DRUG:	WVE-120101
STUDY NUMBER(S):	WVE-HDSNP1-002
PROTOCOL(S) TITLE:	A Multicenter, Open-label Extension Study to Evaluate the Safety, Pharmacodynamics, and Clinical Effects of WVE-120101 in Patients with Huntington's Disease
EUDRACT NUMBER:	2019-003637-42
SPONSOR:	**Wave Life Sciences USA, Inc** 733 Concord Avenue Cambridge, MA 02138 United States of America **Wave Life Sciences UK Limited** 1 Chamberlain Square CS Birmingham, B3 3AX United Kingdom
AMENDMENT NO.	1.0
AMENDMENT DATE:	31 March 2020

[redacted]

CLINICAL PROTOCOL APPROVAL FORM

Sponsor: Wave Life Sciences

I have read and understand the contents of this clinical protocol for Study No. WVE-HDSNP1-002 dated 31 March 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.

[redacted]

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. WVE-HDSNP1-002 dated 31 March 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:	Investigational Product:	Developmental Phase:	EudraCT Number:
Wave Life Sciences	WVE-HDSNP1-002	Phase 1b/2a	2019-003637-42

Title of Study: A Multicenter, Open-label Extension (OLE) Study to Evaluate the Safety, Pharmacodynamics, and Clinical Effects of WVE-120101 in Patients with Huntington's Disease

Protocol Number: WVE-HDSNP1-002

Study Center(s): Approximately 25 study sites worldwide

Objectives:

Primary objective:

- To evaluate the safety and tolerability of long-term exposure to WVE-120101 in patients with early manifest Huntington's disease (HD)

Secondary objectives:

- To evaluate the clinical and pharmacodynamic (PD) effects of WVE-120101 in patients with early manifest HD

Exploratory Objectives:

- To evaluate the pharmacokinetics (PK) of WVE-120101 in plasma
- To evaluate WVE-120101 related excretion in urine
- To evaluate the exposure of WVE-120101 in cerebrospinal fluid (CSF)
- To evaluate the effect of WVE-120101 on exploratory biomarkers

Methodology: This is an open-label extension (OLE) study to evaluate the safety, tolerability, PK, PD, and clinical effects of WVE-120101 in adult patients with early manifest HD who carry a targeted single nucleotide polymorphism, rs362307 (SNP1). The planned duration of this study is approximately 101 weeks. To participate in the study, patients must have completed their Day 168 or 196 visit (depending upon dosing cohort and requirements in a given country) of the Phase 1b/2a clinical study WVE-HDSNP1-001.

Screening may last up to 4 weeks. Patients will be dosed on Day 1 with WVE-120101 administered via the intrathecal (IT) route. Patients will return to the clinic every 4 weeks for dosing visits and safety monitoring. Every 12 weeks, patients will undergo assessments of clinical effects. After the last dosing visit (Week 97), patients will return for 1 follow-up safety visit at Week 101.

Dose Modifications

In the original OLE study protocol, patients who were in the 2 and 4 mg dose cohorts in the Phase 1b/2a study were enrolled into the 4 or 8 mg dose group in this study. Patients who were in the 8 and 16 mg dose cohorts in the Phase 1b/2a study were enrolled into the 8 or 16 mg dose groups, respectively in this study. As of this amendment, patients will receive 16 mg or a higher dose of WVE-120101 in this study. The maximum dose and frequency in this OLE study in a given country will not exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in that country. If a dose lower than the maximum dose described in the Phase 1b/2a study is chosen for multiple dosing based on the safety review of the Phase 1b/2a study data by the Dose Escalation Committee (DEC) and Safety Monitoring Committee (SMC), that dose will be used in this OLE study.

Based on the SMC and DEC review of Phase 1b/2a safety data, the highest tolerated dose level and/or a lower dose level may be selected for multiple dosing and further evaluation in the OLE. If one dose level is selected, all patients will be switched to receive treatment at that dose level. If more than one dose is selected, patients will be randomized 1:1 to the highest tolerated dose and one lower dose to be determined by the DEC in

Sponsor:	Investigational Product:	Developmental Phase:	EudraCT Number:
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agreement with the SMC. The randomization will be stratified by cohort and use a fixed block size. These doses may be further revised based on emerging safety, PD, or clinical effects data in the Phase 1b/2a study. The maximum dose and frequency in this OLE study will not exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in each country.

Dose modification will occur at the next scheduled visit from the date of implementation of this amendment (Amendment 1.0). In addition to the assessments performed at every dosing visit, the Unified Huntington's Disease Rating Scale (UHDRS) and clinical laboratory evaluations should be performed at the visit when a dose is changed.

Number of Patients (Planned): Approximately 50 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.

Inclusion Criteria:

1. Patient has documented ability to understand the written study informed consent forms (ICFs) at the time of screening and has provided signed written informed consent prior to any study procedures.
2. Patient successfully completed their Day 168 or 196 visit (depending upon dosing cohort and requirements in a given country) of the Phase 1b/2a study with WVE-120101, WVE-HDSNP1-001.
3. In the opinion of the Investigator, the patient is able to tolerate all study procedures, is willing to comply with all other protocol requirements, and tolerated study drug in the parent study.
4. Patient is willing to practice highly effective contraception for the duration of the study if the patient or their partner are of childbearing potential. Non-childbearing potential and highly effective methods of contraception are defined in the protocol (Section 5.2.1.1).

Exclusion Criteria

1. 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.
2. Received an investigational drug other than WVE-120101, including an investigational oligonucleotide, within the past 1 year or 5 half-lives of the drug, whichever is longer.
3. Implantable central nervous system (CNS) device that may interfere with ability to administer study drug via lumbar puncture or undergo brain magnetic resonance imaging (MRI) scan.
4. 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).
5. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit.
6. 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.
7. 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.
8. Clinically significant abnormality at Screening electrocardiogram (ECG), including but not limited to a confirmed QT interval corrected for heart rate (QTc) ≥450 msec for males or ≥470 msec for females.

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9. 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.
10. Bone, spine, bleeding, or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture.
11. Inability to undergo brain MRI (with or without sedation).
12. In the opinion of the Investigator, deemed to be at significant risk for suicidal behavior.
13. 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.
14. Anticipates using antiplatelet or anticoagulant therapy during the course of the study. Patients who received antiplatelet or anticoagulant therapy must complete one of the following washout periods before the Screening Visit:
    a. A 7-day washout period for antiplatelet therapy,
    b. A 1-day washout period for anticoagulants (except warfarin), or
    c. A 5-day washout period for warfarin.

Investigational Product, Dose, Route, Regimen: WVE-120101. Patients will receive ≥16 mg (not to exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in each country). The investigational product will be supplied as a lyophilized powder that will be reconstituted into an injectable solution. The route of administration of the reconstituted WVE-120101 solution will be IT injection by direct lumbar puncture.

Reference Therapy, Dose, Route, Regimen: Not applicable. All patients will receive WVE-120101.

Study Duration: The planned duration is 101 weeks. Patients will receive doses every 4 weeks over a period of 97 weeks, then complete a safety follow-up phase.

Endpoints:

Safety Endpoints:

The number of patients with adverse events (AEs), severity of AEs, number of patients with serious AEs (SAEs), clinically significant changes in laboratory values, and the number of patients who withdraw due to AEs.

Clinical Effects Endpoint(s):

- Change from baseline in the Total Functional Capacity (TFC), administered as part of the Unified Huntington's Disease Rating Scale (UHDRS)
- Change from baseline in the motor, cognitive, independence, and functional assessments administered as part of the UHDRS
- Change from baseline in the composite UHDRS (cUHDRS)
- Change from baseline in the Short Problem Behaviors Assessment (PBA-s)

Pharmacodynamic Endpoints:

- Change from baseline in the concentration of mutant huntingtin (mHTT) protein in CSF
- Changes from baseline MRI of the brain

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- Change from baseline in exploratory biomarkers, including but not limited to neurofilament light (NFL)

PK Endpoints:

- PK parameters of WVE-120101 in plasma
- WVE-120101 and WVE-120101-related metabolite excretions in urine
- Concentration of WVE-120101 in CSF

Statistical Methods:

Sample size determination

No sample size calculations were performed. As this is an OLE, the maximum sample size is fixed by the number of patients completing the WVE-HDSNP1-001 study.

Analysis populations

The safety population will include all enrolled patients who have received at least one dose of study medication in the OLE. The safety population analysis set will be used for summaries of safety and clinical effects.

The per-protocol population will be a subset of the safety population and include patients with no major protocol deviations that will interfere with the assessment of the clinical effects endpoints and with at least 80% compliance to the dosing regimen.

The PK population will consist of all patients in the safety population with at least one post-dose plasma or CSF concentration measurement.

Analysis of safety

The primary objective of this OLE is to evaluate the safety of WVE-120101. The safety analysis will be descriptive and will include summaries of treatment-emergent AEs (TEAEs), TEAEs leading to treatment discontinuation, TEAEs by severity, TEAEs by relationship, and serious TEAEs. Changes in laboratory assessments will also be summarized.

Analysis of Clinical Effects and PD

The change from baseline for clinical effects and PD endpoints will be summarized using a mixed model for repeated measures (MMRM) with the safety population. The MMRM will be used to construct 95% confidence intervals and to test if the change is statistically significant.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
3T	3 Tesla
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
$AUC_{0-\tau}$	area under the plasma concentration-time curve over the dosing interval
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measured time point
C	Celsius
CAG	cytosine-adenine-guanine
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CNS	central nervous system
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
cUHDRS	composite Unified Huntington's Disease Rating Scale
DEC	Dose Escalation Committee
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
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HD	Huntington's disease
HED	human equivalent dose
HTT, HTT	*Huntingtin* gene or huntingtin protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
INN	International Nonproprietary Name

Abbreviation	Definition
IRB	Institutional Review Board
IT	intrathecal
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IXRS	interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities
mHTT, mHTT	mutant huntingtin gene or protein
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NFL	neurofilament light
OLE	Open-label extension
PBA-HD	Problem Behaviors Assessment for HD
PBA-s	Short Problem Behaviors Assessment
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PS	phosphorothioate
PT	prothrombin time
QTc	QT interval corrected for heart rate
RNA	ribonucleic acid
RSI	reference safety information
SAE	serious adverse event
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
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TFC	Total Functional Capacity
t_{max}	time of occurrence of C_{max}
U	uracil
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of normal
wtHTT	wild-type huntingtin

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 at the uracil (U) variant of single nucleotide polymorphism (SNP) rs362307 (SNP1).

1.1 Disease Background

Huntington's disease is a rare, progressive neurological disease that results in motor, cognitive, and psychiatric disability and is invariably fatal1. Because it is a genetic, hereditary disease, it can affect multiple family members across generations[2]. 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 501. 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[1,2]. Prevalence in Europe, North America, and Australia is approximately 6 per 100,0003. In the United States alone, approximately 30,000 people have diagnosed HD[4,5] and another 200,000 or more Americans carry the gene and are at risk of developing the disease[5]. 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 that affect the dopamine pathways, which modulate the movement disorder[2].

Huntington's disease is caused by known mutations in a single gene, that are characterized by an expansion of a cytosine-adenine-guanine (CAG) triplet repeat in the *Huntingtin* (*HTT*) gene6. Wild-type HTT (wtHTT) protein is critical for neuronal development[7]. 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[7-10]. 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[2]. In nonclinical studies, lowering the level of mHTT protein as measured in the cerebrospinal fluid (CSF) has been demonstrated to be therapeutic[11,12]. 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[13].

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 of each PS, 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 PRISM™, 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 as compared to stereorandom molecules.

WVE-120101 specifically targets the mHTT messenger ribonucleic acid (mRNA) transcript, at the U variant of 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[13-16].

1.3 Nonclinical Data

The nonclinical program evaluating WVE-120101 encompasses in vitro studies of primary and secondary pharmacology, in vitro and in vivo genetic toxicology, and in vivo safety pharmacology and toxicity studies.

In vitro pharmacology studies confirm that WVE-120101 demonstrates selective knockdown of the mHTT messenger ribonucleic acid (mRNA) and protein through cleavage of the mRNA transcript of the mutant allele with the targeted single nucleotide polymorphism (SNP) rs362307 (SNP1) versus the wild type allele. This selective knockdown results in greater reduction of the mHTT protein over wild type huntingtin (wtHTT) protein produced by this ribonucleic acid (RNA) and, thus, limits the unintended, potentially deleterious effects of decreasing wtHTT7-[10]. In vivo tissue distribution studies in animals 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 of mtHTT. However, in the absence of an animal model recapitulating the mutation observed in this subpopulation of HD patients, no in vivo data are available regarding the concentration required to reduce the level of mHTT in vivo or the potential duration of knockdown. The optimal dose and dosing frequency for efficacy in humans will be explored during clinical development.

In vitro, WVE-120101 is highly protein-bound in rat, monkey, and human plasma (>99%). Following single or multiple monthly intrathecal (IT) administrations of WVE-120101 in rats and monkeys, dose dependent increases were observed in plasma, central nervous system (CNS), and systemic tissues (kidney, liver, and spleen). Systemic accumulation of WVE-120101 after repeated dosing was minimal. No in vitro cytochrome P450 (CYP) inhibition or induction was observed at clinically relevant concentrations of WVE-120101.

In single and repeat-dose IT studies in rats and monkeys, transient, dose-dependent limb dysfunction was observed. In rats findings were observed at dose levels of 0.1 mg (human equivalent dose [HED] 56 mg) in a single-dose study and 0.05 mg (HED 28 mg) and above in repeat doses. These findings resolved within 72 hours. In monkeys, findings were observed at doses up to 6 mg (HED 67.2 mg). Over the course of 9 months in a chronic toxicity study in monkeys, affected animals at doses ≤2 mg experienced only 1 or 2 instances of limb dysfunction at sporadic time points. In monkeys, only the lower hind limbs were affected and findings were completely resolved within 48 hours post-dose. Due to their transience, lack of correlating histopathology, and lack of effect on the ability of animals to eat or ambulate, the findings were considered non-adverse.

Microscopic CNS findings were observed in both rats and monkeys after IT administration of WVE-120101. In rats, after 3 months of repeat IT dosing, cellular infiltrates, minimal to mild non-adverse spinal nerve root degeneration, and gliosis were observed. The findings were dose- and/or dose-concentration dependent, with minimal effects observed at 0.05 mg (dose concentration 2 mg/mL). In monkeys, after 3 to 9 months of repeat IT dosing, minimal to mild (3-month study) or minimal to moderate (9-month study) mononuclear cell infiltrates were observed at all doses evaluated. These findings were considered manifestations of the injection procedure and a general response to the immune-stimulating properties of the oligonucleotide[17,18] and were considered non-adverse.

WVE-120101 demonstrated minimal potential for class effects associated with phosphorothioate oligonucleotides, such as systemic pro-inflammatory effects, activated partial thromboplastin time (aPTT) prolongation, hepatotoxicity, and nephrotoxicitiy[18,19]. In addition, WVE-120101 was not associated with any other toxicities, including mutagenicity or effects on cardiovascular or respiratory function, and WVE-120101 exhibited minimal potential for off-target effects via bioinformatic analysis of the human genome.

In an vivo genotoxicity study in rats, a statistically significant but non-dose-related increase in micronucleated polychromatic erythrocytes was observed in rats. This increase was not considered biologically meaningful, since the values were within the historical control range for the test facility and anti-kinetochore staining demonstrated that the findings were not the result of an aneugenic mechanism. Moreover, because WVE-120101 was negative in an in vitro panel of genotoxicity studies; there were no histological findings in long-term animal studies suggestive of effects on dividing cells; and because oligonucleotides are not known to carry a genotoxic risk; WVE-120101 is unlikely to induce genotoxic effects under the proposed conditions of use.

Based on the results of the nonclinical studies, the risk/benefit for further investigation of WVE-120101 as a disease-modifying agent for the treatment of patients with HD is acceptable. Further details on the nonclinical experience with WVE-120101 can be found in the current version of the Investigator's Brochure (IB).

1.4 Clinical Experience

WVE-120101 is currently being evaluated in a Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics (PK), and

pharmacodynamics (PD) of single and multiple doses of IT WVE-120101 in adult patients with early manifest HD who carry a targeted single SNP, SNP1 (WVE-HDSNP1-001).

In the Phase 1b/2a study, as of the last data cutoff at single doses up to 16 mg (20 March 2020) and multiple doses up to 4 mg (02 March 2020), no stopping criteria have been observed. No related SAEs or related TEAEs associated with the HLGT *Spinal Cord and Nerve Root Disorders* have been reported. No clinically meaningful trends in hematology, coagulation, or chemistry values followed dosing. Final data are not yet available from this study. An independent Safety Monitoring Committee (SMC) will continue to review safety data from study WVE-HDSNP1-001 on an ongoing basis. The SMC will also review data for this OLE study in conjunction to the data from the Phase 1b/2a study to inform decisions in dose escalation and continuation of multiple dosing. If any stopping rules are met in the Phase 1b/2a study, or if the SMC decides to stop the Phase 1b/2a study for any other reason, those decisions will also apply to this study. More detailed information is provided in the Investigator's Brochure.

2 RATIONALE FOR THE STUDY

This open-label extension (OLE) study is being conducted to evaluate the safety, tolerability and clinical effects of monthly IT doses of WVE-120101 over 97 weeks. Patients must complete their Day 168 or 196 visit (depending upon dosing cohort and requirements in a given country) of the prior Phase 1b/2a clinical study (WVE-HDSNP1-001) to be eligible for screening for this extension study.

2.1 Rationale for the Doses, the Dosing Regimen, and Route of Administration

This is an open-label extension study for the Phase 1b/2a clinical study WVE-HDSNP1-001. The clinical starting dose in WVE-HDSNP1-001 was selected in consideration of the data from both single- and 13-week repeat-dose toxicology studies; an animal model possessing the SNP1 variant targeted by WVE-120101 was not available to the Sponsor. The clinical starting dose of 2 mg was based on the no-adverse-effect-level (NOEL) for transient limb dysfunction in monkeys, which is considered the most relevant species for the purposes of clinical assessment. The lack of findings in the monkey at a dose of 2 mg provides a 10-fold safety margin to the HED, on the basis of relative CSF volume. Subsequent doses are selected based on safety assessments from each cohort.

In the original OLE study protocol, patients who were in the 2 and 4 mg dose cohorts in the Phase 1b/2a study were enrolled into the 4 or 8 mg dose group in this study. Patients who were in the 8 and 16 mg dose cohorts in the Phase 1b/2a study were enrolled into the 8 or 16 mg dose groups, respectively in this study. As of this amendment, patients will receive 16 mg or a higher dose of WVE-120101 in this study. The maximum dose and frequency in this OLE study in a given country will not exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in that country. If a dose lower than the maximum dose described in the Phase 1b/2a study is chosen for multiple dosing based on the safety review of the Phase 1b/2a study data by the Dose Escalation Committee (DEC) and Safety Monitoring Committee (SMC), that dose will be used in this OLE study.

Based on the SMC and DEC review of Phase 1b/2a safety data, the highest tolerated dose level and/or a lower dose level may be selected for multiple dosing and further evaluation in the OLE. If one dose level is selected, all patients will be switched to receive treatment at that dose level. If more than one dose is selected, patients will be randomized 1:1 to the highest tolerated dose and one lower dose to be determined by the DEC in agreement with the SMC. The randomization will be stratified by cohort and use a fixed block size. These doses may be further revised based on emerging safety, PD, or clinical effects data in the Phase 1b/2a study. The maximum dose and frequency in this OLE study will not exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in each country. For more details on additional dose modifications refer to Section 4.1.

At the time when the Phase 1b/2a study is completed, the dose and dose interval in this OLE study may be further adjusted. A final determination about the optimal dose and dose-frequency will be made on the basis of data from the WVE-HDSNP1-001 study. It is possible that patients will be up-titrated or down-titrated depending on the dose they were receiving at the time of that decision. Up- or down-titration of the dose will only occur at the cohort level, not on an individual patient level.

The follow-up period will continue to Week 101, 4 weeks after the last dose. Based on PK data from animal studies, the plasma half-life of WVE-120101 is less than 24 hours and the potential for accumulation is low. Clinical data from the ongoing WVE-HDSNP1-001 study show that adverse events tend to occur within the first week or two after dosing. A 4-week follow-up period after the last dose is therefore considered a sufficient period of time to observe potential adverse events.

3 STUDY OBJECTIVES

Primary Objective:

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

Secondary Objectives:

The secondary objectives of this study are to evaluate the clinical and pharmacodynamic effects of WVE-120101 in patients with early manifest HD.

Exploratory Objectives:

The exploratory objectives are:

- To evaluate the PK of WVE 120101 in plasma
- To evaluate WVE-120101 related excretion in urine
- To evaluate the exposure of WVE-120101 in CSF

- To evaluate the effect of WVE-120101 on exploratory biomarkers

4 STUDY DESIGN

4.1 Study Design Overview

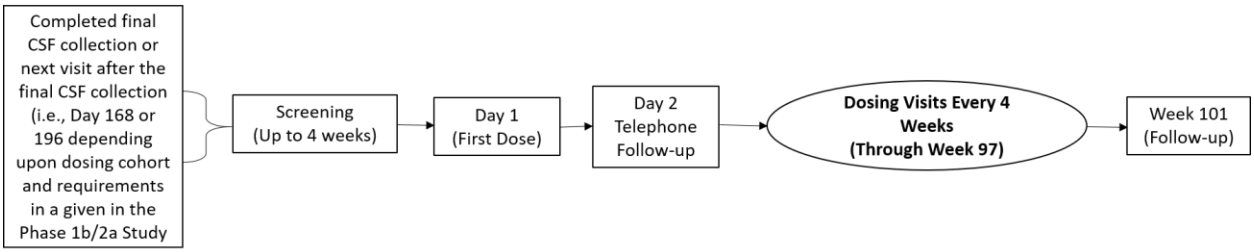
This is an OLE study to evaluate the safety, tolerability, PK, PD, and clinical effects of WVE-120101 in adult patients with early manifest HD who carry a targeted single nucleotide polymorphism, SNP1. The planned duration of this study is approximately 101 weeks. To participate in the study, patients must have completed their Day 168 or 196 (depending upon dosing cohort and requirements in a given country) of the parent Phase 1b/2a clinical study WVE-HDSNP1-001.

Screening may last up to 4 weeks. Patients will be dosed on Day 1 with WVE-120101 administered via the IT route and stay in the clinic for monitoring through 4 hours postdose.

Patients will return to the clinic every 4 weeks for dosing visits and safety monitoring. Every 12 weeks, patients will undergo assessments of clinical effects. After the last dosing visit (Week 97), patients will return for 1 follow-up safety visit at Week 101.

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

Figure 1 Schematic of Study Design



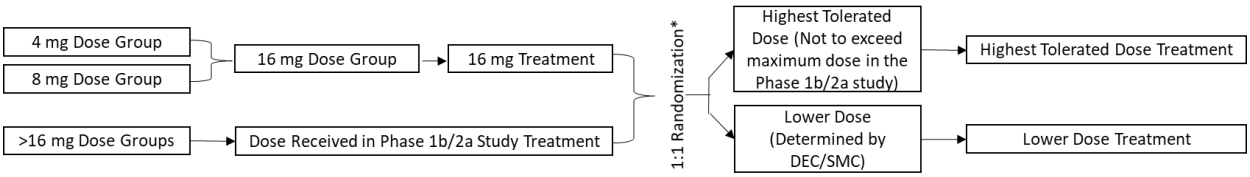
Dose Modifications

In the original OLE study protocol, patients who were in the 2 and 4 mg dose cohorts in the Phase 1b/2a study were enrolled into the 4 or 8 mg dose group in this study. Patients who were in the 8 and 16 mg dose cohorts in the Phase 1b/2a study were enrolled into the 8 or 16 mg dose groups, respectively in this study. As of this amendment, patients will receive 16 mg or a higher dose of WVE-120101 in this study (Figure 2). The maximum dose and frequency in this OLE study in a given country will not exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in that country. If a dose lower than the maximum dose described in the Phase 1b/2a study is chosen for multiple dosing based on the safety review of the Phase 1b/2a study data by the Dose Escalation Committee (DEC) and Safety Monitoring Committee (SMC), that dose will be used in this OLE study.

Based on the SMC and DEC review of Phase 1b/2a safety data, the highest tolerated dose level and/or a lower dose level may be selected for multiple dosing and further evaluation in the OLE. If one dose level is selected, all patients will be switched to receive treatment at that dose level. If more than one dose is selected, patients will be randomized 1:1 to the highest tolerated dose and one lower dose to be determined by the DEC in agreement with the SMC (Figure 2). The randomization will be stratified by cohort and use a fixed block size. These doses may be further revised based on emerging safety, PD, or clinical effects data in the Phase 1b/2a study. The maximum dose and frequency in this OLE study will not exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in each country.

Dose modification will occur at the next scheduled visit from the date of implementation of this amendment (Amendment 1.0). In addition to the assessments performed at every dosing visit, the Unified Huntington's Disease Rating Scale (UHDRS) and clinical laboratory evaluations should be performed at the visit when a dose is changed. Patients will not be asked to restart the treatment phase but will continue to receive doses as originally scheduled, every 4 weeks, at the new dose level.

Figure 2 Dose Modification Scheme



Abbreviations: DEC=Dose Escalation Committee; SMC=Safety Monitoring Committee
*Dose modification randomization. Applicable if 2 doses are studied.

4.1.1 Screening Phase

The screening period is intended to allow determination of patient eligibility for the study. Screening will begin when the study informed consent form (ICF) is signed.

The patient must sign a study ICF on Day 1 of Screening. The ability of the patient to understand the consent form will be documented in the study ICF.

The Screening tests and evaluations must be completed within 4 weeks prior to enrollment. The required screening evaluations are outlined in the Schedule of Assessments (Table 1). Applicable evaluations from the last in-clinic visit in the Phase 1b/2a study WVE-HDSNP1-001 may be used if the last in-clinic visit occurred within 4 weeks prior to the Screening visit for this study (specified in Table 1). Screening assessments can occur over multiple days, provided they are within the Screening period. The Investigator will determine whether the patient meets eligibility criteria and will collect the demographic and medical data permitting full characterization of the patient. In addition, the Investigator should discuss the need for a legally authorized representative to provide consent on behalf of the patient in the event that the patient's cognitive capacity deteriorates during the course of the OLE study to the point that they are no longer able to consent. In addition, patients should identify a study partner (Section 4.1.1.1). These may or may not be the same person.

4.1.1.1 Study Partner

Patients should identify a study partner for the purposes of this trial. The role of the study partner will be to help ensure that the patient complies with study visits and assessments. Patients should have the same study partner throughout the course of the trial. The study partner must sign an acknowledgement of responsibilities form. The study partner does not have to be a legally authorized representative.

4.1.2 Treatment Phase

WVE-120101 will be administered monthly via IT dosing through Week 97. At each visit, patients will be evaluated for safety and tolerability. At the end of each 12-week period, patients will undergo assessments of clinical effects. A schedule of assessments is provided in Table 1.

Up to 1 week before performing lumbar puncture for each dose, 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 8.1.7). Other predose assessments may also be performed up to 1 week before dosing as specifically listed in Table 1.

At all dosing visits, patients should be monitored for a minimum of 4 hours postdose in the clinic. After the first dose only, a follow-up safety phone call will be performed on Day 2.

Immediately after study drug administration, all patients should be ambulatory for approximately 30 minutes postdose. Formal physical examinations targeting the neurological system will be performed at the time points noted in the Schedule of Assessments (Table 1).

Patients who are entering the study may be requested to consent to two additional lumbar punctures (LP) to provide CSF samples at two weeks after the first dose, and two weeks after the sixth dose to allow for more robust PK/PD modeling (see Table 1 for more details). These additional CSF samples will be optional, and consent will be collected as a stand-alone question in the Informed Consent Form. If a patient has already passed the first dose, but not the sixth, and is willing to undergo the additional LP, then CSF will be collected 2 weeks after the sixth dose.

In addition to the above two CSF samples, patients at certain participating sites will undergo additional intensive PK blood and urine sampling as noted in Table 2. This sampling will include additional time points for plasma and a 24-hour urine collection.

Dose Modifications

In the original OLE study protocol, patients who were in the 2 and 4 mg dose cohorts in the Phase 1b/2a study were enrolled into the 4 or 8 mg dose group in this study. Patients who were in the 8 and 16 mg dose cohorts in the Phase 1b/2a study were enrolled into the 8 or 16 mg dose groups, respectively in this study. As of this amendment, patients will receive 16 mg or a higher dose of WVE-120101 in this study. The maximum dose and frequency in this OLE study in a given country will not exceed the maximum dose and frequency described in the Phase 1b/2a

protocol (WVE-HDSNP1-001) approved in that country. If a dose lower than the maximum dose described in the Phase 1b/2a study is chosen for multiple dosing based on the safety review of the Phase 1b/2a study data by the Dose Escalation Committee (DEC) and Safety Monitoring Committee (SMC), that dose will be used in this OLE study.

Based on the SMC and DEC review of Phase 1b/2a safety data, the highest tolerated dose level and/or a lower dose level may be selected for multiple dosing and further evaluation in the OLE. If one dose level is selected, all patients will be switched to receive treatment at that dose level. If more than one dose is selected, patients will be randomized 1:1 to the highest tolerated dose and one lower dose to be determined by the DEC in agreement with the SMC. The randomization will be stratified by cohort and use a fixed block size. These doses may be further revised based on emerging safety, PD, or clinical effects data in the Phase 1b/2a study. The maximum dose and frequency in this OLE study will not exceed the maximum dose and frequency described in the Phase 1b/2a protocol (WVE-HDSNP1-001) approved in each country. For more details on additional dose modifications see Section 4.1.

4.1.3 Follow-Up Visit

All patients are required to complete follow-up assessments, including evaluations of safety, PD, PK, and clinical effects (Table 1). Patients will be followed until Week 101 (4 weeks after the last dose). An early termination (ET) visit will be required in the event of early withdrawal.

4.1.4 Early Treatment Withdrawal and Early Termination

If a patient withdraws from treatment, but wishes to remain in the study, the patient should continue with all planned visits and applicable assessments. PK assessments as well as lumbar punctures (with associated labs) will no longer be necessary unless a patient agrees to allow for one final lumbar puncture. A urine pregnancy test should be completed on the visit after the last dose of treatment.

If a patient withdraws from the study, the patient should complete an early termination visit (Table 1).

4.2 Schedule of Assessments

The schedule of assessments is provided in Table 1. The schedule of additional assessments for patients undergoing intensive PK assessments is provided in Table 2.

Table 1 Schedule of Assessments

Timing of Assessment (Visit Window, if applicable) Event/Assessment	Screening[a]	Treatment									Follow-up	ET
	Wk -4 to Wk -1	Wk 1			Wks (±1 Wk)	Wks (±1 Wk)	Wks (±1 Wk)					
					9	13	25					
					17, 21							
					29, 33	37	49					
					41, 45							
					53, 57	61	73					
					65, 69							
					77, 81							
					89, 93		85					
	Day -28 to Day -1	Day 1	Day 2[d]	Wk 5 (±3 days)				Wk 97 (±1 Wk)	Dose Modification Assessments[b]	Additional CSF Collection[c] (Optional)	Wk 101 (±1 Wk)	
Patient ICF signed	X											
Inclusion/exclusion criteria	X											
Drug screening	X											
Medical history and demographics	X											
C-SSRS[e,f]	X	X		X	X	X	X	X			X	X
UHDRS[e,f]		X		X		X	X	X	X		X	X
PBA-s[e,f]		X		X	X	X	X	X			X	X
Physical examination[a,g]	X	X		X	X	X	X	X			X	X
Targeted postdose physical examination of motor effects[h]		X		X	X	X	X	X				
Serum pregnancy test[i]	X											
Urine pregnancy test[i]		X		X	X	X	X	X				
Adverse event monitoring	X	X	X	X	X	X	X	X		X	X	X

Timing of Assessment (Visit Window, if applicable) Event/Assessment	Screening[a]	Treatment								Follow-up	ET
	Wk -4 to Wk -1	Wk 1		Wk 5 (±3 days)	Wks (±1 Wk)	Wks (±1 Wk)	Wks (±1 Wk)	Wk 97 (±1 Wk)	Dose Modification Assessments[b]	Additional CSF Collection[c] (Optional)	Wk 101 (±1 Wk)	
					9	13	25					
					17, 21							
					29, 33	37	49					
					41, 45							
					53, 57	61	73					
					65, 69							
					77, 81		85					
	Day -28 to Day -1	Day 1	Day 2[d]		89, 93							
Prior and concomitant medications	X	X	X	X	X	X	X	X		X	X	X
Blood pressure/pulse[j]	X	X		X	X	X	X	X			X	X
Temperature	X	X		X	X	X	X	X			X	X
Weight[a,f]	X	X					X	X			X	X
Height	X											
Electrocardiogram[k]	X						X					
Pre-LP PT and platelet[f,l]		X		X	X	X	X	X		X		
Clinical laboratory evaluations[a,f,m]	X	X		X		X	X	X	X			
Urine dipstick[a,f,m]	X	X				X	X	X			X	X
Blood sample for PK[n]		X		X			X					
Blood sample for immunogenicity		X		X			X					
CSF sample for safety, exposure, and PD[o]		X		X	X	X	X	X		X		
Brain magnetic resonance imaging (MRI)[p]	X						X	X				X[q]

Timing of Assessment (Visit Window, if applicable) Event/Assessment	Screening[a]	Treatment									Follow-up	ET
	Wk -4 to Wk -1	Wk 1			Wks (±1 Wk)	Wks (±1 Wk)	Wks (±1 Wk)					
					9	13	25					
					17, 21							
					29, 33	37	49					
					41, 45							
					53, 57	61	73					
					65, 69							
					77, 81		85					
					89, 93							
	Day -28 to Day -1	Day 1	Day 2[d]	Wk 5 (±3 days)				Wk 97 (±1 Wk)	Dose Modification Assessments[b]	Additional CSF Collection[c] (Optional)	Wk 101 (±1 Wk)	
Study drug administration via IT injection[r]		X		X	X	X	X	X				

Abbreviations: CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; ET = early termination; h = hour; ICF = informed consent form; IT = intrathecal; LP= lumbar puncture; PBA-s = Short Problem Behaviors Assessment; PD = pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time; UHDRS = Unified Huntington's Disease Rating Scale.

[a] If Screening is within 4 weeks of the completion of the Phase 1b/2a study, the values from the final visit in the parent study can be used for this assessment.
[b] Dose modification will occur at the next scheduled visit from the date of implementation of this amendment (Amendment 1.0). In addition to the assessments performed at every dosing visit, the UHDRS and clinical laboratory evaluations should be performed at the visit when a dose is changed. See Section 4.1 for more details.
[c] Collect CSF 14 days (± 3 days) after the first dose and 14 days (± 3 days) after sixth dose. Patients should be monitored after the lumbar puncture per institutional standards.
[d] This visit will be a phone call.
[e] Clinical effects measures and C-SSRS should be performed prior to any other assessments that day.
[f] This assessment can be done up to 1-week predose, at each applicable dosing visit.
[g] Physical examination includes (at a minimum): head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, psychiatric, and neurologic systems. For dosing days, physical examination should be done before the dose is given.
[h] Targeted postdose physical examination to assess potential motor effects focuses on the neurologic system, with special attention to the motor system, upper and lower extremity measures of strength, tone, reflexes, and ambulation. This should be performed at 1 and 4 hrs postdose (± 15 mins).
[i] Negative serum pregnancy test documented at Screening for female patients. Negative urine pregnancy test documented predose for female patients.
[j] Blood pressure (systolic and diastolic) and pulse: measured ≤30 mins predose and 4 hours (±15 mins) postdose at each dosing visit. Patient must rest quietly for ≥3 minutes prior to measuring.
[k] Electrocardiogram should be performed (in triplicate) predose, after patient has been resting quietly for ≥5 minutes.
[l] Blood sample tested locally for platelet count and prothrombin time pre-LP to confirm safe to proceed with the lumbar puncture.

[m] Parameters to be assessed are detailed in Table 3.
[n] Performed predose, and 1 and 3 hours (±15 mins) postdose at noted visits. For patients on the intensive PK schedule, follow additional assessments summarized in Table 2.
[o] CSF samples will be tested locally for safety (total protein, glucose and cell counts [white blood cell counts with differential]). No more than 10 mL of CSF total will be collected for safety, exposure, and PD biomarkers.
[p] Only at Screening and at Weeks 49 and 97. The screening visit MRI should be completed after eligibility has been confirmed. On Weeks 49 and 97 the MRI must be performed within 7 days pre-dose.
[q] Complete an MRI at the ET visit if the last per-study protocol MRI was obtained more than 6 months before the ET visit.
[r] Patients should be active through 30 minutes postdose.

Table 2 Schedule of Additional Assessments for Intensive Pharmacokinetic Patients

Timing of Assessment (Visit Window, if applicable) Event/Assessment	Week 1				Week 73					7 Days (±3 days) Post Week 73
	Day 1									
	Predose	0-4 hr Postdose	4-24 hr Postdose	Day 2	Predose	30 min ±5 min Postdose	1 hr ±15min Postdose	3 hr ±15 min Postdose	24 hr ±15 min Postdose	
Blood sample for PK[a]					X	X	X	X	X	X
Urine sample for PK assessments		X	X							
C-SSRS[b]										X
AE Monitoring[b]				X						X
Concomitant Medications[b]				X						X

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; hr = hour; min = minute; PD = pharmacodynamic; PK = pharmacokinetic.

[a]Follow "blood sample for PK" timepoints in Table 1 for Week 1 blood PK.

[b]The visits on Day 2 and 7 days (±3 days) post-Week 73 are unique to the patients being evaluated for intensive PK and additional safety monitoring is required.

4.3 Study Endpoints

Safety Endpoints:

The number of patients with AEs, severity of AEs, number of patients with SAEs, clinically significant changes in laboratory values, and the number of patients who withdraw due to AEs.

Clinical Effects Endpoint(s):

- Change from baseline in the Total Functional Capacity (TFC), administered as part of the Unified Huntington's Disease Rating Scale (UHDRS)
- Change from baseline in the motor, cognitive, independence, and functional assessments administered as part of the UHDRS
- Change from baseline in the composite UHDRS (cUHDRS)
- Change from baseline in the Short Problem Behaviors Assessment (PBA-s)

Pharmacodynamic Endpoints:

- Change from baseline in the concentration of mHTT protein in CSF
- Changes from baseline MRI of the brain
- Change from baseline in exploratory biomarkers, including but not limited to neurofilament light (NFL)

PK Endpoints:

- PK parameters of WVE-120101 in plasma
- WVE-120101 and WVE-120101-related metabolite excretions in urine
- Concentration of WVE-120101 in CSF

4.4 Safety Monitoring Committee Reviews

A Safety Monitoring Committee (SMC) (Section 13.1) will review aggregate safety data while the Phase 1b/2a study is ongoing. Safety data will be reviewed periodically and on an ad hoc basis should any emergent safety concerns arise. Recommendations based on these reviews will be provided to the Sponsor. Any decisions regarding the stopping of the WVE-HDSNP1-001 study will apply to this study if appropriate. The SMC will cease to review safety data from this study once the Phase 1b/2a study is complete.

5 PATIENT SELECTION AND WITHDRAWAL CRITERIA

Approximately 50 patients will be enrolled. Patients will be assigned to study treatment only if they qualify according to all of the following inclusion and exclusion criteria. During Screening, patients who do not meet all remaining inclusion/exclusion criteria will be considered screen failures. Patients who fail screening may be rescreened once if the reason for screen failure is transient and the patient is expected to return to normal after recovery.

5.1 Inclusion Criteria

1. Patient has documented ability to understand the written study ICFs and has provided signed written informed consent prior to any study procedures.

2. Patient successfully completed their Day 168 or 196 visit (depending upon dosing cohort and requirements in a given country) of the Phase 1b/2a study with WVE-120101, WVE-HDSNP1-001.

3. In the opinion of the Investigator, the patient is able to tolerate all study procedures, is willing to comply with all other protocol requirements, and tolerated study drug in the parent study.

4. Patient is willing 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. 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.

2. Received an investigational drug other than WVE-120101, including an investigational oligonucleotide, within the past 1 year or 5 half-lives of the drug, whichever is longer.

3. Implantable CNS device that may interfere with ability to administer study drug via lumbar puncture or undergo MRI scan.

4. 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).

5. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit.

6. 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.

7. 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.

8. Clinically significant abnormality at Screening electrocardiogram (ECG), including but not limited to a confirmed QT interval corrected for heart rate (QTc) ≥450 msec for males or ≥470 msec for females.

9. 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.

10. Bone, spine, bleeding, or other disorder that exposes the patient to risk of injury or unsuccessful lumbar puncture.

11. Inability to undergo brain MRI (with or without sedation).

12. In the opinion of the Investigator, deemed to be at significant risk for suicidal behavior

13. 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.

14. Anticipates using antiplatelet or anticoagulant therapy during the course of the study. Patients who received antiplatelet or anticoagulant therapy must complete one of the following washout periods before the Screening Visit:

    a. A 7-day washout period for antiplatelet therapy,

    b. A 1-day washout period for anticoagulants (except warfarin), or

    c. A 5-day washout period for warfarin.

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 study. 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 one of the following:

- True abstinence, defined as refraining from heterosexual intercourse for the duration of the study, 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 amenorrhoea are not acceptable methods of contraception.

5.3 Withdrawal and Discontinuation

Patients are free to withdraw from the study or discontinue study treatment at any time upon request without prejudice to their future medical care by the Investigator or at the study site. Patient participation in the study may also 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 withdraw or discontinue from study treatment will no longer receive investigational drug.

5.3.1 Withdrawal of Patient from the Study

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

- The patient withdraws consent

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Termination of the study by the Sponsor (See Section 14.4 for additional details)

Any patient who withdraws their consent for participating in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the early termination study procedures and observations (Section 4.1.4) at the time of withdrawal. All information, including the reason for withdrawal from the study, must be recorded in the electronic case report form (eCRF) and source documentation.

5.3.2 Discontinuation of Study Treatment

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

- The patient is withdrawn from the study (Section 5.3)
- The patient experiences a serious or intolerable AE that in the Investigator's opinion requires treatment discontinuation
- A change in the patient's medical condition not consistent with the protocol requirements or that justifies withdrawal from the study or study drug
- Pregnancy (refer to Section 9.5)

If a patient discontinues treatment, they will be encouraged to remain in the study to be monitored and complete applicable study related procedures (see Section 4.1.4 for more details), unless consent is withdrawn. Patients who discontinue treatment due to an AE (Section 9) or pregnancy (Section 9.5) may require longer follow-up.

The reason for discontinuation of study treatment must be recorded in the eCRF and source documentation.

5.3.3 Lost to Follow-up

Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. A minimum of 3 documented contact efforts 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. If contact with the patient is not established after all above attempts, this patient will be considered as lost to follow-up.

5.3.4 Replacements

Patients will not be replaced in this study.

6 INVESTIGATIONAL DRUG

6.1 Method of Assigning Patients to Investigational Drug

Patients who qualify according to all of the inclusion and exclusion criteria will be enrolled into the study. Patients will be assigned to dose groups according to Section 2.1.

6.2 Dose and Investigational Drug Administration

6.2.1 Identity of Investigational Drug

6.2.1.1 WVE-120101

WVE-120101 will be provided as a lyophilized powder in a clear glass vial with a Teflon™ lined rubber stopper, aluminum overseal and plastic flip-off cap. Each vial contains 8 mg of WVE-120101.

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 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): To be assigned

6.2.2 Administration of Investigational Drug

Investigational drug (WVE-120101) will be administered every 4 weeks for up to 97 weeks. The route of administration will be IT by direct lumbar injection, and the total volume of the injection will be 10 mL. WVE-120101 should be reconstituted and diluted with 0.9% sodium chloride prior to injection in accordance with instructions in the pharmacy manual.

The lumbar puncture will be performed by an appropriately trained individual. Up to 1 week prior to the lumbar puncture, a blood sample will be tested locally for platelet count and prothrombin time (PT) to confirm that it is safe to proceed with the lumbar puncture (Section 8.1.7). Patients should not be sedated during administration of study drug. The Study Operations Manual provides detailed instructions on the procedure to be used for lumbar puncture.

Within ≤15 minutes prior to administration of study drug, CSF samples will be collected for safety assessments (Section 8.1.8), drug concentrations (Section 8.2), and PD (Section 8.3) assessments, per the Schedule of Assessments (Table 1). No more than 10 mL of CSF should be collected.

Immediately after each administration of study drug, all patients should be ambulatory for approximately 30 minutes. Formal physical examinations targeting the neurological system will be performed at the time points noted in the Schedule of Assessments (Section 4.2).

6.3 Treatment Compliance

Provided that a patient attends the clinic visits, treatment noncompliance 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 Investigational Drug Packaging and Storage

WVE-120101 will be supplied by the Sponsor as a lyophilized powder in clear glass vials.

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 of according to Sponsor instructions.

Details on reconstitution and administration are provided in the Pharmacy Manual and IB.

6.4.2 Investigational 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 will also be recorded. Only trained site staff are permitted to treat study patients. A study monitor will review the accountability records onsite.

6.4.3 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.

6.4.3.1 Diluent

The diluent is 0.9% Sodium Chloride Injection sterile, preservative-free solution. It will be provided in commercially available single-use vials or plastic ampoules.

7 BLINDING AND RANDOMIZATION

This is an open-label study. If the DEC and SMC endorse multiple dosing at a dose higher than 16 mg in the Phase 1b/2a study, patients in this OLE study may be randomized to new dose levels pending Sponsor decision. The randomization scheme will be assigned by an interactive voice/web response system (IXRS), which will send notifications of the treatment assignment to the designated pharmacy personnel.

8 METHODS OF ASSESSMENT AND ENDPOINTS

8.1 Safety Assessments

- Adverse events (Section 9)
- Medical history and demographics
- Concomitant medications
- Physical examinations (including neurological and psychiatric)
- Vital signs
- Height and weight
- Electrocardiograms
- Clinical laboratory evaluations (including clinical chemistry, hematology, and urinalysis)
- Magnetic resonance imaging (Section 8.5)
- 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 (e.g., vital sign measurements, C-SSRS) that are believed to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

8.1.1 Medical History and Demographics

Any changes in medical history since the completion of the parent study (WVE-HDSNP1-001) will be obtained at the Screening visit. Investigator assessment of medical history at Screening

will include information regarding any significant medical, surgical, psychiatric, and/or neurological conditions and treatments.

The current stage of HD, treatments received, and other details about this condition will be recorded.

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

8.1.2 Prior and Concomitant Medications

Any treatments/medications taken for HD during the time between the end of the Phase 1b/2a study and the patient signing the ICF for the OLE study will be recorded in the patient's eCRF.

All concomitant medications used from the time the patient signs the OLE ICF to the end of the patient's participation in the OLE 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 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 such medication are recorded in full in the eCRF.

8.1.2.1 Restricted Concomitant Medications

Use of all antiplatelet (e.g., aspirin, prasugrel, etc.) or anticoagulant (e.g., heparin, warfarin, etc.) therapy is restricted throughout the study. Patients who take antiplatelet therapy will need to complete a 7-day washout period before undergoing intrathecal administration of the study drug. Patients who receive most anticoagulant therapies will need to complete a 1-day washout period before undergoing intrathecal administration of the study drug. However, because of the longer plasma half-life, patients taking warfarin will need to complete a 5-day washout period before undergoing intrathecal administration of the study drug.

8.1.3 Physical Examination

A physical examination will be performed at the time points noted in the Schedule of Assessments (Section 4.2).

Immediately postdose (through 4 hours postdose), 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, and 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 systems. Other systems should be evaluated as appropriate.

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

8.1.4 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 (Section 4.2) 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 signs 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.

8.1.5 Height and Weight

The patient's height and weight will be measured at the time points described in the Schedule of Assessments (Section 4.2) and recorded in the eCRF and source documents.

8.1.6 12-Lead ECG

Computerized, good quality, 12-lead ECGs will be recorded in triplicate at the time points described in the Schedule of Assessments (Section 4.2). 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 ERT® 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, with the abnormality noted.

8.1.7 Clinical Laboratory Evaluations

Clinical laboratory safety testing will be collected at the time points described in the Schedule of Assessments (Section 4.2) and recorded in the eCRF and source documents. A blood sample will be tested locally up to 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 3.

Table 3 Clinical Laboratory Parameters

Hematology	Coagulation	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 Measures of Inflammation, including: • High Sensitivity C-reactive protein • Complement	Activated partial thromboplastin time Prothrombin time Fibrinogen	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Creatine phosphokinase Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Bilirubin	Urinalysis

8.1.8 Cerebrospinal Fluid Safety Lab

A CSF safety laboratory sample obtained at the times noted on the Schedule of Assessments (Section 4.2) 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).

8.1.9 Suicidality Assessment (Columbia-Suicide Severity Rating Scale)

The C-SSRS is a measure of suicidal ideations and suicidal behaviors20. The C-SSRS is provided in Appendix 1. The 'since last visit' form, will be performed at all time points noted in the Schedule of Assessments (Section 4.2). 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.

8.1.10 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 (Section 4.2). The serum pregnancy test will be determined by a central lab; urine pregnancy tests will be performed locally.

8.1.11 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 (Section 4.2). Drug screen tests will be evaluated by a central laboratory.

8.2 Pharmacokinetic Assessments

Samples for analysis of PK of WVE-120101 and WVE-120101-related metabolite excretions in plasma and urine and concentrations of WVE-120101 in CSF will be collected at the time points specified on the Schedule of Assessments (Section 4.2). The date and time of the sample collection will be recorded.

Patients who are entering the study may be requested to consent to two additional lumbar punctures (LP) to provide CSF samples at two weeks after the first dose, and two weeks after the sixth dose to allow for more robust PK/PD modeling (see Table 1 for more details). These additional CSF samples will be optional, and consent will be collected as a stand-alone question in the Informed Consent Form. If a patient has already passed the first dose, but not the sixth, and is willing to undergo the additional LP, then CSF will be collected 2 weeks after the sixth dose.

In addition to the above two CSF samples, patients at certain participating sites will undergo additional intensive PK blood and urine sampling as noted in Table 2. This sampling will include additional time points for plasma and a 24-hour urine collection.

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

8.3 Pharmacodynamic Assessments

A CSF sample will be collected at the time points noted in the Schedule of Assessments (Section 4.2) to determine the change from baseline in concentration of mHTT protein. In addition, NFL and other exploratory biomarkers in CSF, plasma, and serum may be assessed.

The study may utilize the method described in Wild et al.21 or an alternative method to determine levels of mHTT protein.

8.4 Immunogenicity Assessments

Serum samples will be collected at the times noted on the Schedule of Assessments (Section 4.2) and analyzed at a central laboratory for measurement of anti-drug antibodies to WVE-120101.

8.5 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 (Section 4.2). Sedation is permitted during the MRI. All other eligibility should be confirmed prior to the MRI scheduled at the Screening visit.

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 MRI 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.

8.6 Assessment of Clinical Effects

8.6.1 Unified Huntington's Disease Rating Scale

The Unified Huntington's Disease Rating Scale (UHDRS) is a research tool developed by the Huntington Study Group to provide a uniform assessment of the clinical features and course of HD22. 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 2. In addition, analyses will be performed using the composite UHDRS (cUHDRS), which is based on 4 of the UHDRS components, namely the TFC, Symbol Digit Modalities Test (SDMT), Stroop Interference test, and the total motor impairment score23. All subtests of the UHDRS should be performed except the behavioral assessment, as the PBA-s (Section 8.6.2) 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, 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. 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 higher 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 (e.g., eating, dressing, bathing), and level of care.

8.6.2 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)24, and is contained in Appendix 3.

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.

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.

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 event information will be collected beginning at enrollment (date of signed informed consent) and up to the end of the study. All ongoing AEs at the end of the study will be followed to resolution, or until the Investigator and the Sponsor agree that further follow-up is not required.

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 Screening 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 severity or frequency after exposure to study treatment.

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 way. 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 with completion guidelines for the eCRF, which will further guide them on how to record the data, including AEs.

Any medical condition that is present at the time 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, it should

be recorded as an AE. This includes any spontaneously reported worsening of depression, i.e., not based on the study rating scales.

In addition to observations of the patient, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are considered clinically significant will be documented on the AE page in the eCRF. Worsening of symptoms that are only detected on clinical effects rating scales will not be reported as AEs.

Adverse events will be assessed at each visit by direct questioning as well as elicited from physical 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.

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 criteria described in Table 4.

Table 4 Definitions of AE Severity

AE Severity	Definition
Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Moderate; minimal, local or noninvasive intervention indicated.
Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.

Abbreviations: AE = adverse event.

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 severity.

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. All AEs, regardless of relationship, will be recorded in the eCRF. In addition, SAEs will be reported to regulatory authorities as required by local regulation (Section 9.3.4).

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 5.

Table 5 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, i.e., 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.

Abbreviation: 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. A life-threatening event does not include an AE that, had it occurred in a more severe form, might have caused death.

Serious AEs must be reported (Section 9.3.4) and will be followed through the follow-up visit. Serious AEs that occur after the final follow-up visit need not be reported unless the Investigator considers them related to study drug.

The Sponsor clinical physician will provide a Sponsor causality statement for all SAEs.

9.3.2 Suspected, Unexpected, Serious Adverse Reaction

A suspected, unexpected, serious adverse reaction (SUSAR) is an SAE for which there is a reasonable possibility that the drug caused the event, and this SAE has not been previously identified as an expected/listed adverse event. A list of expected AEs (if applicable) is provided in the current version of the IB and is considered the Reference Safety Information (RSI) for the study. Generally, the indication for which a product is intended would not be on the list of expected adverse events, but if it did occur, would not be considered "unexpected" for SUSAR reporting. As an example, a flare-up of neurological symptoms consistent with the underlying disease under treatment that required hospitalization would constitute an SAE; however, the event would not be considered unexpected. An exception would be if the reporter believed that investigational drug worsened the underlying neurological condition.

9.3.3 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 Investigator until resolution. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

9.3.4 Serious Adverse Event Reporting

9.3.4.1 Reporting Requirements

Any AE that meets SAE criteria (Section 9.3.1) must be reported to the Sponsor and/or designee immediately (i.e., within 24 hours) after the time site personnel first learn about the event using the SAE Report Form provided for the study. Regardless of causality, all SAEs must be reported and will be collected and recorded from the time the patient signs the ICF until completion of the final follow-up visit. All SAEs must also be recorded in the patient's source documentation and on the AE page of the patient's eCRF.

The initial report should include at least the following information:

- Study Number
- Patient's identification number
- Description of the event
- Date and time of onset of the event
- Seriousness criteria
- Causality assessment to study drug

If follow-up is obtained, or requested by the Sponsor and/or designee, the additional information should be emailed on an SAE Report Form to the Sponsor and/or designee in a timely manner according to the procedures outlined above. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

The Investigator will be responsible for reporting all SAEs to the Institutional Review Board (IRB) or Ethics Committee (EC). The Sponsor will be responsible for reporting to the regulatory authorities and Central Ethics Committees, as per local requirements.

9.3.4.2 SAE Contact Information

Serious adverse event contact information is provided below:

[redacted]

9.4 Overdose

Study drug is 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 drug.

9.5 Pregnancies

If a patient or the partner of a patient becomes pregnant during the course of the study, the pregnancy must be reported and monitoring of the mother and fetus should be conducted until the pregnancy outcome.

If a female patient becomes pregnant during the study, she must be discontinued from study drug; although 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.

Any pregnancy (the patient or partner of a patient) should be followed until the outcome of the pregnancy is known.

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

Based on the expected date of delivery, the Sponsor will attempt follow-up to determine the outcome of the pregnancy.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

No sample size calculations were performed. As this is an OLE, the maximum sample size is fixed by the number of patients completing the WVE-HDSNP1-001 study.

10.2 Disposition of Patients

Screened patients are defined as any patient who signed informed consent.

Enrolled patients consist of all screened patients who meet all eligibility criteria.

10.3 Analysis Populations

The safety population will include all enrolled patients who have received at least one dose of study medication in the OLE. The safety population will be the analysis set used for summaries of safety and clinical effects.

The per-protocol population will be a subset of the safety population and include patients with no major protocol deviations that will interfere with the assessment of the clinical effects' endpoints and with at least 80% compliance to the dosing regimen.

The PK population will consist of all patients in the safety population with at least one post-dose plasma or CSF concentration measurement.

10.4 Statistical Methods

Analysis will include summaries of data collected in this OLE study as well as integrated OLE data and repeat dosing data collected in WVE-HDSNP1-001.

10.4.1 Study Drug Exposure and Compliance

The extent of study drug exposure and compliance will be summarized by dose group for the safety population.

10.4.2 Analysis of Safety Data

The summary of safety results will be presented by dose group. All safety analyses will be performed on the safety population using the following common rules:

- The OLE baseline value is defined generally as the last available value from WVE-HDSNP1-001 before first dose in WVE-HDSNP1-002.
- The repeat dosing baseline value is defined generally as the last available value before initiation of repeat dosing. Initiation of repeat dosing can occur in either WVE-HDSNP1-001 or WVE-HDSNP1-002.
- Adverse event observation periods are defined as follows:
    - Pre-OLE treatment AEs are AEs that developed or worsened between the date of signed informed consent for the OLE and the date of first dose of study drug in the OLE.
    - OLE on-treatment adverse events are AEs that developed or worsened from the first dose of study drug in the OLE to study completion/discontinuation. Summaries of TEAEs will include all OLE on-treatment AEs.
    - Repeat dosing on-treatment adverse events are AEs that developed or worsened from the first dose of repeat dosing to study completion/discontinuation. Initiation of repeat dosing can occur in either WVE-HDSNP1-001 or WVE-HDSNP1-002. Summaries of repeat dosing TEAEs will include all repeat dosing on-treatment AEs.
- For quantitative safety parameters based on central laboratory/reading measurement descriptive statistics will be used to summarize results and change from baseline values by visit and dose group.

Adverse Events

Treatment-emergent AEs, treatment-emergent SAEs, and TEAEs leading to treatment discontinuation will be summarized by dose group based on Medical Dictionary for Regulatory Activities (MedDRA) coding of verbatim terms reported by investigators.

Adverse event incidence tables will present, by system organ class (SOC) and preferred term, the number and percentage of patients experiencing an AE. Multiple occurrences of the same event will be counted once in the tables. The denominator for computation of percentages is the safety population within each dose group.

Adverse event incidence tables will present, by SOC and preferred term, the number and percentage of patients experiencing an AE by severity and by relationship to treatment. In tabulating the severity of adverse events, the highest severity will be assigned to a subject with more than one occurrence of the same adverse event. The highest level of association will be reported in subjects with differing relationships for the same adverse event.

Similar tables will be generated summarizing repeat dosing TEAEs. Listings of all AEs, SAEs, deaths, and AEs leading to study discontinuation will be provided.

Clinical Laboratory Evaluations

Summary statistics of laboratory variables including CSF safety laboratory variables will be calculated for each visit or study assessment by dose group. Laboratory data will also be categorized as low, normal, or high based on the reference ranges of the central laboratory. Frequencies and percentages will be presented by dose group for the shifts in these categories from baseline to post-baseline assessment time points. A listing of clinically significant hematology and chemistry findings will be provided.

Other Safety Evaluations

Summary statistics of vital signs, ECG, and height and weight variables will be calculated for each visit or study assessment by dose group.

Columbia-Suicide Severity Rating Scale

Listings of patients who respond “yes” to item 4 or 5 on the C-SSRS at any point in the study will be provided.

Immunogenicity

Anti-drug antibody assay results to WVE-120101 will be described categorically. Summary statistics for anti-drug antibody titer results will be provided.

10.4.3 Pharmacokinetic Analyses

The plasma, urine, and CSF WVE-120101 concentration as well as WVE-120101-related metabolite data will be summarized for patients in the PK population.

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

For each dose group, the plasma and urine WVE-120101 concentration data will be analyzed by noncompartmental PK analysis. The parameters listed in Table 6 will be determined. Additional PK parameters may be evaluated if deemed appropriate. Pharmacokinetic parameters for each dose group will be summarized for each WVE-120101 dose level.

The CSF concentration data will be summarized in tabular format.

Table 6 Pharmacokinetic Parameters of WVE-120101 after Multiple Dose Administration

Parameter	Definition
C_{max}	Maximum observed concentration
t_{max}	Time of occurrence of C_{max}
$AUC_{0-\tau}$	Area under the plasma concentration-time curve over the dosing interval
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the last measurable concentration.

10.4.4 Clinical Effects and Pharmacodynamic Analyses

The change from baseline for clinical effects and PD endpoints will be summarized using a mixed model for repeated measures (MMRM) with the safety population. The MMRM will include the relevant baseline measure, time, dose-group and time by dose-group interactions. The MMRM will be used to construct 95% confidence intervals and to test if the change is statistically significant. Summaries will be based on data collected during the OLE and, separately, OLE data integrated with repeat dosing data from WVE-HDSNP1-001.

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 Code of Federal Regulations (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. Due to the natural progression of the disease, patients may lose the ability to understand the ICF after providing original consent. As a result, patients should identify a potential legally authorized representative at Screening.

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 or their legally authorized representatives must sign the revised form.

Before Screening, each prospective patient will be given a full explanation of the study and be allowed to read the approved 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 the study by signing the appropriate ICF.

In addition to signing the approved ICF, patients will be asked to sign a supplementary consent form to specify whether or not they agree to allow their leftover samples to be stored and used for future medical or pharmaceutical research regarding Huntington's disease.

The Investigator will retain the signed original ICF(s) and give a copy of the signed original form(s) to the patient and/or their legally authorized representative.

11.5 Specimen Management and Storage

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 15 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 study-specific manual.

12 INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study in accordance with GCP guidances. These items 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 United States Code of Federal Regulation by providing the following essential documents, including but not limited to:

- IRB/EC approval
- A fully executed Clinical Study Agreement
- 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 study registers in accordance with all national, state, and local laws or regulations.

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

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 their 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 13.3) to oversee any publication or presentation of the study results.

Subsequently, individual Investigators may publish results from the study in compliance with their agreements with the Sponsor. A pre-publication manuscript is to be provided to the Sponsor at least 45 days prior to the submission of the manuscript to 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 aggregate safety data periodically and on an ad hoc basis should any emergent safety concerns arise. Safety data will be reviewed in aggregate while the WVE-HDSNP1-001 study is ongoing. The SMC will cease to review data from this study once the WVE-HDSNP1-001 study is complete.

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

13.2 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.

13.3 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.

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 (e.g., 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 (i.e., 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.

14.2 Data Quality Assurance

14.2.1 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 in accordance with the data completion guidelines. 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 his or her formal approval of all the information on the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she 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.

14.2.2 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 to the Sponsor any audit reports received.

14.3 Management of Protocol Amendments and Deviations

14.3.1 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.

14.3.2 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. A major protocol deviation is any deviation that impacts the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

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 in the clinical study management system and on monitoring reports 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.

14.4 Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor may terminate the study, or close an individual study site. Reasons for terminating a study or closing a site may include, but are not limited to, the following:

1. The research can no longer meet its stated scientific purpose, and this assessment has been confirmed by the medical ethical review committee;

2. Severe non-compliance to this protocol as judged by the investigator and/or the Sponsor;

3. Unforeseen circumstances that prevent continuation of the research (e.g., financial issue).

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.

14.5 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 CSRs.

In accordance with local 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 study registers.

15 REFERENCES

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