, good quality, 12-lead ECGs will be recorded in triplicate at the time points described in the Schedule of Assessments (Table 1, Table 2, and Table 3). Recordings will be obtained in the supine position after the patient has rested comfortably for ≥5 minutes.

The ECG tracing will be submitted and read by a centralized reviewer (details will be provided in the ECG Study Manual). The following should be recorded on the trace and eCRF: whether the ECG is normal or abnormal and, if deemed abnormal, whether the abnormality is clinically significant or not clinically significant and note the abnormality.

8.2.6 Clinical Laboratory Evaluations

Clinical laboratory safety testing will be collected at the time points described in the Schedule of Assessments (Table 1, Table 2, and Table 3) and recorded in the eCRF and source documents. A blood sample will be tested locally within 1 week prior to the lumbar puncture to determine platelet count and prothrombin time, and thereby confirm that it is safe to proceed with the lumbar puncture. Other safety laboratory samples will be analyzed at a central laboratory. Local testing on these samples may be conducted as clinically indicated.

The parameters to be assessed are presented in Table 5.

Table 5 Clinical Laboratory Parameters

Hematology	Clinical chemistry	Urine dipstick
Complete blood count, including: • White blood cell count (with differential) • Red blood cell count • Hemoglobin • Hematocrit • Platelet count • Reticulocyte count • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration Activated partial thromboplastin time Prothrombin time C-reactive protein Fibrinogen Complement	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Creatine phosphokinase Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Bilirubin	Urinalysis

8.2.7 Cerebrospinal Fluid Safety Lab

A CSF safety laboratory sample obtained at the times noted on the Schedule of Assessments (Table 1, Table 2, and Table 3) will be evaluated at a local lab. The following parameters will be assessed: total protein, glucose, and cell counts (white blood cell counts with differential).

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for HD and stored for a maximum of 10 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.2.8 Suicidality Assessment (Columbia-Suicide Severity Rating Scale)

The C-SSRS is a measure of suicidal ideations and suicidal behaviors[30]. The C-SSRS, provided in Appendix 2, consists of 2 forms: a form measuring symptoms at Screening (baseline/screening version) that includes a lifetime history, and a form measuring symptoms since the last study visit ('since last visit' version). The baseline/screening form will be performed at the Screening visit, and the 'since last visit' form will be performed at all later time points, as described in the Schedule of Assessments (Table 1, Table 2, and Table 3). A trained rater will complete this scale. The findings should be confirmed by the clinical opinion of the Investigator.

The Investigator should be notified if a patient responds "yes" to any of the questions. The Investigator will provide care according to local standards, which may include referral to specialists, medical treatment, or hospitalization as necessary.

8.2.9 Pregnancy Testing

For female patients of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit and a negative urine pregnancy test must be documented at the times noted on the Schedule of Assessments (Table 1, Table 2, and Table 3). The serum pregnancy test will be determined by a central lab; urine pregnancy tests will be performed locally.

8.2.10 Drug Screening

A urine drug screen for opioids, cocaine, amphetamines, methadone, barbiturates, methamphetamine, and phencyclidine will be performed at the times noted on the Schedule of Assessments (Table 1, Table 2, and Table 3). Drug screen tests will be evaluated by a central laboratory.

8.3 PHARMACOKINETIC ASSESSMENTS

Cerebrospinal fluid as well as plasma and urine samples for analysis of exposure toWVE-120101 will be collected at the time points specified on Schedule of Assessments (Table 1, Table 2, and Table 3). The date and time of the sample collection will be recorded.

Samples will be analyzed by a central laboratory to determine concentrations of WVE-120101 using a validated method.

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for HD and stored for a maximum of 10 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited

and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.4 PHARMACODYNAMIC ASSESSMENTS

A CSF sample will be collected at the time points noted in the Schedule of Assessments (Table 1, Table 2, and Table 3) to determine the change from baseline in concentration of mHTT protein. In addition, exploratory biomarkers (e.g., neurofilament light and total tau) may be assessed.

The study may utilize the method described in Wild et al[1] or an alternative method to determine levels of mHTT protein. Following unblinding, the study randomization will be provided to the bioanalytical laboratory to enable analysis of the PD samples.

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of treatments for HD and stored for a maximum of 10 years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.5 Immunogenicity Assessments

Serum samples will be collected at the times noted on the Schedule of Assessments (Table 1 and Table 2) and analyzed at a central laboratory for measurement of anti-drug antibodies to WVE-120101.

All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited and the samples are not lost, deteriorated, or destroyed accidentally or illegally. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

8.6 MAGNETIC RESONANCE IMAGING

A 3 Tesla (3T) MRI of the whole brain (without contrast) will be performed at the time points noted on the Schedule of Assessments (Table 1, Table 2, and Table 3). Sedation is permitted during the MRI.

The MRI will be assessed for safety purposes, in addition to exploratory structural assessments. Exploratory assessments will include, but are not limited to, volumetric assessments. Changes in MRIs of the brain will be characterized in patients receiving WVE-120101.

The MRI will be performed by an appropriately trained individual. Detailed instructions on how the MRI will be performed and transferred to the central reader are provided in the Imaging Manual. The scans will be evaluated by a central reader.

8.7 ASSESSMENT OF CLINICAL EFFECTS

8.7.1 Unified Huntington's Disease Rating Scale

The UHDRS is a research tool developed by the Huntington Study Group to provide a uniform assessment of the clinical features and course of HD[31]. The scale consists of 6 subtests, including motor assessment, cognitive assessment, behavioral assessment, an independence scale, functional assessment, and TFC, and is provided in Appendix 1. All subtests of the UHDRS should be performed except the behavioral assessment, as the PBA-s (Section 8.7.2) collects similar behavioral information.

The motor assessment evaluates motor features of HD with standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability. The total motor impairment score is the sum of all the individual motor ratings, with higher scores indicating more severe motor impairment than lower scores.

The cognitive assessment consists of a lexical verbal fluency test, Symbol Digit Modalities Test (SDMT), and the Stroop Interference test. The Stroop Test results are reported as the raw number of correct answers given in a 45-second period. Results for the other tests are reported as the raw number of correct responses. Higher scores indicate better cognitive performance.

The independence scale is used to follow disease progression in functional disability. The scale is rated from 100 (no special care needed) to 0 (tube-fed, total bed care).

The functional assessment checklist is a 25-question assessment that screens for capacity to complete the tasks mentioned in the assessment alone. The questions are asked in the presence of a family or friend to get the clinician's best judgment based on both responses. A response of "yes" is given a score of 1. A high score indicates better functioning.

The TFC is a brief interview involving the patient and a close family member or friend familiar with the patient's functioning. The measure has 5 items and addresses basic activities of living: occupation, handling finances, domestic responsibilities, activities of daily living (eg, eating, dressing, bathing), and level of care.

The change from baseline to the last measured time point will be determined.

8.7.2 Short Problem Behaviors Assessment

The PBA-s is a shorter version of the Problem Behaviors Assessment for HD (PBA-HD), a semi-structured interview designed to elicit information about behavioral symptoms relevant to HD. The shorter version was developed by the Behavioral Phenotype Working Group of the European Huntington's Disease Network (EHDN)[32].

The PBA-s contains 11 items, each measuring a different behavioral problem that is rated for both severity and frequency on a 5-point scale. Severity and frequency ratings are multiplied to provide an overall score for each symptom. The PBA-s is provided in Appendix 3.

Interviews are conducted with the patient. The final rating is determined by assessing all available information, including the interviewer's own observations of the patient's behavior. A caregiver should not be interviewed as part of the PBA-s for this study.

The change from baseline to the last measured time point will be determined.

9 ADVERSE EVENTS

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study treatment or their clinical significance.

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to the end of the study.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment. Patients will be instructed to contact the Investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment (excluding worsening of results on the UHDRS or PBA-s rating scales).

9.1 ELICITING AND DOCUMENTING ADVERSE EVENTS

All AEs reported or observed during the study, including AEs resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states, will be recorded on the AE page in the eCRF and in the site source notes. The eCRFs used to document AEs are designed to help ensure this information is collected in a standard manner. Information to be collected includes event term, date and time of onset, date and time of resolution, Investigator-specified assessment of severity and relationship to study treatment, action taken with respect to study treatment, seriousness, any required treatment or evaluations, and outcome. All AEs will be followed to adequate resolution. The sites will be provided completion guidelines for the eCRF, which will further guide them on how to record the data, including AEs. The MedDRA will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not worsen should not be reported as an AE. However, if it worsens at any time during the study, this should be recorded as an AE. This includes any spontaneously reported worsening of depression (ie, not based on the study rating scales).

In addition to observations of the patient, AEs identified from any study data (eg, laboratory values, physical examination findings, ECG changes, C-SSRS) or identified from review of other documents that are considered clinically significant will be documented on the AE page in the eCRF. The eCRFs also include a form specifically for a detailed neurological assessment, with instructions to report any worsening as an AE. Worsening of symptoms that are only detected on clinical effects rating scales will not be reported as AEs.

Adverse events (AEs) will be solicited at each visit by direct questioning as well as elicited from physical and neurological examination by site staff. In addition, all sites in the study must ensure patients have a 24-hour telephone number to contact medical site staff for the duration of the study, in case of emergent AEs or SAEs.

If there is any doubt as to whether a clinical observation is an AE, the event should be reported. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

Pregnancy is not considered an AE. However, if a patient becomes pregnant during the course of the study, the pregnancy must be reported and monitored as described in Section 9.5.

9.2 DEFINITIONS OF ADVERSE EVENT SEVERITY AND RELATIONSHIP TO STUDY DRUG

9.2.1 Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. Adverse event severity will be evaluated using the NCI CTCAE version 4.0, published 28 May 2009. For AEs not included in the NCI CTCAE, the Investigator will be required to assess the intensity of the adverse drug/biologic experience using the criteria in Table 6.

Table 6 Definitions of AE Severity Using NCI CTCAE Criteria

Grade	AE Severity	Definition
1	**Mild**	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	**Moderate**	Moderate; minimal, local or noninvasive intervention indicated.
3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care.
4	**Life threatening**	Life-threatening consequences; urgent intervention indicated.
5	**Death**	Death related to AE.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

Changes in the severity of an AE should be documented in the eCRF to allow an assessment to be performed of the duration of the event at each level of intensity.

9.2.2 Relationship to Study Drug

The Investigator's assessment of an AE's relationship to study treatment is part of the documentation process, but it is not a factor in determining what is or is not reported in the study.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria presented in Table 7.

Table 7 Guidelines for Determining the Relationship (if any) Between Adverse Event and the Study Drug

AE Relationship	Definition
Definite	This relationship suggests that a definite causal relationship exists between treatment administration and the AE, and that other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study treatment is re-administered.
Probable	This relationship suggests that a reasonable temporal sequence of the event with treatment administration exists and, based upon the known pharmacological action of the treatment, known or previously reported adverse reactions to the treatment or class of treatment, or judgment based on the Investigator's clinical experience, the association of the event with the study treatment seems likely. The event disappears or decreases on cessation of study treatment.
Possible	This relationship suggests that the study treatment caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of treatment administration or follows a known response pattern to the study treatment, but could also have been produced by other factors.
Unlikely Related	This relationship suggests an improbable (but not impossible) association between the study medication and the reported event.
Not Related	This relationship suggests no association between the study treatment and the reported event.

Abbreviations: AE = adverse event.

9.3 SERIOUS ADVERSE EVENTS

9.3.1 Serious Adverse Event Criteria

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect not present at Prescreening. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or 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.

Serious AEs must be reported (Section 9.3.3) and will be followed through resolution. Serious AEs that occur after the final follow-up visit need not be reported unless the Investigator considers them related to study drug.

9.3.2 Serious Adverse Event Follow-up

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs regardless of relationship to study drug will be followed by the

[redacted]

9.3.3.2 SAE Contact Information

[redacted]

[redacted]

9.4 OVERDOSE

The study drugs are planned to be administered by trained study staff. Administration will be performed in accordance with the IB and instructions in the Pharmacy Manual. Any incidence of overdose should be recorded as an SAE.

No clinical data are available regarding overdose with WVE-120101. As with any agent, if overdose occurs, general supportive measures and close observation should be instituted. Misuse of the study drug for illegal purposes is not expected in this study as patients have no direct access to the study drugs.

9.5 PREGNANCIES

If a female subject becomes pregnant during the study, she must be discontinued from study drug but the patient may continue to be followed in the study. The Medical Monitor should be notified by the Investigator and a Pregnancy Notification Form should be completed. The patient should be followed until the outcome of the pregnancy is known.

Pregnancy in and of itself is not an SAE. However, complications of the pregnancy should be reported to the sponsor within 24 hours of knowledge by the Investigator (eg, if the mother is hospitalized for dehydration) and an SAE form must be completed.

10 STATISTICAL METHODS

10.1 GENERAL CONSIDERATIONS

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, standard deviation (SD), median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Patient-level data will be presented in data listings.

Analyses will primarily be descriptive; confidence intervals will be presented where appropriate.

Details on the statistical analysis will be provided in the Statistical Analysis Plan (SAP).

10.2 SAMPLE SIZE DETERMINATION

The sample size was not calculated on the basis of statistical hypothesis testing. However, based on the results of Wild et al.[1], for each of the active doses, 9 patients per active dose group will yield a two-sided 90% confidence interval width for mHTT in CSF of approximately ±110 fM.

10.3 STUDY PATIENTS

10.3.1 Analysis Populations

The following study populations will be evaluated:

- Safety population will include all randomly assigned patients who receive at least 1 dose of WVE-120101.
- PD population will include all patients in the safety population who have at least 1 postbaseline CSF sample.
- PK population will include all patients in the safety population who have sufficient plasma or CSF concentration data, as determined by the pharmacokineticist, for inclusion in the descriptive statistical analysis.
- Per Protocol Population will include all patients in the Safety population who have no major protocol deviations.

The Safety population will be used for the safety analysis, demographics, and other baseline patient characteristics; the PD population will be used for the PD analysis; the PK population will be used for the PK analysis; and the Per Protocol population will be used for all analyses of clinical effects.

10.3.2 Patient Disposition

The number and percentage of patients screened, randomized, and included in the safety, PK, PD, and Per Protocol populations, and those who complete the study will be presented by dose cohort. The number and percentage of randomized patients who withdraw prior to completion and the primary reason for withdrawal will be summarized by dose cohort.

Study completion information, will be presented by patient in a data listing. A by-patient listing of patients who are screen failures, and the reason for screen failure, will also be presented.

10.3.3 Demographics and Other Baseline Characteristics

Summary statistics for demographic and other baseline characteristics data will be provided by dose cohort for the safety population.

Medical history will be summarized by dose cohort and overall using system organ class (SOC) and preferred term (PT). Events will be summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given PT.

Medical history findings including the verbatim term will be presented by patient in a data listing. Demographic and baseline data will be provided by patient in data listings.

10.3.4 Protocol Deviations

Assessment of protocol deviations as ‘minor’ or ‘major’ will be determined blinded to treatment and prior to database unblinding. A protocol deviations log will be finalized before unblinding and final database lock. Protocol deviations will be presented by patient in a data listing.

10.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately by the number and percentage of patients per dose cohort for each World Health Organization (WHO) drug class and PT. Medications will be coded using the WHO drug dictionary, Anatomical Therapeutic Chemical (ATC) classes, and PT. Patients will be counted only once for a given prior or concomitant medication.

Medications with a start date before the first dose of study drug will be classified as prior medications. Any medication that the patient began taking after the first dose of study drug will be classified as concomitant. Any medication that a patient started before the first dose of study drug and continued to take during the study will be classified as both prior and concomitant. Any medication that was stopped on the same day as the first dose of study drug will be considered a prior medication. If the stop date of a given medication is missing, then the medication will be classified as concomitant.

Concomitant and prior medications will be presented by patient in data listings.

10.3.6 Study Drug Exposure and Compliance

Exposure to study drug, duration of exposure, and overall treatment compliance will be summarized. Study drug dosing information will be presented by patient in data listings.

10.4 PHARMACOKINETIC ANALYSES

The plasma and CSF WVE-120101 concentration data will be summarized for patients in the PK population.

The individual patient plasma concentration-time data will be listed and displayed graphically on linear and log scales. The plasma concentration-time data will be summarized descriptively in tabular and graphical formats (linear and log scales).

For each cohort, the plasma WVE-120101 concentration data will be analyzed by noncompartmental PK analysis. The parameters listed in Table 8 and Table 9 will be determined. Additional PK parameters may be evaluated if deemed appropriate. Pharmacokinetic parameters for each dose cohort will be compared across WVE-120101 dose levels.

The CSF concentration data will be summarized in tabular format.

Table 8 Pharmacokinetic Parameters of WVE-120101 after Single-Dose Administration

Parameter	Definition
C_{max}	Maximum observed concentration
t_{max}	Time of occurrence of C_{max}
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration

Table 9 Pharmacokinetic Parameters of WVE-120101 after Multiple Dose Administration

Parameter	Definition
C_{max}	Maximum observed concentration
t_{max}	Time of occurrence of C_{max}
λ_z	Terminal elimination rate constant
$AUC_{0-\tau}$	Area under the plasma concentration-time curve over the dosing interval

10.5 PHARMACODYNAMIC ANALYSES

Pharmacodynamic analyses will be performed for all patients in the PD population. Summary statistics will be provided for PD endpoints by dose cohort and visit. The change from baseline (Day 1) to the last measured time point will be determined. Individual patient data will be listed. Additional details on the statistical analysis of PD endpoints will be provided in the SAP.

10.6 IMMUNOGENCITY ASSESSMENT

Immunogenicity analyses will be performed for all patients. Summary statistics will be provided as appropriate. Individual patient data will be listed. Additional details on the statistical analysis of immunogenicity will be provided in the SAP.

10.7 MAGNETIC RESONANCE IMAGING

Summary statistics will be provided for MRI data by dose cohort and visit. Individual patient data will be listed. Additional details on the statistical analysis of MRI data will be provided in the SAP.

10.8 CLINICAL EFFECTS ANALYSES

Clinical effects analyses will be performed for all patients in the Per Protocol population.

10.8.1 Unified Huntington's Disease Rating Scale

Summary statistics will be provided for each subtest of the UHDRS (TFC, motor, cognitive, independence, and functional assessments) by dose cohort and visit. A composite score of some or all of the components of the UHDRS may also be calculated. The change from baseline to the last measured time point will be determined. Individual patient data will be listed. Additional details on the statistical analysis of UHDRS data will be provided in the SAP.

10.8.2 Short Problem Behaviors Assessment

Summary statistics will be provided for PBA-s data by dose cohort and visit. The change from baseline to the last measured time point will be determined. Individual patient data will be listed. Additional details on the statistical analysis of PBA-s data will be provided in the SAP.

10.9 SAFETY ANALYSES

Safety data will be analyzed descriptively overall and by treatment group and dose cohort, and no formal statistical comparisons will be performed. Data from unscheduled visits (laboratory tests, vital signs, physical examinations, and ECGs) will not be included in the tables, but will be included in the by-patient listings.

10.9.1 Adverse Events

Adverse events will be collected and recorded from the time the patient signs the ICF at the Prescreening Visit to the study completion. The verbatim AE term will be coded to the PT and SOC using terminology from the MedDRA.

A TEAE is defined as an AE that is first identified, or is identified to worsen in intensity, at a time point occurring after the first dose of study drug. The numbers and percentages of patients with any TEAE, with any TEAE assessed by the Investigator as related to study drug or to study procedures, and with any treatment-emergent SAE will be summarized by treatment group and overall. Treatment-emergent AEs will be tabulated by relationship to study drug and by severity; these summaries will be presented by SOC and PT, by treatment group and overall. In these tabulations, each patient will contribute only once (ie, the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

All AEs and SAEs occurring during the study (pretreatment, treatment, and follow-up) will be presented by patient in data listings. By-patient listings will also be provided for deaths, SAEs, and AEs leading to study drug discontinuation.

10.9.2 Clinical Laboratory Evaluations

Laboratory test values and changes from baseline over time will be summarized for each continuous clinical laboratory parameter. Shift tables showing the pattern of change from baseline to postbaseline visit(s) will be presented.

All laboratory data will be presented by patient in data listings. For hematology and chemistry laboratory data, the laboratory normal ranges will be provided, and individual abnormal laboratory values will be flagged and clinical significance will be indicated. A separate listing of only clinically significant hematology and chemistry findings will be provided.

10.9.3 Vital Signs

The actual value and change from baseline to each postbaseline assessment will be summarized for vital signs (systolic and diastolic blood pressure, pulse rates, and weight). Height and body mass index will also be presented. Vital signs measurements will be presented by patient in data listings.

10.9.4 Electrocardiogram

Summary statistics will be provided for ECG data by dose cohort and visit. Individual patient data will be listed.

10.9.5 Magnetic Resonance Imaging (Safety)

Summary statistics will be provided for MRI safety data by dose cohort and visit. Individual patient data will be listed. Additional details on the statistical analysis of MRI data will be provided in the SAP.

10.9.6 Cerebrospinal Fluid Safety Lab

Cerebrospinal fluid safety lab values and changes from baseline over time will be summarized for each continuous clinical laboratory parameter. Shift tables showing the pattern of change from baseline to each postbaseline visit will be presented.

All data will be presented by patient in data listings.

10.9.7 Columbia-Suicide Severity Rating Scale

Data from the C-SSRS will be descriptively summarized by dose cohort. By-patient listings of the results will be provided.

10.10 INTERIM ANALYSES

Administrative analyses including mHTT may be performed for planning purposes. These analyses will include unblinded summaries by treatment group. The implementation of these analyses by the Sponsor is described in a Data Access Plan.

10.11 DATA QUALITY ASSURANCE

10.11.1 Electronic Case Report Forms and Data Management

All data relating to the study will be recorded in the patient's source documentation and eCRF to be provided by the Sponsor or designee via the electronic data capture (EDC) system. The eCRFs are to be completed within 5 working days of the patient's visit, except for results of tests performed outside the Investigator's office. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, all observations, and patient status. The Investigator is responsible for verifying that all data entries on the eCRFs are accurate and correct and ensuring that all data are entered in a timely manner, as soon as possible after information is collected. An explanation should be provided for all missing data. The Investigator must provide, through EDC, formal approval of all the information on the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for whom the Investigator is responsible.

The Sponsor will retain the final eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be placed in the Investigator's study file.

A record of patient screen failures, including the reason for the failure, will be maintained for patients who do not qualify for enrollment.

11 REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

11.1 DECLARATION OF HELSINKI

The Sponsor and Investigator(s) will ensure that this study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

11.2 GOOD CLINICAL PRACTICE

The study will be conducted according to the study protocol and SOPs that meet the guidelines provided by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical studies, and any other applicable local regulatory requirements.

11.3 INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES

Federal regulations and ICH guidelines require that approval be obtained from an IRB or EC before participation of human patients in research studies. Before study onset, the protocol, informed consent form, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB or EC. Documentation of all IRB/EC approvals and of the IRB/EC compliance with ICH guideline E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/EC approvals should be signed by the chairman or designee and must identify the IRB/EC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted. The study protocol, appendices, and ICFs must be approved by the IRB/EC.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding one year or otherwise specified by the IRB/EC. The Investigator must promptly supply the Sponsor or its designee, the IRB/EC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

11.4 INFORMED CONSENT FORMS

Signed ICFs in compliance with the Declaration of Helsinki, current ICH and GCP guidelines, US Title 21 CFR Part 50, and applicable local regulations will be obtained from each patient before enrolling the patient in the study or performing any unusual or non-routine procedure that involves risk to the patient. Patients may sign 2 separate ICFs. Some patients may sign an ICF to indicate consent specifically for Prescreening procedures. All patients will sign a study ICF prior to Screening and subsequent study procedures.

Informed consent form templates will be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF(s) must be reviewed by the Sponsor or its designee or both before IRB/EC submission. Once reviewed, the ICF(s) will be submitted by the Investigator to his or her IRB/EC for review and approval before the start of the study. If the ICF(s) is revised during the course of the study, all actively participating patients must sign the revised form.

Before Prescreening (as applicable) and Screening, each prospective patient will be given a full explanation of prescreening procedures or the study and be allowed to read the approved Prescreening/Study ICF. Once the Investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in Prescreening or the study by signing the appropriate ICF.

The Investigator will retain the signed original ICF(s) and give a copy of the signed original form(s) to the patient.

12 INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB/EC but will not result in protocol amendments.

12.1 CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the Sponsor, its designee, applicable regulatory agencies, or the IRB/EC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2 INVESTIGATOR DOCUMENTATION

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/EC approval.
- A fully executed Clinical Trial Agreement.
- Original Investigator-signed Investigator agreement page of the protocol.
- Curriculum vitae for the Investigator and each sub-investigator listed on the IRB/EC application.
- Financial disclosure information, as applicable.
- IRB/EC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient.
- Laboratory certifications and normal ranges for any local laboratories used by the site.

12.3 STUDY CONDUCT

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

12.4 ADHERENCE TO PROTOCOL

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

12.5 ADVERSE EVENTS AND STUDY REPORT REQUIREMENTS

By participating in this study the Investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the IRB/EC as appropriate.

12.6 INVESTIGATOR'S FINAL REPORT

Where applicable, the Investigator should inform the institution of study completion; the investigator/institution should provide the IRB/EC with a summary of the study's outcome and the Sponsor and regulatory authority(ies) with any reports required.

12.7 RECORDS RETENTION

The Investigator/institution will retain essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, these documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

12.8 PUBLICATIONS

All information regarding WVE-120101 supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use Sponsor's confidential information solely to accomplish the study and will not use such information for any other purposes without the prior written consent of the Sponsor. The Investigator is obligated to provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used toward the development of WVE-120101 and may be disclosed by the Sponsor to regulatory authority(ies), other investigators, corporate partners, and consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Committee will be formed (Section 13.4) to oversee any publication or presentation of the study results. Subsequently, individual Investigators may present or publish results from the study in compliance with their agreements with the Sponsor. A draft abstract/manuscript is to be

provided to the Sponsor at least 30 days prior to submission of the abstract/manuscript to a medical/scientific organization or a publisher.

13 STUDY COMMITTEES

13.1 SAFETY MONITORING COMMITTEE

An unblinded, independent SMC consisting of at least 3 members (including a statistician and 2 physicians of whom 1 must be a neurologist) will review unblinded, aggregate safety data periodically. In addition, the SMC will review SAEs that occur in the sentinel patients and TEAEs that meet the stopping criteria. The SMC will also review dose recommendations from the Dose Escalation Committee and the chairperson will endorse the decisions. Details on safety reviews are provided in Section 4.3.

Further details regarding the SMC, including committee membership, will be provided in a SMC Charter.

13.2 DOSE ESCALATION COMMITTEE

The decision on escalation to each subsequent single dose will be made by the Dose Escalation Committee. In addition, the Dose Escalation Committee will determine if a single-dose cohort can proceed to multiple dosing. The Dose Escalation Committee will review blinded data. This committee will include, but is not limited to, a Sponsor representative, a Medical Monitor, and a member of the Clinical Advisory Committee. Details on safety reviews are provided in Section 4.3. Further details regarding the Dose Escalation Committee, including committee membership, will be provided in a Dose Escalation Committee Charter.

13.3 CLINICAL ADVISORY COMMITTEE

A Clinical Advisory Committee, consisting of a Study Investigator and experts in Huntington's disease, will be formed to provide advice regarding protocol and study conduct. Further details regarding the Clinical Advisory Committee, including committee membership, will be provided in a Clinical Advisory Committee Charter.

13.4 PUBLICATIONS COMMITTEE

A Publications Committee, consisting of Investigators participating in the study, at least one member of the Clinical Advisory Committee, and representatives from the Sponsor as appropriate, will be formed to oversee any publication or presentation of the study results, which will reflect the experience of all participating study centers.

14 STUDY MANAGEMENT

14.1 MONITORING

14.1.1 Monitoring of the Study

Monitoring and auditing procedures developed by the Sponsor or designee will be followed in order to comply with ICH GCP guidelines.

Before a study center can enter a patient into the study, a representative of the Sponsor or designee will assess the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. The Investigator responsibilities will be documented in a Clinical Trial Agreement between the Sponsor and the Investigator.

Note that if the Sponsor or designee has experience with the study center within the previous 12 months, an abbreviated qualification assessment may be performed via e-mail and/or telephone.

During the study, a monitor from the Sponsor or designee will have regular contact with the study center for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being recorded accurately in the source documents and eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. Verification will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not sent to the Sponsor or designee previously.
- Confirm AEs and SAEs have been documented properly in the eCRFs and confirm any SAEs have been forwarded to the Sponsor, and those SAEs that met criteria for reporting (ie, serious adverse drug reactions) have been forwarded to the IRB/EC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/EC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or regulatory authorities access to all study records.

The Investigator should notify the Sponsor promptly of any audits scheduled by any regulatory authorities and will promptly forward copies of any audit reports received to the Sponsor.

14.2 MANAGEMENT OF PROTOCOL AMENDMENTS AND DEVIATIONS

14.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol, other than minor clarifications and typographical corrections, must be submitted in writing to the Investigator's IRB/EC and regulatory authorities for approval before patients can be enrolled into an amended protocol.

14.2.2 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/EC and agreed to by the Investigator.

The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from the protocol to eliminate an immediate hazard to study patients without prior IRB/EC approval. As soon as possible after such an occurrence, the implemented deviation, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/EC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. As required by local regulatory authorities, the Investigator will notify the IRB/EC of any applicable protocol deviations in a timely manner.

14.3 STUDY TERMINATION

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to temporarily suspend or terminate the study at any time for any reason including (but not limited to) safety issues, ethical issues, or severe noncompliance.

The end of the study is defined as the date on which the last patient completes the last visit (includes follow-up visit).

Upon completion or termination of the study, the study monitor will conduct site closure activities with the Investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and SOPs.

14.4 FINAL REPORT

Whether the study is completed or terminated prematurely, the Sponsor will ensure that a final report is prepared and provided to the regulatory agency(ies), as applicable. The Sponsor will also ensure that the clinical study reports (CSRs) in marketing applications meet the standards of the ICH Guideline E3: Structure and content of clinical study reports (CSRs).

Where required by applicable regulatory requirements, a Principal Investigator will be identified for the approval and signoff of the clinical study report. The Principal Investigator will be

provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

The Investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

15 REFERENCES

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