CLINICAL PROTOCOL

A PHASE 2A, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RANGING STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PTC518 IN SUBJECTS WITH HUNTINGTON'S DISEASE

PTC518-CNS-002-HD

05 OCTOBER 2023

VERSION 6.0

PTC THERAPEUTICS, INC.
100 CORPORATE COURT
SOUTH PLAINFIELD, NJ 07080 US

PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

PTC Therapeutics Substance Identifier	PTC518
EudraCT Number	2021-003852-18
Protocol Number	PTC518-CNS-002-HD
Protocol Version	6.0
Protocol Version Date	05 October 2023
Protocol Phase	Phase 2a
Protocol Title	A Phase 2a, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of PTC518 in Subjects With Huntington's Disease
PTC Clinical Lead	[redacted]
PTC Medical Monitor	
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PTC THERAPEUTICS PROTOCOL APPROVAL SIGNATURES

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PTC Therapeutics, Inc.

Date

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Date

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Date

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PTC Therapeutics, Inc.

Date

The eSignature page is located on the last page.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for PTC518. I have read the PTC518-CNS-002-HD Protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SYNOPSIS

Name of Sponsor/Company: PTC Therapeutics, Inc.		
Name of Investigational Product: PTC518		
Name of Active Ingredient: PTC518		
Protocol Number: PTC518-CNS-002-HD	**Phase:** 2a	**Country:** Global
Title of Study: A Phase 2a, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety and Efficacy of PTC518 in Subjects With Huntington's Disease		
Studied Period: 12 months of treatment and 6 months of follow-up		

Objectives:

Primary Objectives:

- Evaluate the safety of PTC518 compared with placebo in subjects with Huntington's disease (HD)
- Evaluate the pharmacodynamic (PD) effects of PTC518 through the reduction in blood total huntingtin (tHTT) protein levels

Secondary Objectives:

- Assess the effects of PTC518 on change in caudate volume via volumetric magnetic resonance imaging (vMRI) (key secondary)
- Assess the effects of PTC518 on change in composite Unified Huntington's Disease Rating Scale (cUHDRS)
- Determine the effect of PTC518 on mutant huntingtin (mHTT) protein in cerebrospinal fluid (CSF) at Month 12
- Determine the effect of PTC518 on blood mHTT levels at Month 12

Exploratory Objectives:

- Determine the effect of PTC518 on mHTT protein in CSF at Month 3
- Determine the effect of PTC518 on blood mHTT levels at Month 3
- Assess the effect of PTC518 on change in whole brain, and putamen volume via vMRI
- Assess the effect of PTC518 on change in ventricular volume via vMRI
- Assess change after 12 months of treatment in clinical scales
- Determine the effect of PTC518 on huntingtin (*HTT*) mRNA in blood

Pharmacokinetic Objective:

- Evaluate the concentration of PTC518 in subjects with HD

Endpoints:

Safety Endpoints:

- Safety profile as characterized by treatment-emergent adverse events (TEAEs), laboratory abnormalities, neurofilament light chain (NfL) levels in plasma and CSF, electrocardiogram (ECG), vital signs, [redacted], Columbia Suicide Severity Rating Scale (C-SSRS), and physical examination

Primary Efficacy Endpoint:

- Change from Baseline in blood tHTT protein at Month 3

Secondary Endpoints:

- Change from Baseline in caudate volume as assessed via vMRI at Month 12 (key secondary)
- Change from Baseline in cUHDRS scores at Month 12
- Change from Baseline in blood tHTT protein at Month 12
- Change from Baseline in CSF mHTT protein at Month 12
- Change from Baseline in blood mHTT protein at Month 12

Exploratory Endpoints:

- Change from Baseline in CSF mHTT protein at Month 3
- Change from Baseline in blood mHTT protein at Month 3
- Change from Baseline in whole brain, putamen, and ventricular volume (as assessed by vMRI) at Month 12
- Change from Baseline in Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) sub-score at Month 12
- Change from Baseline in other UHDRS sub-scores including Total Motor Score (TMS), Symbol Digit Modalities Test (SDMT), and Independence Scale (IS) at Month 12
- Change from Baseline in the short form of the Problem Behaviors Assessment (PBA-s) (substituting for the UHDRS Behavioral Examination) at Month 12
- Change from Baseline in wearable accelerometer assessment Timed Up and Go (TUG), 2-minute walk distance, and postural sway at Month 12
- Change from Baseline in the Functional Rating Scale (FuRST) 2.0 questionnaire at Month 12
- Change over time in blood *HTT* mRNA
- Change over time in plasma and CSF NfL

[redacted]

Pharmacokinetic Endpoint

- Plasma trough concentration (C_{trough}) and accumulation ratio of PTC518 in plasma over time and accumulation ratio of PTC518 in CSF at Visits 5 through 8

Study Design/Methodology:

This is a Phase 2a randomized, placebo-controlled, dose-ranging study to evaluate the safety and efficacy of PTC518. The study will be composed of 2 groups (Stage 2 group and Mild Stage 3 group), further broken into 6 parts (Parts A, B, C, D, E, and F), each of which will consist of an active treatment arm and a placebo arm. The Stage 2 group will consist of Parts A, B, and C, and will include subjects who qualify as Stage 2 disease based on the Huntington's disease Integrated Staging System (HD-ISS) criteria. The Mild Stage 3 group will consist of Parts D, E, and F, and will include subjects who qualify as Mild Stage 3 disease based on the HD-ISS criteria.

Approximately 144 subjects who satisfy all enrollment criteria at Screening will undergo Baseline evaluations and be randomized to Parts A, B, D, or E (depending on their stage of disease, as described above), after which they will be randomized to treatment arms within Part A or D (5 mg or matching placebo) or Part B or E (10 mg or matching placebo) in a 2:1 ratio (active treatment to matching placebo) for 12 months. A Data and Safety Monitoring Board (DSMB) will closely monitor the safety of subjects. As specified in the DSMB Charter, the DSMB will undertake an unblinded review of safety data from the 5 and 10 mg dosing

groups and provide a recommendation on when Parts C and F (20 mg or matching placebo) can be initiated.

At that time, subjects will be randomized to any study Part that is currently open for enrollment (depending on their stage of disease) and then to either active treatment or placebo (in a 2:1 ratio) within that Part.

Subjects will return to the clinic every month until Visit 5 (Month 3) and then quarterly until Visit 8 (Month 12). Upon completion of Visit 8 (Month 12), subjects will have the option to enroll in Study PTC518-CNS-004-HD, a Phase 2 long-term extension study, to receive PTC518.

For subjects not enrolling in Study PTC518-CNS-004-HD, Visit 8 will be considered the End of Treatment visit, and there will be a Follow-Up Safety Visit (Month 13) via telephone/telehealth to collect adverse event data and an additional Follow-Up Safety Visit on Month 16 (ie, approximately 4 months after the last dose of study drug) to collect adverse events [redacted]. A final Follow-Up Safety Visit will occur on Month 18 via telephone/telehealth to collect adverse event data.

Sample Size Justification:
The sample size calculation for each disease stage is based on mean change from Baseline in blood tHTT protein at Month 3 (primary endpoint) assuming PTC518 has the same effect on blood tHTT protein reduction. With an effect size of 0.85 (ie, the magnitude of treatment difference is 85% of one standard deviation), achievement of 85% power at 2-sided alpha level 0.05 would require 24 subjects. Approximately 24 subjects will be randomized to each active treatment arm and approximately 36 additional subjects per disease stage will be randomized to placebo. An additional 18 subjects (per disease stage) may be randomized to the maximum tolerated dose.

Number of Subjects (Planned):
Up to 252 adult male and female subjects (126 per disease stage) will be enrolled.

Diagnosis and Main Criteria for Inclusion:
Individuals eligible to participate in this study include those who meet all of the following inclusion criteria:

1. Ambulatory male or female patient aged 25 years and older, inclusive
2. Subject is willing and able to provide informed consent and comply with all protocol requirements.
3. Genetically confirmed HD diagnosis with a cytosine-adenine-guanine (CAG) repeat length from 40 to 50, inclusive. CAG repeat length may be determined analytically through amplification.

Eligibility for HD-ISS Stage 2 Group (Parts A, B, and C)	**Eligibility for HD-ISS Mild Stage 3 Group (Parts D, E, and F)**
4. A UHDRS IS score of 100 5. A UHDRS TFC score of 13 6. A score between 0.18 and 4.93 inclusive on the normed version of the HD prognostic index (PIN_{HD})	9. A UHDRS TFC score of 11 or 12, or a UHDRS TFC score of 13 with an UHDRS IS score of <100

7. Women of childbearing potential (WOCBP) must agree to use highly effective methods of contraception during dosing and for 6 months after stopping the study medication. Women of childbearing potential are defined as women who are fertile,

following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
Female partners of enrolled males who are of childbearing potential should consider use of highly effective methods of contraception while the enrolled male is taking study drug and for 6 months after stopping study drug.
Highly effective contraception methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly and include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

In case of use of oral contraception, WOCBP should have been stable on the same pill for a minimum of 3 months prior to Screening.
Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

8. Sexually active and fertile males must use a condom during intercourse while taking study drug and for 6 months after stopping study drug and should neither father a child nor donate sperm in this period. A condom is required to be used also by vasectomized men in order to prevent potential delivery of the drug via seminal fluid.

Main Criteria for Exclusion:

Individuals are not eligible to participate in this study if they have met or meet any of the following exclusion criteria:

1. Inability or unwillingness to swallow oral tablets
2. Receipt of an experimental agent within 90 days or 5 half-lives prior to Screening or anytime over the duration of this study, including RNA- or DNA-targeted HD-specific investigational agents (such as antisense oligonucleotides), cell transplantation, or any other experimental brain surgery
3. Any history of gene therapy exposure for the treatment of HD
4. Participation in an investigational study or investigational paradigm (such as exercise/physical activity, cognitive therapy, brain stimulation, etc) within 90 days prior to Screening or anytime over the duration of this study. Observational studies (such as ENROLL-HD) are not exclusionary.
5. Presence of an implanted deep brain stimulation device
6. [redacted]
7. Brain and spinal pathology that may interfere with CSF homeostasis and circulation, increased intracranial pressure (including presence of a shunt for the drainage of CSF or an implanted central nervous system catheter), malformations, and/or tumors
8. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
9. At significant risk of suicide as measured by the C-SSRS Baseline version with a moderate risk rating or higher score
10. Risk of a major depressive episode, psychosis, confusional state, or violent behavior as assessed by the investigator
11. Any medical history of brain or spinal disease that would interfere with the lumbar puncture process or safety assessments
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
13. Any medical history or condition that would interfere with the ability to complete the protocol-specified assessments (eg, implanted shunt, conditions precluding magnetic resonance imaging scans)
14. Antidepressant, antipsychotic, or benzodiazepine use, unless receiving a stable dose for at least 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study. Benzodiazepine use for sedation for study-related procedures during the course of the study is permitted.
15. History of illicit/illegal drug use, or alcohol use in the high-risk category of risk drinking levels according to the World Health Organization for a duration of 1 month or longer that in the opinion of the investigator could compromise the interpretability of study results
16. Clinically significant medical condition, which in the opinion of the investigator could adversely affect the safety of the subject or impair the assessment of study results (eg, inability to fast or any known hypersensitivity to PTC518 or its excipients)

17. Current significant renal impairment defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 at Screening
18. Current hepatic impairment resulting in elevated liver function test (aspartate transaminase, alanine transaminase, alanine phosphatase) at 3 times the upper limit of normal at Screening
19. Pregnancy, planning on becoming pregnant during the course of the study or within 6 months of end of treatment, or currently breastfeeding
20. Use of medications that are moderate or strong inhibitors of cytochrome P450 (CYP) 3A4 within 1 week of Screening or medications that are moderate or strong inducers of CYP3A4 within 2 weeks of Screening or planned use of moderate or strong CYP3A4 inhibitor or inducer medications during the study period
21. A diagnosis of Juvenile-Onset Huntington's Disease

Investigational Product, Dosage and Mode of Administration:
PTC518 tablets will be administered orally QD. The PTC518 active dosing arms will be 5 mg and 10 mg until the DSMB recommends initiation of a 20 mg dose as specified in the DSMB Charter.

Duration of Treatment: 12 months

Reference Therapy, Dosage and Mode of Administration:
Matching placebo tablets will be administered orally QD.

Criteria for Evaluation:
Safety:
Safety assessments will include observed TEAEs, clinical laboratory tests (including assessment of plasma and CSF NfL), vital signs, ECG, C-SSRS, [redacted], [redacted], and physical examination
Efficacy:
Blood tHTT protein (primary), vMRI (caudate volume; key secondary), cUHDRS (secondary), CSF mHTT protein (secondary), blood mHTT protein (secondary)
Exploratory:
CSF mHTT protein, blood mHTT protein, vMRI (whole brain, putamen, and ventricular volume), UHDRS (except behavioral), PBA-s, Opal wearable device, FuRST 2.0, blood *HTT* mRNA, plasma and CSF NfL, [redacted]
Pharmacokinetics:
Pharmacokinetic assessment will include plasma C_{trough} (Visits 3 through 8). Accumulation ratio will be calculated and reported in plasma (Visits 3 through 8) and CSF (Visits 5 through 8).

Statistical Methods:
A repeated measure analysis model (repeat on visit) will be used to compare each dose with placebo for blood tHTT protein levels. The model will include treatment, visit, treatment by-visit interaction and baseline blood tHTT, CAG, age, and CAG by age interaction as covariates. Nominal p values and 95% confidence interval for each pairwise comparison at Month 3 (active versus placebo) will be provided. The model will include disease stage (by PIN_{HD} bin for Stage 2 only and by TFC score for Mild Stage 3 only) as a stratification factor. The key secondary endpoint (change from baseline in caudate volume at Month 12) will be analyzed by a mixed model repeated measures (MMRM) model, using all available vMRI data up to the Month 12 Visit. The model will include fixed effects for treatment, baseline vMRI, and disease stage (by PIN_{HD} bin for Stage 2 only and by TFC for Mild Stage 3 only). The

intercept and time of collection will be included as a random effect nested withing subjects. The unstructured covariance matrix will be used in the model. The rate of changes will be compared between treatments and the least squares (LS) mean differences at Month 12 will also be provided. A similar model will be used for whole brain, putamen, and ventricular volume.

For change from baseline in cUHDRS, a MMRM analysis (repeat at visit) will be performed using all data collected up to 12 months. The model will use treatment group, visits (categorical), treatment by-visit interaction, disease stage as fixed factors, age, CAG, and age by CAG interaction as covariates. The LS mean estimates for the change from Month 12, the difference between pairwise comparison with placebo, confidence intervals, and 2-sided p values will be presented. A similar model will be used for UHDRS sub-scores and PBA-s. Rate of changes in these scores will also be explored.

For by disease stage analyses, PIN_{HD} category (0.180 to 0.679, 0.680 to 1.520, or 1.521 to 4.930) will be used as fixed factor for Stage 2 only, and TFC score (11, 12, or 13) will be used as fixed factors for Mild Stage 3 only.

The same analysis used for blood tHTT protein will be used for blood and CSF mHTT protein. Dose-response relationships will be explored.

Demographic and baseline characteristics, disposition, safety, and efficacy endpoints will be summarized descriptively by dose group. Statistical models will be applied to understand the relationship between UHDRS components to blood and CSF assessments.

Endpoints will be evaluated primarily with both disease stages combined, and by each disease stage.

PTC Therapeutics (PTC) plans to conduct an interim analysis to confirm the pharmacokinetic (PK) and PD expectations and to evaluate safety when approximately 36 subjects from the 5 mg dosing group (Parts A and/or D), and 36 subjects from the 10 mg dosing group (Parts B and/or E), including placebo, have completed 12 weeks of treatment.

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[redacted]

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event(s) of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC_{0-24}	Area under the concentration-time curve from 0 to 24 hours
BAC	Bacterial artificial chromosome (transgenic mouse model of Huntington's disease)
BSI	Boundary Shift Integral
CAG	Cytosine-adenine-guanine
CAP	Cytosine-adenine-guanine-Age Product
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Plasma trough concentration
cUHDRS	Composite Unified Huntington's Disease Rating Scale
CYP	Cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
EOS	End of study
EOT	End of treatment
ET	Early Termination
FSH	Follicle-stimulating hormone
FuRST	Functional Rating Scale
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HCG	Human chorionic gonadotropin
HD	Huntington's disease
HD-ISS	Huntington's disease Integrated Staging System
HDL	High-density lipoprotein
HTT	Huntingtin (protein)
HTT	Huntingtin (gene)
ICF	Informed consent form
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	Independence Scale
ITT	Intent-to-Treat
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LS	Least squares
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mHTT	Mutant huntingtin
MMRM	Mixed model repeated measures

Abbreviation or Specialist Term	Explanation
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NfL	Neurofilament light chain
NHP	Nonhuman primate
PBA-s	Problem Behaviors Assessment (short form)
PD	Pharmacodynamic
PI_{HD}	Huntington's disease prognostic index
PIN_{HD}	Normed version of the Huntington's disease prognostic index
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Prothrombin time
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDMT	Symbol Digit Modalities Test
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TFC	Total Functional Capacity
tHTT	Total huntingtin
TMS	Total Motor Score
[redacted]	[redacted]
TUG	Timed Up and Go
UHDRS	Unified Huntington's Disease Rating Scale
US	United States
vMRI	Volumetric magnetic resonance imaging
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

Huntington's disease (HD) is a rare, autosomal dominant, progressive, neurodegenerative disorder characterized by motor, cognitive, and psychiatric symptoms. Late-stage disease is marked by severe inability to walk, speak, swallow, or care for oneself, culminating in the need for full-time care and ultimately death, typically 15 to 18 years after the onset of symptoms (Caron 2020a).

Huntington's disease is a polyglutamine or "polyQ" disease caused by an expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat near the N terminus of the huntingtin (*HTT)* gene. This expansion leads to production of mutant huntingtin (mHTT) protein containing a polymorphic polyglutamine tract. The primary mechanism of HD pathogenesis is believed to be a toxic gain-of-function of mHTT, which leads to progressive neurodegeneration (Li 2006, Caron 2020a). In several nonclinical models of HD, reduction of mHTT improves HD neuropathology (Yamamoto 2000, Wang 2014, Evers 2018, Miniarikova 2018, Caron 2020b), thus confirming the importance of mHTT lowering as a therapeutic target in HD. Decreases in mHTT of between [redacted] are targeted for optimal therapeutic benefit, though decreases of [redacted] have been associated with potential therapeutic benefit (Garriga-Canut 2012, Kordasiewicz 2012, Lu 2013, Stanek 2014, Tabrizi 2019).

The Huntington's disease Integrated Staging System (HD-ISS) has been developed to help define cases of HD and provide a 4-part staging system that encompasses the full progression of the disease (Tabrizi 2022). The criteria for staging within this paradigm are as follows:

- Stage 0: ≥40 CAG repeats
- Stage 1: Features of Stage 0 with biomarkers of pathogenesis
- Stage 2: Features of Stage 1 with clinical signs or symptoms
- Stage 3: Features of Stage 2 disease with functional change. Stage 3 is further broken down by Mild, Moderate, and Severe.
  - Mild: Individuals who do not require assistance with routine activities, though these activities might be difficult to perform or take a long time.
  - Moderate: Individuals who require assistance with some routine activities.
  - Severe: Individuals who cannot do any routine activities independently.

This study intends to enroll subjects who qualify as either Stage 2 or Mild Stage 3 disease.

PTC518 is an orally bioavailable, proprietary small molecule being developed by PTC Therapeutics (PTC) for the treatment of HD. PTC518 modulates splicing of the *HTT* pre-mRNA, resulting in the inclusion of a pseudo exon (from within an intron) with premature termination codon that leads to the degradation of *HTT* mRNA and subsequent reduction in HTT protein levels.

PTC518 thus represents a promising therapeutic for the treatment of HD.

1.1. Study Rationale

Prior to the development of this Phase 2a study, PTC518 was extensively evaluated in in vivo and in vitro nonclinical pharmacology models, in a comprehensive toxicology program, and in

Study PTC518-CNS-001-HD (Study CNS-001), a Phase 1 study in healthy volunteers. Together, the resulting data validate that PTC518 treatment results in dose-dependent pre-mRNA splicing and reduced protein levels, and that PTC518 treatment is safe and well tolerated in the clinic at single doses as high as [redacted] mg and multiple doses as high as [redacted] mg for 21 days.

The present 12-month double-blind study with a 6-month Safety Follow-Up will allow for the quantification of the effect of PTC518 on total huntingtin protein (tHTT) reduction in subjects with HD and evaluation of the safety of PTC518 over 12 months of treatment. To mitigate potential risks to subjects, Part C, which includes the 20 mg dose, will not be initiated without Data and Safety Monitoring Board (DSMB) recommendation.

The time course in untreated patients for HTT protein, mRNA, and other indicators of drug response in the blood is not available. The use of a concurrent placebo control allows for a direct assessment comparison to determine the effect of active treatment. In a disease state that does not have an approved disease modifying treatment option, such as HD, the inclusion of a placebo arm does not pose any ethical concerns.

The patient population for this study was selected to reduce variability in an otherwise heterogeneous disease population by identifying subjects with active disease who either have not yet experienced functional decline (Stage 2) or have very limited features of functional decline (Mild Stage 3). This patient population was also selected as the population of subjects most likely to benefit from stabilization of disease from treatment with PTC518, being those with only limited functional decline due to disease progression.

In this study, at randomization, subjects will thus be enrolled in the study based upon CAG repeat length and Baseline measures of the Symbol Digit Modalities Test (SDMT), Total Motor Score (TMS), Independence Scale (IS), and Total Functional Capacity (TFC). These factors will be used to identify and enroll subjects with active disease who have not yet experienced functional decline (Stage 2) or who have only very limited features of functional decline (Mild Stage 3), which may indicate a disease progression amenable to intervention.

The Huntington's disease prognostic index (PI_{HD}) or its normed version (PIN_{HD}) score can be used to predict likelihood of HD progression. The PIN_{HD} score will be calculated at Screening to identify subjects eligible for participation in the Stage 2 group in the study, as it predicts progression into Stage 3. The Unified Huntington's Disease Rating Scale (UHDRS) TFC and IS scores will also be calculated at Screening to identify subjects eligible for participation in the Stage 2 or Mild Stage 3 group in the study.

Based on the kinetics of PTC518-mediated HTT lowering in humans, it is expected that the maximal extent of tHTT protein lowering in blood from patients with HD could be achieved between 4 and 6 weeks. The 12-month dosing regimen can further demonstrate that a steady-state decrease in blood tHTT levels is maintained over time with continued PTC518 treatment.

In addition to the primary endpoints of tHTT protein change from Baseline and safety, the present study includes exploratory clinical outcome endpoints to assess the effect of PTC518 on subjects' cognition and motor function as measured by the UHDRS. The UHDRS has been extensively studied and developed to assess disease progression in multiple domains. The short form of the Problem Behaviors Assessments (PBA-s) has been included for assessment of disease progression in the behavioral domain. Cognitive impairment, motor function loss, and

accelerated brain volume loss in the caudate and putamen are key features of this disorder and have a notable impact on quality of life. The assessment of more sensitive and early motor changes via Opal wearable devices will also be included in this study as an exploratory endpoint. Studying these endpoints over 12 months will provide insight into the rate of change in earlier stages of disease and identify key measurements that may be early indicators of HD progression.

1.2. Overall Study Design

This is a Phase 2a randomized, placebo-controlled, dose-ranging study to evaluate the safety and efficacy of PTC518 and to determine the HTT protein lowering effect of these doses after 12 months of treatment in subjects with HD. The study will be composed of 2 groups (Stage 2 group and Mild Stage 3 group), further broken into 6 parts (Parts A, B, C, D, E, and F) each of which will consist of an active treatment arm and a placebo arm. The Stage 2 group will consist of Parts A, B, and C and will include subjects who qualify as Stage 2 disease based on the HD-ISS criteria. The Mild Stage 3 group will consist of Parts D, E, and F and will include subjects who qualify as Mild Stage 3 disease based on the HD-ISS criteria.

Individuals who sign an informed consent form (ICF) will enter Screening to determine eligibility for the study. At Screening, potential subjects will have their gene mutation status confirmed by the investigator (either via historical gene sequencing or through an in-study gene sequencing assessment) and undergo additional evaluation to confirm they meet the enrollment criteria.

Subjects who satisfy all enrollment criteria at Screening will undergo baseline evaluations and first be randomized to Part A, B, D, or E (depending on their stage of disease, as described above), after which they will be randomized to treatment arms within Part A or D (5 mg or matching placebo) or Part B or E (10 mg or matching placebo) in a 2:1 ratio of active treatment to matching placebo for 12 months. As specified in the DSMB Charter, the DSMB will undertake an unblinded review of safety data from the 5 and 10 mg dosing groups and provide recommendation on when Parts C and F (20 mg or matching placebo) can be initiated.

At that time, subjects will be randomized to any study Part that is currently open for enrollment (depending on their stage of disease) and then to either active treatment or placebo (in a 2:1 ratio) within that Part.

Randomization will be stratified based on PIN_{HD} score for the Stage 2 group and by TFC score for the Mild Stage 3 group (Section 5.4).

Once assigned treatment, subjects will take their assigned dose of study medication once a day. Subjects will be asked to return to the clinic every month after randomization until Visit 5 (Month 3) and then quarterly until Visit 8 (Month 12) or receive home care services in lieu of in-person visits (Section 3.6) to undergo study assessments. On Month 12, subjects will take their final dose of study medication and complete the end of study (EOS) assessments. Upon completion of Visit 8 (Month 12), subjects will have the option to enroll in Study PTC518-CNS-004-HD, a Phase 2 long-term extension study, to receive PTC518.

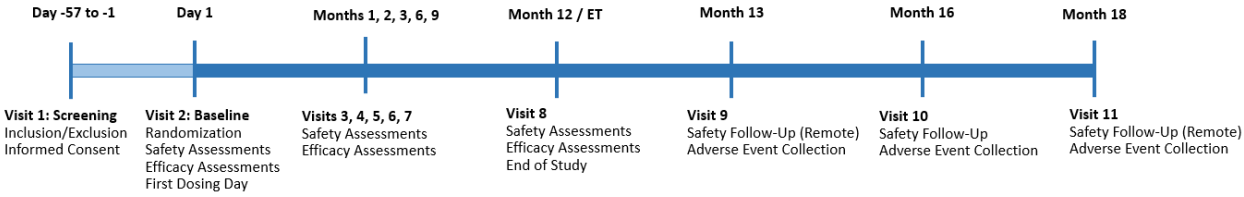
For subjects not enrolling in Study PTC518-CNS-004-HD, Visit 8 will be considered the End of Treatment visit, and there will be a Follow-Up Safety Visit on Month 13 via telephone/telehealth to collect adverse events (AEs) and an additional Follow-Up Safety Visit on Month 16 (ie, approximately 4 months after the last dose of study drug) to collect AEs [redacted]

[redacted]. A final Follow-Up Safety Visit will occur on Month 18 via telephone/telehealth to collect adverse event data.

The safety profile will be characterized via the assessment of treatment-emergent adverse events (TEAEs) and serious TEAEs, laboratory abnormalities, neurofilament light chain (NfL) levels in in plasma and cerebrospinal fluid (CSF), and vital signs, the Columbia Suicide Severity Rating Scale (C-SSRS), electrocardiogram (ECG), [redacted], and physical examination.

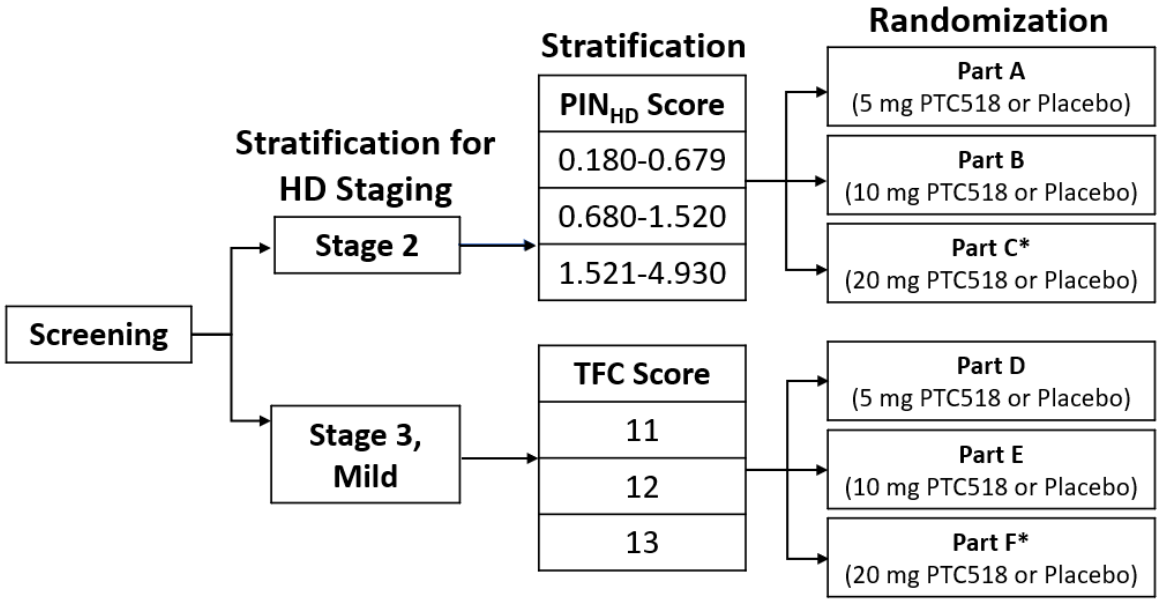
The primary efficacy assessment includes blood collection for tHTT protein at Month 3. Secondary efficacy assessments include volumetric magnetic resonance imaging (vMRI) for change in caudate volume (key secondary); other secondary efficacy assessments include blood and CSF collection for mHTT protein at Month 12, and cUHDRS scores. Exploratory assessments will include blood and CSF collection for mHTT protein at Month 3, clinical scales (UHDRS sub-scores [with the exception of the behavioral examination], PBA-s [substituting for the behavioral examination], and Functional Rating Scale [FuRST] 2.0); assessment of gait, balance, and postural sway via Opal wearable devices; plasma and CSF NfL; [redacted]; and blood *HTT* mRNA. A complete Schedule of Assessments can be found in Table 4 and the study design is pictured in Figure 1.

Figure 1: Study Design



Abbreviations: ET, Early Termination

Figure 2: Randomization Schema



Note: *Enrollment for Parts C and F will only be initiated by recommendation of the DSMB following an unblinded review of safety data from the 5 and 10 mg dosing groups.

1.3. Risk/Benefit Assessment

As described in previous sections, HD is a relentlessly progressive, neurodegenerative disorder. Early in the course of the disease, patients exhibit subtle symptoms; as the disease progresses, involuntary writhing movements become more pronounced, voluntary motor capabilities decline, and speech and swallowing are increasingly impaired, while aggressive and disinhibited behavior become more frequent. Late-stage disease is marked by severe inability to walk, speak, swallow, or care for oneself, culminating in the need for full-time care and ultimately death, typically 15 to 18 years after the onset of symptoms (Caron 2020a).

There are currently no disease modifying interventions approved for use in HD; without intervention, the patient population to be included in this study will face continued progression, loss of function, and inevitably, death. The disease progression and mortality of the disease indicate that HD represents a high unmet medical need. Reduction of mHTT has been confirmed as an important therapeutic target.

As described above, in Study CNS-001, multiple doses of PTC518 were associated with marked reductions in full-length *HTT* mRNA and HTT protein levels. Pharmacokinetic-pharmacodynamic (PD) modeling based on interim data from Study CNS-001 have predicted that the exposures at the 5-mg and 10-mg doses will be associated with reductions of [redacted] in full-length *HTT* mRNA levels. Decreases in mHTT of between [redacted] are targeted for optimal therapeutic benefit, though decreases of [redacted] have been associated with potential therapeutic benefit (Garriga-Canut 2012, Kordasiewicz 2012, Lu 2013, Stanek 2014, Tabrizi 2019). In order to more fully characterize the safety and PD of PTC518 over 12 months of treatment, these 5-mg and 10-mg doses have been selected for Parts A and D and Parts B and E, respectively. A DSMB will closely monitor the safety of subjects. As specified in the DSMB Charter, the DSMB may recommend initiation of Parts C and F, with a 20-mg QD dose, which is anticipated to result in decreases in full-length *HTT* mRNA levels of approximately [redacted]. It is anticipated that the selected doses will be associated with potential therapeutic benefit and the slowing of disease progression in this Phase 2a study.

Study CNS-001 also provides evidence of PTC518 safety and tolerability at single doses ranging from [redacted] and multiple doses of [redacted] for durations of up to 21 days. In this study, PTC518 was safe and generally well tolerated. In both the single ascending dose (SAD) and multiple ascending dose (MAD) portions of the study, the overall incidence of AEs was comparable between subjects who received placebo and those who received PTC518. There were no events considered to be dose-limiting toxicities, and all AEs were resolved at the time of the interim analysis cut-off date. There were also no clinically significant laboratory abnormalities or ECG findings at any dose in either portion of the study.

Based on the nonclinical and clinical data to date, PTC518 has a favorable risk/benefit profile in subjects with HD. For a detailed list of potential risks associated with PTC518 treatment, see the current Investigator's Brochure.

1.3.1. Summary of Safety Risks

There are no important identified or important potential risks for PTC518.

[redacted]

For further details on each risk, risk mitigation strategies as well as adverse drug reactions recognized to date, and other important safety topics for PTC518, see Section 6 of the Investigator's Brochure (IB), Summary of Data and Guidance for the Investigator.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives

- Evaluate the safety of PTC518 compared with placebo in subjects with HD
- Evaluate the PD effects of PTC518 through the reduction in blood tHTT protein levels

2.2. Secondary Objectives

- Assess the effects of PTC518 on change in caudate volume via vMRI (key secondary)
- Assess the effects of PTC518 on change in composite Unified Huntington's Disease Rating Scale (cUHDRS)
- Determine the effect of PTC518 on mHTT protein in CSF at Month 12
- Determine the effect of PTC518 on blood mHTT levels at Month 12

2.3. Exploratory Objectives

- Determine the effect of PTC518 on mHTT protein in CSF at Month 3
- Determine the effect of P TC518 on blood mHTT levels at Month 3
- Assess the effect of PTC518 on change in whole brain, and putamen volume via vMRI
- Assess the effect of PTC518 on change in ventricular volume via vMRI
- Assess change after 12 months of treatment in clinical scales
- Determine the effect of PTC518 on *HTT* mRNA in blood

2.4. Pharmacokinetic Objective

- Evaluate the concentration of PTC518 in subjects with HD

2.5. Safety Endpoints

- Safety profile as characterized by TEAEs, laboratory abnormalities, NfL levels in plasma and CSF, ECG, vital signs, C-SSRS, [redacted], and physical examination

2.6. Primary Efficacy Endpoint

- Change from Baseline in blood tHTT protein at Month 3

2.7. Secondary Endpoints

- Change from Baseline in caudate volume as assessed via vMRI at Month 12 (key secondary)
- Change from Baseline in cUHDRS scores at Month 12

- Change from Baseline in blood tHTT protein at Month 12
- Change from Baseline in CSF mHTT protein at Month 12
- Change from Baseline in blood mHTT protein at Month 12

2.8. Exploratory Endpoints

- Change from Baseline in CSF mHTT protein at Month 3
- Change from Baseline in blood mHTT protein at Month 3
- Change from Baseline in whole brain, putamen, and ventricular volume (as assessed by vMRI) at Month 12
- Change from Baseline in UHDRS TFC sub-score at Month 12
- Change from Baseline in other UHDRS sub-scores including TMS, SDMT, and IS at Month 12
- Change from Baseline in the short form of the PBA-s (substituting for the UHDRS Behavioral Examination) at Month 12
- Change from Baseline in wearable accelerometer assessment Timed Up and Go (TUG), 2-minute walk distance, and postural sway at Month 12
- Change from Baseline in the FuRST 2.0 questionnaire at Month 12
- Change over time in blood *HTT* mRNA
- Change over time in plasma and CSF NfL

[redacted]

2.9. Pharmacokinetic Endpoint

- Plasma trough concentration (C_{trough}) and accumulation ratio of PTC518 in plasma over time and accumulation ratio of PTC518 in CSF at Visits 5 through 8

3. INVESTIGATIONAL PLAN

3.1. Number of Subjects

Up to 252 adult male and female subjects will be enrolled (126 per disease stage).

3.2. Treatment Assignment

Treatment will be assigned via an Interactive Response Technology (IRT) after subject screening and eligibility is confirmed. Subjects will first be randomized to Part A or Part B or Parts D or E in a 1:1 randomization ratio, depending on their HD-ISS staging criteria (Section 4.1) and then to active treatment (5 mg in Parts A and D and 10 mg in Parts B and E) or matching placebo within each part in a 2:1 ratio of active treatment to placebo. As specified in the DSMB Charter, the DSMB will undertake an unblinded review of safety data from the 5 and 10 mg dosing groups and provide a recommendation on when Parts C and F (with a 20 mg active treatment arm) can be initiated. At that time, subjects will be randomized to any study Part that is currently open for enrollment, and then to either active treatment or matching placebo (in a 2:1 ratio) within that Part. An additional 18 subjects (per disease stage) may be randomized to the maximum tolerated dose.

3.3. Dose Justification

As described in Section 1, a [redacted] decrease in mHTT is the target as the range optimally associated with decreased pathology and anticipated therapeutic benefit in patients though it has been shown that reductions as low as [redacted] may be associated with potential therapeutic benefit (Garriga-Canut 2012, Kordasiewicz 2012, Lu 2013, Stanek 2014, Tabrizi 2019).

In Study CNS-001, PTC518-mediated HTT pre-mRNA splicing was dose-dependent across all cohorts in both the SAD and MAD portions of the study. [redacted]. On the basis of these clinical data, a pharmacokinetic (PK)-PD compartment model was used to simulate percentage of mRNA decreases (and thus the anticipated magnitude of HTT protein lowering) at additional potential clinical doses.

[redacted] respectively, which are within the target range of reduction from baseline. Nonclinical data in a BAC (bacterial artificial chromosome) transgenic mouse model of HD showed a [redacted].

[redacted]

Evidence for the safety of the selected doses is provided by the Phase 1 trial, Study CNS-001, and the results of the comprehensive nonclinical toxicology program to date. In Study CNS-001, single doses ranging from [redacted] have been safe and generally well tolerated. In both SAD and MAD portions of the study, the overall incidence of AEs was comparable between subjects who received placebo and those who received PTC518. There were no events considered to be dose-limiting toxicities, and all AEs were resolved at the time of the interim analysis cut-off date. There were also no clinically significant laboratory abnormalities or ECG findings at any dose in either portion of the study.

[redacted]

In the toxicology program conducted to date in rats and nonhuman primates (NHPs), a no-observed-adverse-effect level was identified in the 28-day rat and NHP studies, the 3-month rat and NHP studies, the 6-month rat study, and the 9-month NHP study (chronic studies). [redacted]

Thus, based upon the totality of the clinical and nonclinical safety data to date, and the anticipated reduction in *HTT* mRNA and HTT protein derived from clinical data and PK-PD modeling, the doses of 5, 10, and 20 mg are expected to be safe, well tolerated, and beneficial to subjects with HD.

3.4. Criteria for Study Termination

PTC reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The investigator, after consultation with the medical monitor, reserves the right to discontinue the study at the investigator site for safety reasons at any time.

Based on unblinded review of the safety data, the DSMB may recommend continuation of the study unchanged, study interruption, dose arm termination, study termination, modification of the study, or alteration in the DSMB monitoring plan.

After a decision to terminate the study, investigators must contact all current study participants within a period set by PTC. As directed by PTC, all study materials must be collected, and all electronic data entry forms completed to the greatest extent possible.

3.5. End of Study Definition

The study will end when the last subject has completed the final assessment.

3.6. Home Care Services

If for unforeseen reasons subjects are unable to have an on-site visit on Month 1 or 2, with approval from both the Principal Investigator and medical monitor, they may be offered an opportunity to have some study assessments performed in their home. In order to conduct the home visits, the subject must agree to utilize home care services. A licensed nurse will then contact the subject to schedule the visits. The home care nurse, the home care agency, and the home care services provider may have access to the subject's personal data including their individually identifiable protected health information, such as the subject's name, address, or phone number. This type of information will only be used as necessary to schedule and conduct the home visits and will not be provided to PTC. Table 3 outlines the assessments that may be done via home care services.

Table 3: Home Care Services for Subjects Unable to Have On-Site Visits at Month 1 and Month 2 (Contingent on Approval of Principal Investigator and Medical Monitor)

Month 1 and Month 2		
Home Health Visit	Site Telephone/Telehealth Visit	On-Site Visit
Clinical laboratory assessments Blood *HTT* mRNA Blood HTT protein Plasma NfL PK Vital signs ECG Urine pregnancy test	Concomitant Medications Adverse Events Drug accountability Dispense Study Drug (via local site procedures for shipment or couriered delivery) C-SSRS	UHDRS

Abbreviations: C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; HTT, huntingtin (protein): *HTT*, huntingtin (gene); NfL, neurofilament light chain; PK, pharmacokinetics; UHDRS, Unified Huntington's Disease Rating Scale

3.7. Unscheduled Visits

Unscheduled visits are permitted at the investigator's discretion.

At minimum, adverse events and concomitant medications data must be collected at all unscheduled visits. Unscheduled visits may also include any of the following assessments, at the investigator's discretion:

- Physical examination
- Body weight
- Vital signs
- Pregnancy test
- Dispense study drug (if applicable)
- Drug accountability
- ECG

[redacted]

- Blood HTT protein
- Plasma NfL

- Clinical laboratory assessments
- UHDRS Part II (SDMT only)
- UHDRS Part V
- UHDRS Part VI
- [redacted]
- C-SSRS

In addition, if a subject is intended to enroll in the Phase 2 long-term extension study (Study PTC518-CNS-004-HD), but that study is not yet locally approved by regulatory and/or ethics authorities, the subject may continue within this study attending unscheduled visits approximately every 3 months prior to the end of study visit in order to ensure study treatment is not interrupted and to continue to assess safety parameters. Upon local approval of the Phase 2 long-term extension study (PTC518-CNS-004-HD), the subject will return for the End of Study Visit and will transition into the long-term extension study.

Table 4: Study Design and Schedule of Assessments

	Screening	Baseline		Treatment Period						Safety Follow-Up			Notes
Study Month	**Days -57 to -8**	**Days -22 to -1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /EOS/ EOT /ET**	**Month 13**	**Month 16**	**Month 18**	**The Safety Follow-up visits must be performed for all subjects following either the EOT or ET visit.**
Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Window (days)				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Informed consent	X												
Inclusion/Exclusion	X	X	X										
Medical history	X												
Physical examination	X					X	X	X	X				A complete physical exam will be performed at Visit 1 (Screening) and Visit 8/ET. A brief physical examination, including a neurological examination, will occur at all other timepoints.
Demographics	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X		
Body weight and height		X		X	X	X	X	X	X				Height will be collected at Baseline only.
Vital signs	X		X	X	X	X	X	X	X				
Pregnancy test	X	X	X	◄ (Monthly) ►									For WOCBP, a serum HCG at Screening and Baseline. Urine HCG monthly from Day 1 through the last Safety Follow-up Visit. For months where an on-site visit is not scheduled, subjects will complete a urine pregnancy test at home to be reported to the investigator and documented in the eCRF. Subjects will self-report all pregnancies through 6 months after last dose of study drug.
Randomization			X										
Dispense study drug			X	X	X	X	X	X					
Drug accountability				X	X	X	X	X	X				

	Screening	Baseline		Treatment Period						Safety Follow-Up			Notes
Study Month	**Days -57 to -8**	**Days -22 to -1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /EOS/ EOT /ET**	**Month 13**	**Month 16**	**Month 18**	**The Safety Follow-up visits must be performed for all subjects following either the EOT or ET visit.**
Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Window (days)				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
ECG	X		X	X	X	X	X	X	X				
[redacted]													
Sample for genetic sequencing	X												Subjects with documentation of CAG repeat length are exempt from genetic sequencing requirements. CAG repeat length may be determined analytically through amplification.
Plasma PK			X	X	X	X	X	X	X		X		Plasma samples will be taken predose and 4 (±2) hours postdose on Day 1 (Visit 2) through Month 12 (Visit 8). One additional plasma sample will be taken at Month 16 (Visit 10).
Blood *HTT* mRNA			X	X	X	X	X	X	X		X		On Day 1, only a predose sample is required. Subsequent samples should be collected at the same time as PK samples (ie, predose and 4 [±2] hours postdose). An additional sample will be collected at Month 16 (Visit 10).

	Screening	Baseline		Treatment Period						Safety Follow-Up			Notes
Study Month	**Days -57 to -8**	**Days -22 to -1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /EOS/ EOT /ET**	**Month 13**	**Month 16**	**Month 18**	**The Safety Follow-up visits must be performed for all subjects following either the EOT or ET visit.**
Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Window (days)				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Blood HTT protein			X	X	X	X	X	X	X		X		On Day 1, only a predose sample is required. Subsequent samples should be collected at the same time as PK samples (ie, predose and 4 [±2] hours postdose). An additional sample will be collected at Month 16 (Visit 10).
Plasma NfL			X	X	X	X	X	X	X		X		All samples to be drawn predose
Clinical laboratory assessments	X	X		X	X	X	X	X	X				Safety laboratory assessments at Baseline should be performed fasted. All other safety laboratory assessments are not required to be performed fasted. Serology performed at Screening only.
CSF collection		X				X	X	X	X				It is recommended that CSF collection be done at least 3 days prior to Day 1. Sample collection may be done up to 8 days prior to Visits 5 through 8. CSF collection must be performed predose.
UHDRS Part I (Motor Assessment)	X		X			X	X	X	X				
UHDRS Part II (Cognitive Assessment)	X (SDMT only)		X	X (SDMT only)	X (SDMT only)	X (SDMT only)	X (SDMT only)	X (SDMT only)	X				At Screening, only SDMT is required to confirm eligibility. Only SDMT is done at Visits 3, 4, 5, 6, and 7.
UHDRS Part IV (Functional Assessment)	X		X			X	X	X	X				

	Screening	Baseline		Treatment Period						Safety Follow-Up			Notes
Study Month	**Days -57 to -8**	**Days -22 to -1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /EOS/ EOT /ET**	**Month 13**	**Month 16**	**Month 18**	**The Safety Follow-up visits must be performed for all subjects following either the EOT or ET visit.**
Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Window (days)				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
UHDRS Part V (Independence Scale)	X		X			X	X	X	X				
UHDRS Part VI (Functional Capacity)	X		X			X	X	X	X				
UHDRS Part VII (Clinical Summary)			X			X	X	X	X				
UHDRS Part VIII (Clinical Disposition)			X			X	X	X	X				
PIN_{HD} Calculation	X												TMS and SDMT will be performed at this visit to calculate PIN_{HD}. Only subjects who qualify for enrollment into the Stage 2 group will have PIN_{HD} calculated.
PBA-s			X						X				The PBA-s will be used instead of Part III of the UHDRS.
Timed Up and Go (TUG), 2-minute walk test, and postural sway test			X			X	X	X	X				The Opal wearable device will be worn during these assessments. Each test will be conducted twice: once with a concurrent cognitive interference task and once without.
FuRST 2.0			X			X	X	X	X				
[redacted]													
vMRI		X				X			X				Imaging can be done up to 8 days prior to all vMRI visits after Screening.

	Screening	Baseline		Treatment Period						Safety Follow-Up			Notes
Study Month	**Days -57 to -8**	**Days -22 to -1**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12 /EOS/ EOT /ET**	**Month 13**	**Month 16**	**Month 18**	**The Safety Follow-up visits must be performed for all subjects following either the EOT or ET visit.**
Visit	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Window (days)				**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	Safety follow-up at Visit 9 may be done by telephone/telehealth. Information about AEs will be collected from the signing of consent through 6 months after the last dose of study medication.
C-SSRS	X	X		X	X	X	X	X	X				The "Baseline" version of the C-SSRS version will be used at Screening and Baseline. The "Since Last Visit" version of the C-SSRS will be used at all other timepoints.

Abbreviations: AE, adverse event; CAG, cytosine-adenine-guanine; CSF, cerebrospinal fluid; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; eCRF, electronic case report form; EOS, end of study; EOT, end of treatment; ET, Early Termination; FuRST 2.0, Functional Rating Scale; HCG, human chorionic gonadotropin; HTT, huntingtin (protein); *HTT*, huntingtin (gene); IS, Independence Scale; NfL, neurofilament light chain; PBA-s, short form of the Problem Behaviors Assessment; PIN_{HD}, normed version of the Huntington's disease prognostic index; PK, pharmacokinetics; SDMT, Symbol Digit Modalities Test; TFC, Total Functional Capacity; TMS, Total Motor Scale; [redacted]; TUG, Timed Up and Go; UHDRS, Unified Huntington's Disease Rating Scale; vMRI, volumetric magnetic resonance imaging; WOCBP, women of childbearing potential

4. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will include approximately 24 subjects randomized to each active treatment arm, and up to 72 subjects randomized to placebo arm who satisfy all entry criteria.

4.1. Subject Inclusion Criteria

Individuals eligible to participate in this study include those who meet all of the following inclusion criteria:

1. Ambulatory male or female patients aged 25 years and older, inclusive
2. Subject is willing and able to provide informed consent and comply with all protocol requirements
3. Genetically confirmed HD diagnosis with a CAG repeat length from 40 to 50, inclusive. CAG repeat length may be determined analytically through amplification.

Eligibility for HD-ISS Stage 2 Group (Parts A, B, and C)

4. A UHDRS IS score of 100
5. A UHDRS TFC score of 13
6. A score between 0.18 and 4.93 inclusive on the normed version of the HD prognostic index (PIN_{HD})

Eligibility for HD-ISS Mild Stage 3 Group (Parts D, E, and F)

9. A UHDRS TFC score of 11 or 12, or a UHDRS TFC score of 13 with an UHDRS IS score of <100

7. Women of childbearing potential (WOCBP) must agree to use highly effective methods of contraception during dosing and for 6 months after stopping the study medication. Women of childbearing potential are defined as women who are fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   Female partners of enrolled males who are of childbearing potential should consider use of highly effective methods of contraception while the enrolled male is taking study drug and for 6 months after stopping study drug.

   Highly effective contraception methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly and include the following:

   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Intravaginal

  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

In case of use of oral contraception, WOCBP should have been stable on the same pill for a minimum of 3 months prior to Screening.

Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

8. Sexually active and fertile males must agree to use a condom during intercourse while taking study drug and for 6 months after stopping study drug and should neither father a child nor donate sperm in this period. A condom is required to be used also by vasectomized men in order to prevent potential delivery of the drug via seminal fluid.

4.2. Subject Exclusion Criteria

Individuals are not eligible to participate in this study if they have met or meet any of the following exclusion criteria:

1. Inability or unwillingness to swallow oral tablets
2. Receipt of an experimental agent within 90 days or 5 half-lives prior to Screening or anytime over the duration of this study, including RNA- or DNA-targeted HD-specific investigational agents (such as antisense oligonucleotides), cell transplantation, or any other experimental brain surgery
3. Any history of gene therapy exposure for the treatment of HD
4. Participation in an investigational study or investigational paradigm (such as exercise/physical activity, cognitive therapy, brain stimulation, etc) within 90 days prior to Screening or anytime over the duration of this study. Observational studies (such as ENROLL-HD) are not exclusionary.
5. Presence of an implanted deep brain stimulation device

[redacted]

7. Brain and spinal pathology that may interfere with CSF homeostasis and circulation, increased intracranial pressure (including presence of a shunt for the drainage of CSF or an implanted central nervous system catheter catheter), malformations, and/or tumors
8. Hospitalization for any major medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
9. At significant risk of suicide as measured by the C-SSRS Baseline version with a moderate risk rating or higher score
10. Risk of a major depressive episode, psychosis, confusional state, or violent behavior as assessed by the investigator
11. Any medical history of brain or spinal disease that would interfere with the lumbar puncture processor safety assessments
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
13. Any medical history or condition that would interfere with the ability to complete the protocol-specified assessments (eg, implanted shunt, conditions precluding MRI scans)
14. Antidepressant, antipsychotic, or benzodiazepine use, unless receiving a stable dose for at least 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study. Benzodiazepine use for sedation for study-related procedures during the course of the study is permitted.
15. History of illicit/illegal drug use, or alcohol use in the high-risk category of risk drinking levels according to the World Health Organization for a duration of 1 month or longer that in the opinion of the investigator could compromise the interpretability of study results
16. Clinically significant medical condition, which in the opinion of the investigator could adversely affect the safety of the subject or impair the assessment of study results (eg, inability to fast or any known hypersensitivity to PTC518 or its excipients)
17. Current significant renal impairment defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 at Screening
18. Current hepatic impairment resulting in elevated liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP]) at 3 times the upper limit of normal at Screening
19. Pregnancy, planning on becoming pregnant during the course of the study or within 6 months of end of treatment, or currently breastfeeding
20. Use of medications that are moderate or strong inhibitors of cytochrome P450 (CYP) 3A4 within 1 week of Screening or medications that are moderate or strong inducers of CYP3A4 within 2 weeks of Screening or planned use of moderate or strong CYP3A4 inhibitor or inducer medications during the study period (Appendix 1)

21. A diagnosis of Juvenile-Onset Huntington's Disease

4.3. Screen Failures

Any subject who does not meet inclusion or exclusion criteria within the defined screening window prior to randomization will be considered a screen failure. Screen failures will be captured in the electronic data capture system (EDC). Screen failures may be rescreened after consultation with the medical monitor.

4.4. Subject Discontinuation or Withdrawal

Subjects will receive study treatment until protocol-specified study completion or treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. In the event that a subject discontinues from the study prematurely, and unless consent is withdrawn, all efforts must be made to collect efficacy and safety data and to complete the Early Termination Visit (Visit 8). The following conditions require subject discontinuation from all study treatment:

- At their own request
- If a subject experiences an AE that is deemed related to treatment with PTC518 and in the investigator's or PTC's medical judgment continuation of treatment would be detrimental to the subject
- At the specific request of a regulatory agency or DSMB for termination of treatment of an individual subject or all subjects under the protocol
- Subject participation in another clinical study using an investigational agent or investigational medical device
- Refusal of sexually active fertile subjects (excluding female subjects who have been sterilized) to use medically accepted methods of contraception
- If a subject becomes pregnant
- Significant noncompliance with the protocol in the opinion of the investigator or PTC
- Any situation in which the investigator determines that the subject should not continue in the study

The date PTC518 is discontinued and the reason for discontinuation will be recorded in the source documents and in the electronic case report form (eCRF). The medical monitor (and designee) must be informed via email when a subject discontinues study drug.

When PTC518 is discontinued, the investigator is expected to perform all the evaluations according to the subject's original schedule and as required at the Early Termination Visit and any additional evaluations that may be necessary to ensure that the subject is free of untoward effects.

4.5. Enrichment Criteria

Enrichment is defined as the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it

would be in an unselected population (FDA 2019). Due to the highly variable population of patients with HD, the enrichment strategy for this Phase 2a study is intended to select for subjects who have preserved capacity for activities of daily living, work, finances, and self-care, but have reduced performance on motor and cognitive tests and are predicted to experience functional impact on activities of daily living within 3 years. The TMS and SDMT from the UHDRS will be assessed at Screening (along with CAG repeat length and age) and used to identify this population via a validated HD prognostic index for pre-manifest patients with HD (Long 2017).

The PI_{HD} or its normed version (PIN_{HD}) can be used to predict likelihood of HD progression, with higher scores indicating greater risk of functional decline (Long 2017). Natural history survival curves generated using the PI_{HD} show the disease trajectory in patients with a particular PI_{HD} score. The PIN_{HD} score allows researchers to predict disease progression in a studied population with a high degree of certainty.

Historically, disease progression was commonly indexed by the CAG-Age Product (CAP), which is a type of burden score of age and CAG expansion that has several variants. When CAP is supplemented with the TMS and SDMT from the UHDRS, predictive likelihood of HD progression increases. Using these enrichment criteria, a group of subjects with HD and no functional decline (measured via the TFC and IS) can be identified and changes in blood HTT levels after treatment can be measured. This group is likely to experience decline without HTT-lowering treatment as it has been found that earlier stages of HD are marked by increases in mHTT levels in CSF compared to controls (Ehrhardt 2021).

At Screening, subjects' cognitive and motor functions will be assessed by SDMT and TMS scores, respectively. Enrolled subjects who qualify for the Stage 2 group will present with no functional decline as assessed by the TFC and IS. Subjects in the Stage 2 group will be included in the study based on the calculation of PIN_{HD} scores as calculated by the IRT prior to randomization. Subjects with PIN_{HD} scores between 0.18 and 4.93 inclusive will be eligible for enrollment into the Stage 2 group in the study. The following formula will be utilized to calculate the PIN_{HD} score:

$$PI_{HD}=51\times(TMS)+(-34)\times SDMT+7\times (age)\times(CAG-34).$$

The PI_{HD} score is converted to a normalized score using the following conversion:

$$PIN_{HD}=(PI_{HD}-883)/1044$$

The Enroll-HD database (periodic data update 5) was utilized to identify the 0.18 to 4.93 range of PIN_{HD} scores for inclusion in the study.

Subjects in the Mild Stage 3 group will qualify for enrollment if they present with a TFC score of 11 or 12, or 13 with an IS score of <100.

4.6. Lost to Follow-Up

A subject is considered lost to follow-up if he or she does not complete the study and attempts to contact the subject are unsuccessful. Efforts must be made on the part of the site to avoid any subject being lost to follow-up during the study. Before any subject is considered lost to follow-up, a minimum of 2 documented telephone contact attempts and 1 certified letter within a week of the most recent planned study assessment must be sent in efforts to contact the subject.

After being considered lost to follow-up, a subject's status may be changed if the subject makes contact at a later time provided the study is ongoing.

5. TREATMENT OF SUBJECTS

5.1. Description of Study Drug

PTC518 drug product is a solid dosage formulation for oral administration. See Section 6.1 for a full description of the study drug.

5.2. Concomitant Medications

Any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, self-prescribed drugs, and street drugs) that are taken by a subject at Screening, during PTC518 administration, and for the remainder of the study are considered concomitant medications. Information regarding any concomitant medications will be collected and documented in the eCRF and in the source documents by the clinic staff.

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of "health supplements" (eg, creatine, glutamine), herbal remedies, growth hormone, and self-prescribed drugs at any time during this clinical study of PTC518. If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any other drug(s) should consider the subject's safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more relevant underlying event, and whether use of a concomitant medication will compromise the outcome or integrity of the study.

Vaccination for the prevention of COVID-19 is permissible. The last dose of the vaccine must be received at least 2 weeks prior to visit assessments.

Subjects and caregivers should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over the-counter, or illicit) before and during the course of the study. The investigator is encouraged to consult the medical monitor or designee with questions relating to specific drugs and their potential for interactions with PTC518.

5.3. Treatment Compliance

Records of study drug used, dosages administered, and intervals between visits are kept during the study. Study drug accountability is performed on an ongoing basis by the study staff and checked by the monitor during site visits and at the completion of the study.

Treatment compliance is defined as taking ≥80% of the medication over the course of the study.

5.4. Randomization and Blinding

After subjects complete all baseline procedures on Day 1 and are eligible to be randomized, site staff will utilize an IRT system to assign study medication to each subject. Subjects will first be randomized to Parts A or B or Parts D or E in a 1:1 ratio, depending on their HD-ISS staging criteria (Section 4.1) after which they will be randomized to active treatment or placebo within each part in a 2:1 ratio of active to placebo. As specified in the DSMB Charter, a DSMB will undertake an unblinded review of safety data from the 5 and 10 mg dosing groups and provide recommendation on when Parts C and F, with a 20 mg active treatment arm, can be initiated at that time, subjects will be randomized to any study Part that is currently open for enrollment, and then to either active treatment or placebo (in a 2:1 ratio) within that Part.

Enrollment for the Stage 2 group will be stratified by PIN_{HD} score, with the following stratification classes:

- 0.180-0.679
- 0.680-1.520
- 1.521-4.930

Enrollment for the Mild Stage 3 group will be stratified by TFC score, with the following stratification classes:

- 11
- 12
- 13

The randomization code will be kept strictly confidential and accessible only to the unblinded study statistician who is not directly involved in the conduct of the study. The study will be performed in a double-blind fashion. The investigator and study staff (including processing laboratory personnel), the subjects, and PTC's staff will remain blinded to the treatment until after the database is locked.

During the double-blind treatment period, the identity of the treatments will be concealed by the use of a placebo that is matched to the active drug in appearance, taste, odor, packaging, labeling, and schedule of administration. Unblinding will only occur in the case of subject emergencies before study completion and at the conclusion of the study. Except for emergency unblinding, individual subjects, parents/caregivers, and site personnel will not be informed of the randomized treatment assignments until the implications of revealing such data for the overall PTC518 clinical development program have been determined by PTC.

Emergency unblinding should only occur after the investigator deems the subject's emergency warrants the unblinding of the treatment. Unblinding of the treatment can only be performed by the investigator in the IRT system. Unblinding instructions are provided in the IRT system instruction manual.

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug

PTC518 drug product is a film-coated tablet dosage form for oral administration. PTC518 active and matching placebo tablets are white to off-white round coated tablets that will be provided in 2 dosage strengths of 5- and 20-mg tablets. The placebo tablets contain the same compendial excipients and is manufactured in the same tablet sizes with the same appearance to match the respective 5-mg or 20-mg PTC518 tablets.

6.2. Study Drug Packaging and Labeling

The active and placebo tablets will be provided in cartons containing 5 blister cards. Each blister card will contain 21 tablets with a mix of PTC518 and/or matching placebo tablets. The labeling will comply with the applicable (local) laws and regulations.

6.3. Study Drug Storage

Study personnel must ensure that all study drug supplies are kept in a secure locked area with access limited to authorized personnel. Study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics or allow study drug to be used other than as directed by this protocol. Only the trained study site personnel will handle the study drug dispensation and accountability. Refer to the pharmacy manual or clinical label for the storage conditions of the active and placebo.

6.4. Administration

Tablets of PTC518 or placebo will be administered orally, QD. The 4 dosing arms will include 5 mg, 10 mg, 20 mg, or matching placebo for 12 months.

Study drug will be taken by the subject orally, at home (except on days where the subject is instructed to take the dose in the clinic), in a single daily dose. Subject/caregiver must be instructed not to split the tablet(s) and subjects are instructed not to chew the study drug. All (3) tablets for the day should be taken either all at once (if tolerated) or one after another until all tablets are consumed. Tablets may be taken with or without food every day, at the same time each day.

6.4.1. Missed Doses and Overdoses

Study drug may be taken with or without food every day, at the same time each day starting at Visit 2 for the duration of the study. If a subject is late taking a dose of study drug, the dose should be taken as close to the usual time as possible in this case. PTC does not recommend specific treatment for an overdose of PTC518. The investigator will use clinical judgment to treat any overdose. Any overdose should be reported on the drug accountability log.

6.5. Study Drug Accountability

The investigator is responsible for keeping accurate records of the clinical supplies received from PTC or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study.

After confirmation by the study monitor, all unused investigational material (drugs and packaging) must be returned to PTC or its designee by the end of the study. If the Standard Operating Procedure (SOP) at any site states that the drug cannot be returned and must be disposed of on-site, PTC must review the SOP of that site prior to any final disposition done by site. Records documenting the date of study medication destruction or shipping, and amount destroyed or shipped should be kept.

The Drug Accountability Records are considered as source data and will be archived at the site.

7. ASSESSMENT OF EFFICACY

7.1. Pharmacodynamic and Pharmacokinetic Parameters

Assessment of the PD and PK effect of PTC518 will be evaluated using the assessments outlined in the Schedule of Assessments (Table 4). Blood samples will be taken for PK, *HTT* mRNA, and HTT protein, which will be collected via vena puncture or via an intravenous catheter placed in a vein in the arm following the local standard procedures. Additionally, CSF samples will be collected by lumbar puncture, carried out by a qualified physician and in accordance with the local procedures. Information on equipment and further details on the sampling procedures, including volumes of blood and CSF to be collected, will be documented in a separate instruction laboratory manual.

The total volumes of blood and CSF to be collected during the study are approximately 320 mL and up to 100 mL, respectively.

7.1.1. Pharmacodynamic Parameters

Pharmacodynamic parameters will include assessment of tHTT protein (in blood), *HTT* mRNA (in blood), mHTT protein (in CSF), and mHTT protein (in blood).

7.1.2. Pharmacokinetic Parameters

Sampling for PK analysis in plasma and CSF will be performed as described in Table 4.

7.2. Other Efficacy Assessments

7.2.1. Volumetric Magnetic Resonance Imaging

The loss of brain tissue is a continuous variable of disease progression in HD. Volumetric magnetic resonance imaging will be used to effectively detect changes in brain volume during the study.

Volumetric magnetic resonance imaging will be used to assess change over the treatment period using the Boundary Shift Integral (BSI). The BSI uses the shift in intensity differences on a pair of registered intensity-normalized images to quantify the difference between the 2 images. The BSI determines the total volume through which the boundaries of a given cerebral structure have moved and, hence, the volume change, directly from voxel intensities. This technique is considered the gold standard to measure global brain or regional atrophy (tissue loss). Using serial MRI scans, semi-automated region delineation with volume change is estimated using BSI, and will be used to validate vMRI changes (Prados 2015). The following brain areas will be assessed at Visit 2 (Baseline) and Visits 5 and 8:

- Whole brain
- Caudate
- Putamen
- Lateral ventricles

7.2.2. Unified Huntington's Disease Rating Scale

The UHDRS comprises 7 subscales with separate scoring for each part:

- Part I is an assessment of motor function. Part I includes 31 items with a 5-point ordinal scale ranging from 0 to 4 with the highest score indicating inability to perform the motor task. The "Diagnosis Confidence Level" is also collected as a portion of the UHDRS Motor Assessment.
- Part II is an assessment of cognitive function and includes 3 items with higher scores indicating better cognitive performance. The 3 items include a Verbal Fluency Test, SDMT, and Stroop Interference Test. In the Verbal Fluency Test, subjects are asked to enumerate either words beginning with a given letter within a limited amount of time (phonological fluency) or words within a given category, such as animals (semantic fluency). The SDMT is a symbol substitution neuropsychological test that examines a person's attention and speed of processing. This test requires a person to substitute geometric symbols for numbers while scanning a response key. Oculomotor scanning, working memory, motor persistence, and visuomotor coordination are also required in order to score higher on the test. In order to prevent a learning effect from confounding the result of the SDMT, 3 different versions of the test will be administered at different timepoints for each subject. The Stroop Interference Test assesses the ability to selectively attenuate to specific items on the test, either word name or word color, when the 2 are interfering variables.
- Part III is a behavioral assessment. The PBA-s will be substituted for this behavioral assessment in this study.
- Part IV is a measure of functional capacity. Huntington's Disease Functional Capacity Scale is reported as the TFC, which has a total of 25 yes or no questions assessing the TFC of the individual. A score of 1 is given to all yes replies.
- Part V is a measure of independence. The IS is measured on a scale from 10 to 100 with higher scores indicating better functioning.
- Part VI is a measure of functional capacity. Functional Capacity is measured using 5 items with a 3- or 4-point ordinal scale ranging from 0 to 2 or 0 to 3 with the highest score indicating higher functional capacity.
- Part VII is the clinical summary. An examination summary is performed by the examiner to take into account all aspects of the UHDRS.

7.2.3. Problem Behavior Assessment (Short Form)

The short form of the Problem Behavior Assessment is a semi-structured clinical interview that measures the occurrence and severity of 11 different behavioral symptoms in subjects with HD.

7.2.4. Opal Wearable Device Assessments

It has been noted in previous HD studies that bradykinesia, hypokinesia, gait speed, cadence, and increase in stride time are associated with HD decline. In order to assess changes in gait, balance, and postural sway, Opal wearable devices will be worn by the subject during 3, on-site

assessments: TUG in 3 m walkway, 2-minute walk distance, and a postural sway test. Each test will be conducted twice: once with a concurrent cognitive interference task and once without.

7.2.5. Functional Rating Scale

The FuRST 2.0 is a standardized HD-specific 24-item patient-reported outcome measure specifically designed to assess functional ability in pre-manifest and early-manifest HD.

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

The following have been defined as parameters regarding safety and tolerability:

- Abnormalities in vital signs
- [redacted]
- Abnormalities in ECG parameters
- Abnormalities in clinical laboratory tests
- NfL levels in plasma and CSF
- Changes in C-SSRS scores
- TEAEs up to EOS
- TEAEs leading to premature discontinuation of study drug
- Treatment-emergent serious adverse events (SAEs) up to EOS
- Abnormalities in physical examination
- [redacted]

8.1.1. Demographic/Medical History

Demographic data and medical history will be collected at the times indicated in the Schedule of Assessments (Table 4).

8.1.2. Vital Signs

Supine blood pressure, supine pulse rate, respiration rate, body temperature, and oxygen saturation will be assessed at the timepoints indicated in the Schedule of Assessments (Table 4). Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range. Subjects must be supine for at least 5 minutes before blood pressure and pulse rate measurements.

8.1.3. Weight and Height

Body weight and height will be measured at the timepoints indicated in the Schedule of Assessments (Table 4).

8.1.4. Physical Examination

A complete physical examination will be performed at the timepoints specified in the Schedule of Assessments (Table 4). A complete physical examination includes general appearance, head, eyes, ears, nose, mouth, throat, thyroid, chest and lungs, abdomen, extremities, neuromuscular system, skin, and lymph nodes.

[redacted]

8.1.6. Electrocardiogram

Subjects will be in a supine position for approximately 5 minutes prior to ECG measurements. Measurements will be taken at the times indicated in the Schedule of Assessments (Table 4) and will be classified as normal/abnormal. In case of a classification as "abnormal," the abnormality will be described and its relevance in terms of clinical significance documented. The ECGs will be performed in triplicate.

[redacted]

8.1.8. Laboratory Assessments

A summary of clinical laboratory tests to be performed is presented in Table 5, with the timing of assessments as indicated in the Schedule of Assessments (Table 4). Clinically significant laboratory abnormalities which require clinical intervention or further investigation must be reported by the investigator as an AE or SAE as appropriate (Section 8.2.3).

Safety blood samples will be taken under fasted conditions at Baseline. All other safety laboratory assessments are not required to be taken under fasted conditions. As a rule, the blood samples will be taken from the subject by puncture of a vein in the cubital or the antebrachial region. The samples will be sent to a central laboratory in accordance with specifications.

8.1.9. Neurofilament Light Chain Levels

The levels of NfL, a biomarker of neuronal injury, will be assessed in plasma and CSF as indicated in Table 4.

Table 5: Summary of Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis[a]	Others	CSF
Hemoglobin	Urea	Urobilinogen	Pregnancy test[c]	NfL
Hematocrit	Creatinine	Nitrite	FSH[d]	WBC[e]
RBC count	Glucose	pH	Serology (HIV, hepatitis B and hepatitis C)[a]	RBC[e]
Platelet count	Sodium	Glucose		Protein[e]
Mean corpuscular volume	Potassium	Albumin	Coagulation (PT [sec], PT [INR], aPTT)	Glucose[e]
Mean corpuscular hemoglobin	ALT	Erythrocytes	Urine drug screen[a]	
WBC count	AST	Leukocytes	Plasma NfL	
WBC differential	GGT	Ketones		
Neutrophils	Bilirubin (total, direct and indirect)	Microscopy[b]		
Band neutrophils	ALP	Specific gravity		
Eosinophils	Albumin	Bilirubin		
Monocytes	Cholesterol (total)			
Basophils	LDL			
Lymphocytes	HDL			
	Triglycerides			
	LDH			
	Bicarbonate			
	Calcium			
	Chloride			
	Total protein			
	Uric acid			

Abbreviations: ALP, alkaline phosphatase; ALT, alkaline aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CSF, cerebrospinal fluid; FSH, follicle-stimulating hormone; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NfL, neurofilament light chain; PT, prothrombin time; RBC, red blood cell; WBC, white blood cell

[a] Only during Screening.

[b] Only if urine dipstick is positive and marked as at least '++' for erythrocytes/leucocytes and albumin.

[c] Serum pregnancy testing at Screening and Baseline; at other timepoints urine pregnancy testing is acceptable. For months when no in-person visit is scheduled, a home pregnancy test will be taken by the subject and reported to the investigator.

[d] Required of postmenopausal females only during Screening.

[e] Assessment of CSF WBC, RBC, protein, and glucose will be performed by local laboratories.

8.1.10. Columbia Suicide Severity Rating Scale

The C-SSRS is a measure used to identify and assess individuals at risk for suicide. Questions are phrased for use in an interview format but can be completed as a self-report measure if necessary. The C-SSRS measures 4 constructs: suicidal ideation, the intensity of ideation, suicidal behavior, and lethality. It includes "stem questions," which, if endorsed, prompt additional follow-up questions to obtain more information.

The C-SSRS suicidal ideation construct comprises 5 categories, all of which maintain binary responses (yes/no) to indicate a presence or absence of ideation. The 5 categories included in the C-SSRS ideation construct are as follows:

Category 1 – Wish to be Dead;

Category 2 – Non-specific Active Suicidal Thoughts;

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

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

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

The C-SSRS intensity of ideation construct is measured by evaluating on a 1 to 5 ordinal scale the following parameters: frequency, duration, controllability, deterrents, reason for and ideation.

A yes/no binary response is also utilized in assessing suicidal behavior for the following categories: actual attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, suicidal behavior, and suicide. Actual attempts are then scored based on their potential/actual lethality and/or medical damage.

The outcome of the C-SSRS is a numerical score obtained from the aforementioned categories.

8.1.10.1. Virus Serology

Virus serology (HIV, hepatitis B, and hepatitis C) will be assessed at the timepoints specified in the Schedule of Assessments (Table 4).

8.1.10.2. Pregnancy Screen

Pregnancy testing will be performed as indicated in Table 4. Subjects will complete a urine pregnancy test monthly from Day 1 through the last Safety Follow-Up either at the site or at home (for months where an on-site visit is not scheduled). All pregnancy tests will be documented in the source and eCRFs.

Subjects will self-report all pregnancies through 6 months after last dose of study drug.

8.2. Adverse Events, Serious Adverse Events, and Other Safety Reporting

8.2.1. Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a study intervention in humans, whether or not it is considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease in a study subject who is administered with study intervention in this study.

For this protocol, untoward medical occurrences that meet and do NOT meet the criteria of an AE include the following:

Events Meeting the AE Definition

- All AEs during the course of treatment with study intervention
- All AEs resulting from medication misuse, abuse, withdrawal, or overdose of study drug
- All AEs resulting from medication errors, such as dispensing or administration error outside of what is described in the protocol
- Apparent unrelated illnesses, including worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory or ECG abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event

Events NOT Meeting the AE Definition

- Laboratory abnormalities associated with a clinical event should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring and should not be reported as AEs.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition (see Section 8.2.10).
- Preexisting condition (eg, allergic rhinitis) must be noted on the appropriate eCRF for Screening but should not be reported as an AE unless the condition worsens, or the episodes increase in frequency during the AE reporting period.
- Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs, unless the medical condition for which the procedure was performed meets the definition of an AE. For example, an acute appendicitis that occurs during the treatment with study intervention should be reported as the AE, and the resulting appendectomy should be recorded in the source documents and eCRF. If a surgical procedure was planned prior to entry into the study, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an AE. Note that, as described in Section 8.2.2, any hospitalization occurring as the consequence of an AE during the study period should be reported as an SAE.

Each AE is to be classified as serious or nonserious by the investigator using medical and scientific judgment.

Treatment of AEs will be symptom-based and at the discretion of the investigator.

8.2.2. Definition of Serious Adverse Events

An SAE is an untoward medical occurrence or effect at any dose, regardless of whether it is considered to be related to the study intervention, which results in one of the following:

- Results in death. This includes all deaths on treatment or within 6 months after last study intervention administration, including deaths due to disease progression. Any death occurring later than 6 months following the last dose need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported AE should be the event that caused the death.
  In addition, any AE resulting in death that occurs post the AE reporting period and that the investigator assesses as possibly related to the study intervention should also be reported as serious.

- Is life-threatening. This refers to an event in which the subject was at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Requires hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the study intervention, procedures required by the study protocol, or treatment-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Emergency room visits that do not require admission to the hospital do not fall into this category, but the event may still be serious due to another seriousness criterion.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Any other medically important event that the investigator or PTC judges to be serious or which is defined as serious by the regulatory agency in the local country. These are AEs that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether an AE is serious based on the above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death, or congenital anomaly (including that in an aborted fetus). Note: Hospitalization for social circumstances without any other accompanying SAE should not be reported as an SAE.

8.2.3. Adverse Events Reporting

Adverse events will be reported by the subject.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the subject to discontinue the study intervention (see Section 4.4).

Each subject will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by PTC Pharmacovigilance Department to obtain specific follow-up information in an expedited fashion.

All AEs are to be recorded in the source documents and on the eCRF using concise medical terminology; whenever possible, terms contained in the Medical Dictionary for Regulatory Activities (MedDRA) should be employed. In addition, the following information should be recorded:

- Indication of whether the event is serious or nonserious (see Section 8.2.2)
- Relationship to study intervention (see Section 8.2.5)
- Severity of the event (see Section 8.2.5)

- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

Table 6 summarizes the investigator site requirements for recording AEs on the eCRF and for reporting SAEs and adverse events of special interest on the SAE Report Form to PTC Pharmacovigilance Department.

Table 6: Investigator Site Requirements for Recording/Reporting Adverse Events

Event	Recorded on the eCRF	Reported to PTC Pharmacovigilance Within 24 Hours of Awareness
Serious AE	All	All
Nonserious AE	All	None
AESI	Not applicable	Not applicable
Other, eg, exposure during pregnancy or breastfeeding	All (regardless of whether associated with an AE)	All (regardless of whether associated with an AE)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; eCRF, electronic case report form

8.2.4. Time Period and Frequency for Collecting/Reporting Adverse Event Information

The AE (both serious and nonserious) collection and AE reporting period begins with the signing of the ICF and continues until 6 months after the last dose of study medication. All AEs during this time period must be recorded whether or not the event is considered drug related.

For subjects who are screen failures, the active collection period for AEs ends when screen failure status is determined. Any SAEs occurring during screening procedures should be reported, and the appropriate causality assessment (ie, "not related" to study intervention) section of the SAE Report Form must be completed.

If the subject withdraws from the study and also withdraws consent for the collection of future information, the active collection period for AEs ends when consent is withdrawn.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly notify PTC Pharmacovigilance Department via the SAE Report Form.

8.2.4.1. Serious Adverse Event Reporting

All SAEs (both initial and follow-up) must be reported via the SAE Report Form to PTC Pharmacovigilance Department immediately, and under no circumstance should this exceed 24 hours from awareness. In addition, the AE portion of the eCRF must also be completed.

The SAE Report Form must be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE Report Form must be faxed or emailed to the PTC Pharmacovigilance Department and to the site Institutional Review

Board (IRB)/Independent Ethics Committee (IEC) (if required by local regulations) within 24 hours. The investigator's signature must be obtained as soon as possible after the report is submitted, and the report revised if necessary and submitted to PTC Pharmacovigilance Department. The investigator will maintain a copy of the SAE Report Form on file at the study site.

Follow-up information to the SAE should be clearly documented as "follow-up" in the SAE Report Form and must also be faxed or emailed to the same party within the same timelines. All follow-up SAE Report Forms for the event must be signed by the investigator as per instructions above. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to PTC should be redacted so that the subject's name, address, and other personal identity information are obscured. Only the subject's study number and initials are to be provided (in regions where the provision of such information is permitted). The information in the AE portion of the eCRF and the SAE Report Form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

The PTC Pharmacovigilance Department contact information for reporting SAEs is provided below. This information is also provided in the SAE Report Form.

PTC Pharmacovigilance Department
Email: Pharmacovigilance@ptcbio.com
SAE Fax Line: +1-908-325-0355

8.2.5. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.2.5.1. Assessment of Severity of Adverse Events

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. For each episode, the highest severity grade attained should be reported.

The investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories (Table 7).

Table 7: Grading of Adverse Events

Grade	Adjective	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade	Adjective	Description
4	Life-threatening	Sign or symptom results in urgent intervention.
5	Fatal	Sign or symptom results in death.

Abbreviations: ADL, activities of daily living

8.2.5.2. Describing Adverse Event Relationship to Study Intervention

The investigator should provide an assessment of the relationship of the AE/SAE to the study intervention, and each occurrence of each AE/SAE as outlined in Table 8. The investigator will use clinical judgment to determine the relationship.

The investigator will also consult the Investigator's Brochure in his/her assessment.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an AE/SAE has occurred, and the investigator has minimal information to include in the initial SAE Report Form to PTC Pharmacovigilance Department. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE Report Form to PTC Pharmacovigilance Department.

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product.

- If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If a relationship cannot be excluded but there is a clear alternate cause that is more likely to have caused the AE than study intervention, the AE should be considered "unlikely related."
- If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "possibly or probably related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable," the event will be considered to be related to the investigational product or the purposes of expedited regulatory reporting. An assessment of "unlikely related" will be considered unrelated for regulatory reporting purposes.

The investigator may change his/her opinion of causality in light of follow-up information and must send an SAE Follow-Up Report Form with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements (Table 8).

Table 8: Relationship of Study Intervention to Adverse Event

Relationship	Description
Probably	A clinical event in which a relationship to the study intervention seems probable because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; improvement upon withdrawal of the drug; recurrence upon rechallenge with the drug; lack of alternative explanations for the event.

Relationship	Description
Possible	A clinical event occurring coincident with administration of the study intervention, and which may or may not be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal or rechallenge may be lacking.
Unlikely	A clinical event with a temporal relationship to the study intervention exposure that does not preclude causality but for which there is a clear alternate cause that is more likely to have caused the adverse event than study intervention. Such alternatives include a concomitantly administered drug, the subject's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to the study intervention seems improbable because of factors such as inconsistency with known effects of the study intervention, lack of a temporal association with study intervention administration, lack of association of the event with study intervention withdrawal or rechallenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors

8.2.6. Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE Report Form, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (see Section 4.6).

All AEs should be followed up by the investigator until they are resolved or the investigator assesses them as chronic or stable. The investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, PTC Pharmacovigilance should be informed via email or fax.

A subject withdrawn from the study because of an AE must be followed by the investigator until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized. Follow-up may need to continue after the subject has discontinued from the study, and additional investigations may be requested by the medical monitoring team.

The investigator must submit any updated SAE information to PTC Pharmacovigilance Department within 24 hours of receipt of the information.

8.2.7. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to PTC of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study intervention under clinical investigation are met.

As the sponsor of the study, PTC has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. PTC will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and PTC policy and forwarded to investigators as necessary.

An investigator who receives SUSAR report(s) or other safety specific information (eg, summary or listing of SAEs) from PTC will review and then file it along with the reference safety information (Investigator's Brochure) and will notify the IRB/IEC, if appropriate, according to local requirements.

8.2.8. Exposure During Pregnancy or Breastfeeding

Exposure to the study intervention under study during pregnancy or breastfeeding are reportable to PTC Pharmacovigilance within 24 hours of investigator's awareness.

8.2.8.1. Exposure During Pregnancy

PTC Pharmacovigilance must be notified in the event that a female subject in the study, or a female partner of a male subject in the study, becomes pregnant on-study or within 6 months of the last dose of the study medication on an Investigational and Marketed Products Pregnancy Report Form (hereafter referred to as Pregnancy Report Form; refer to the study manual for details). This must be reported whether or not an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

Written consent is required prior to collecting and reporting any information on a female partner of a male subject in the study.

In any of the 4 situations listed below, the subject will be provided with a Pregnancy/Pregnant Partner Data Release Form to request their consent to follow the progress of the pregnancy and the birth and the health of their child.

- Subject becomes pregnant while participating in the study.
- Female partner of a male subject in the study becomes pregnant.
- Subject becomes pregnant up to 6 months after completion of the study.
- Female partner of a male subject in the study becomes pregnant up to 6 months after the partner completed the study.

Because the risk to an unborn child is unknown, the subject should be asked to sign the Pregnancy/Pregnant Partner Release Form. However, signing this form is voluntary; it is up to the subjects to decide whether to agree to the collection of this information or not. Upon signing, the subject's and the child's medical records relating to the pregnancy and delivery, and the health of the child, will be reviewed for up to 1 year of age.

If possible, the investigator should follow the subject, or the pregnant female partner of a male subject, until completion of the pregnancy and notify the medical monitor of the outcome within 5 days or as specified below. The investigator must provide this information as a follow-up to the initial Pregnancy Report Form via the Pregnancy Outcome Section (refer to the study manual for details).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs (ie, report the event to PTC Pharmacovigilance Department and follow up by completion of appropriate AE eCRFs and submission of the SAE Report Form).

All information collected with regard to the pregnancy, the delivery of the child, and the health of the child is confidential to the limit allowed by law. These data will be coded to hide the subject's identity and the identity of the child. In particular, the subject's name and the child's name will not be reproduced on any other paper or electronic document. These data will not be disclosed voluntarily by PTC. However, regulatory agencies may have to examine these data to ensure that the study is done properly.

Of note, if the pregnant female partner of a male subject participating in the study does not wish to provide such information, this will not prevent the partner from continuing with the study.

Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study (see Section 4.4).

8.2.8.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female subject is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to PTC Pharmacovigilance Department within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Investigational and Marketed Products Pregnancy Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the subject enrolled in the study, so the information is not recorded on an eCRF. However, a copy of the completed Investigational and Marketed Products Pregnancy Report Form is maintained in the investigator site file. An exposure during breastfeeding report is not created when a PTC drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding via SAE Report Form.

8.2.9. Cardiovascular and Death Events

No cardiovascular or death events have been observed in clinical studies with PTC518.

8.2.10. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

8.2.10.1. Progression of Underlying Disease

If the progression of the underlying disease is greater than that which would normally be expected, or if the investigator considers that there may be a causal relationship between the study drug or protocol design/procedures and the disease progression, and meets the seriousness

criteria, then it must be reported to PTC Pharmacovigilance Department within 24 hours of awareness.

8.2.10.2. Abnormal Findings Associated With the Disease Being Studied

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline of this study and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, should not be reported as AEs or SAEs.

8.2.11. Contraceptive Guidance

8.2.11.1. Male Subject Reproductive Inclusion Criteria

Male subjects are eligible to participate if they agree to the following requirements during the treatment period and for at least 6 months after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS, either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male subjects (refer to the list of highly effective methods in Section 8.2.11.4).

8.2.11.2. Female Subject Reproductive Inclusion Criteria

A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP (per definition in Section 8.2.11.3).

OR

- Is a WOCBP and using an acceptable contraceptive method as described in Section 8.2.11.4 during the intervention period and for a minimum of 6 months after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention. The investigator is responsible for review of medical history, menstrual history, and recent

sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8.2.11.3. Women of Childbearing Potential

Women of childbearing potential are defined as women who are fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Postmenopausal is defined as no menses ≥12 months without an alternative medical cause. In addition, a high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

8.2.11.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Women of childbearing potential must agree to use highly effective methods of contraception during dosing and for 6 months after stopping the study medication.

Female partners of enrolled males who are of childbearing potential should consider use of highly effective methods of contraception while the enrolled male is taking study drug and for 6 months after stopping study drug.

Highly effective contraception methods are defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly and include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

In case of use of oral contraception, WOCBP should have been stable on the same pill for a minimum of 3 months prior to Screening.

Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

8.2.12. Adverse Events of Special Interest

Not Applicable

8.2.13. Medication Errors

Table 9 shows the requirements for reporting medication errors.

Table 9: Investigator Site Requirements for Recording/Reporting Medication Errors

Event	Recorded on the eCRF	Reported to PTC Pharmacovigilance Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Abbreviations: AE, adverse event; eCRF, electronic case report form; SAE, serious adverse event

Medication errors include the following:

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study subject
- Administration of expired study intervention
- Administration of an incorrect dosage
- Administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by PTC that the study intervention under question is acceptable for use.

Such medication errors occurring to a study subject are to be captured in source documents and in the eCRF as applicable.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded in source documents, and if applicable, any associated AEs, serious and nonserious, are recorded on the AE page of the eCRF.

If a medication error is associated with an SAE, this must be reported to PTC Pharmacovigilance Department within 24 hours of awareness on the SAE Report Form.

9. STATISTICS

This section outlines the statistical and analytical methods to be used in the study. Exploratory analyses of the data not described in the following subsections may be conducted as deemed appropriate. Additional details will be provided in the statistical analysis plan (SAP), which will be finalized before study unblinding.

9.1. Subject Populations for Analysis

Intent-to-Treat (ITT) Population: All randomized subjects who take at least 1 dose of study drug. The ITT Population will be used in all efficacy analysis and subjects will be analyzed according to their randomized treatment.

Per Protocol (PP) Population: All subjects in the ITT population who have no major protocol deviations that affect the validity of the efficacy measurements. The PP Population will be used for sensitivity analysis of the efficacy endpoint. The criteria for inclusion in the PP Analysis Set will be finalized prior to study unblinding and detailed in the SAP.

Safety Population: All randomized subjects who receive at least 1 dose of study drug, with subjects grouped according to the treatment they actually receive. The Safety Population will be used in all safety analyses.

PK Population: All randomized subjects who take at least 1 dose of study drug. This analysis set comprises all subjects included in the Safety Population who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the PK assessment (ie, without major protocol violations or deviations).

9.2. Sample Size Determination

The sample size calculation for each disease stage is based on mean change from Baseline in blood tHTT protein at Month 3 (primary endpoint), assuming PTC518 has the same effect on blood tHTT protein reduction. With an effect size of 0.85 (ie, the magnitude of treatment difference is 85% of one standard deviation), achievement of 85% power at 2-sided alpha level 0.05 would require 24 subjects. Approximately 24 subjects will be randomized to each active treatment arm and approximately an additional 36 subjects per disease stage will be randomized to placebo. An additional 18 subjects (per disease stage) may be randomized to the maximum tolerated dose. Up to 252 adult male and female subjects (126 per disease stage) will be enrolled.

9.3. Statistical Methods

9.3.1. General Approach

Summary tables for continuous variables will contain the following statistics: N, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence intervals as appropriate. Summary tables for categorical variables will include N and percentage in each category. Graphical techniques will be used when such methods are appropriate and informative. By-subject listings will be created.

Endpoints will be evaluated primarily with both disease stages combined, and by disease stage.

Transformations of the data may be explored if warranted by the distribution of the data.

9.3.2. Safety Analyses

The safety analysis will be performed for the Safety Population. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) CTCAE by treatment group. All TEAEs will be tabulated by System Organ Class and MedDRA Preferred Term. On-study laboratory abnormalities including hematology and chemistry will be summarized using worst grade per NCI CTCAE criteria.

9.3.2.1. Adverse Events

AEs will be tabulated using the MedDRA classification system. The frequency of subjects experiencing a specific AE will be tabulated by treatment group, System Organ Class, Preferred Term, seriousness (nonserious versus serious), worst severity, outcome, and relationship to study drug. Subject with AEs leading to death or to discontinuation from treatment, and SAEs will be listed.

9.3.2.2. Laboratory Abnormalities

The severity of laboratory abnormalities will be graded using the CTCAE whenever possible. The frequency of subjects experiencing a specific laboratory abnormality will be tabulated by treatment group and worst severity. In addition, the number and percentage of subjects experiencing a specific laboratory abnormality will be tabulated similarly.

9.3.2.3. Other Safety Assessments

The results of vital sign measurements, body weight assessments, and ECG assessments will be summarized by treatment group by using appropriate descriptive statistics.

9.3.3. Efficacy Analyses

9.3.3.1. Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in blood tHHT protein at Month 3. The null hypothesis of this study is that the mean change from Baseline for blood tHTT protein is the same in the PTC518 arm and in the placebo arm versus the alternative that they are different.

A repeated measure analysis model (repeat on visit) will be used to compare each dose with placebo for blood tHTT protein levels. The model will include treatment, visit, treatment by-visit interaction and baseline blood tHTT, CAG, age, and CAG by age interaction as covariates. Nominal p values and 95% confidence interval for each pairwise comparison at Month 3 (active vs placebo) will be provided. The model will include disease stage (by PIN_{HD} bin for Stage 2 only and by TFC for Mild Stage 3 only) as a stratification factor.

For Stage 2, PIN_{HD} will be used as a stratification factor with the following stratification classes:

- 0.180 to 0.679
- 0.680 to 1.520
- 1.521 to 4.930

For Mild Stage 3, TFC will be used as stratification factors with the following stratification classes:

- 11
- 12
- 13

9.3.3.2. Analysis of Secondary Endpoints

The key secondary endpoint (change from baseline in caudate volume as assessed via vMRI at Month 12) will be analyzed by a mixed model repeated measures (MMRM) model using all available vMRI data up to the Month 12 Visit. The model will include fixed effects for treatment, baseline vMRI, and disease stage (by PIN_{HD} bin for Stage 2 only and by TFC for Mild Stage 3 only). The intercept and time of collection will be included as a random effect nested within subjects. The unstructured covariance matrix will be used in the model. The rate of changes will be compared between treatments and the least squares (LS) mean differences at Month 12 will also be provided.

For change from baseline in cUHDRS, a MMRM analysis (repeat at visit) will be performed using all data collected up to 12 months. The model will use treatment group, visits (categorical), treatment by-visit interaction, disease stage as fixed factors, CAG, age, and CAG by age interaction as covariates. The LS mean estimates for the change from Month 12, the difference between pairwise comparison with placebo, confidence intervals, and 2-sided p value will be presented. A similar model will be used for UHDRS sub-scores and PBA-s. Rate of changes in these scores will also be explored.

For by disease stage analyses, PIN_{HD} category (0.180 to 0.679, 0.680 to 1.520, or 1.521 to 4.930) will be used as a fixed factor for Stage 2 only, and TFC score (11, 12, or 13) will be used as a fixed factor for Mild Stage 3 only.

A repeated measure analysis model, similar to the analysis model used for blood tHTT protein, will be used for blood and CSF mHTT protein. Dose-response relationships will be explored and a by-visit summary of blood tHTT and blood and CSF mHTT protein will be displayed.

An analysis of covariance model with dose and Baseline in the model will be used to analyze change from Baseline to Month 12 in mHTT protein (in blood and CSF). Nominal p values and 95% confidence interval for each pairwise comparison will be calculated.

9.3.3.3. Analysis of Exploratory Endpoints

Change from Baseline in CSF mHTT protein and in blood mHTT protein at Month 3 will be summarized descriptively.

Change from Baseline in imaging parameters whole brain, putamen, and ventricular volume (as assessed by vMRI) will be summarized descriptively.

Change from Baseline in PBA-s, and UHDRS sub-scores, including TFC, TMS, SDMT, and IS, will be summarized descriptively. The relation between these parameters with blood HTT protein will be explored.

Change from Baseline in the FuRST 2.0 questionnaire will be summarized descriptively.

Change over time in blood *HTT* mRNA will be summarized descriptively.

Change over time in concentrations of NfL protein (in plasma and CSF) and [redacted] will be summarized descriptively.

Change from Baseline in wearable accelerometer assessment TUG, 2-minute walk distance, and postural sway will be summarized descriptively.

9.3.4. Analysis of Pharmacokinetic Endpoints

Individual and descriptive plasma concentration at predose and postdose will be reported for each visit. Individual and descriptive accumulation of study drug will be calculated and reported for both plasma and CSF using predose concentrations at Visits 3 through 8 for plasma and at Visits 5 through 8 for CSF, respectively.

9.3.5. Baseline Descriptive Statistics

9.3.5.1. Disposition

Subjects who did not complete the treatment or study will be summarized. Reasons for treatment/study discontinuation will be summarized.

9.3.5.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics at study entry will be summarized with frequency tables for categorical variables and descriptive statistics such as the mean, standard deviation, median, and range, as appropriate, for quantitative variables.

9.3.5.3. Medical History and Prior Medication

Medical history and prior medication information will be summarized by treatment group.

9.3.6. Extent of Exposure and Concomitant Medications

Exposure to study drug will be summarized descriptively by treatment group.

Concomitant medication information will be summarized by treatment group.

9.4. Planned Interim Analyses

PTC plans to conduct an interim analysis to confirm the PK and PD expectations and to evaluate safety when approximately 36 subjects from the 5 mg dosing group (Parts A and/or D), and 36 subjects from the 10 mg dosing group (Parts B and/or E), including placebo, have completed 12 weeks of treatment. An independent analysis team will conduct the unblinded analysis. Only summary level results will be shared with the PTC study team. The study will maintain double-blinding for investigators and the sponsor study team at a subject level until after the database is locked. More details will be provided in an interim SAP.

9.5. Statistical Significance

The significance level will be 0.05, using 2-sided tests for the primary efficacy endpoint.

9.6. Missing Data

Missing data will not be imputed for summaries for all safety endpoints and for by-visit summaries for all the PD parameters including tHTT protein (in blood).

For the primary analysis of the primary endpoint, MMRM model will be used on the available data assuming the missing assessments are missing at random. Missing data will be imputed using the multiple imputation procedure (Rubin 1987, Ouyang 2017) to further assess the influence of missing primary endpoint data and details of the method will be provided in the SAP. Briefly, these methodologies will include multiple imputation under an assumption of missing not at random and tipping-point analyses to explore how extreme the difference between randomized treatments would have to be among subjects with missing data to overwhelm the treatment effect obtained in the primary. In these analyses, the multiple imputation approach will be expanded to allow for varying impact of missing data by incorporating a shift parameter in the imputation model. The range of values for the shift parameter will explore the varying missing data assumptions, including the scenario where the imputation model is completely based on the control group (ie, control-based imputation).

More details of missing data handling will be provided in the SAP.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

In accordance with 21 Code of Federal Regulations Part 312.56 and/or relevant ICH guidelines, PTC or a designee will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (FDA 2020), the monitoring visits provide PTC with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this study. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by PTC. The investigator/institution guarantees direct access to source documents by PTC or a designee and appropriate regulatory authorities.

It is important that the investigator and relevant institutional personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.1. Study Monitoring

Before a potential investigational site can be selected to conduct the study, a representative of PTC or its designee will visit the investigational study site to:

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

During the study, a monitor from PTC or representative will have regular contacts with the investigational site, 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 accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to PTC.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to PTC and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

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

10.2. Audits and Inspections

PTC may conduct audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of Good Clinical Practice (GCP) and ICH related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the investigator must inform PTC immediately that such request has been made.

The investigator will permit such audits by PTC or Health Authorities and facilitate them by providing access to the relevant source documents.

10.3. Safety Oversight

External oversight for this study will be provided by a DSMB as defined in the DSMB Charter. The primary responsibility of the DSMB is to protect the safety and welfare of subjects participating in this clinical study and to ensure the integrity of the clinical study. To maintain the blinding and integrity of the study, procedures will be implemented to ensure that the DSMB and independent statistician have sole access to unblinded safety data.

Specifically, for this study, the DSMB will be responsible for the following:

- Examining accumulated safety data, PK, PD, biomarker, and compliance data in order to make recommendations concerning continuation, termination, or modification of the study based on the safety of the interventions under study
- Reviewing major study design modifications proposed by PTC or the investigators prior to implementation of those modifications
- Reviewing the general progress of the study as regards accrual, protocol violations, and study conduct

11. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, PTC, PTC's representatives, a regulatory authority, IEC, and/or IRB may conduct a quality assurance audit. Reasons for quality assurance audit may include, but are not limited to, random selection, geographic proximity, suspected GCP violation, high enrolling site, recurring protocol deviations, etc. The purpose of an audit or inspection by PTC is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact PTC immediately if contacted by a regulatory agency about an inspection.

11.1. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to, the following:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc (either the tests were not done, the incorrect tests were done, or the tests were not done within the time frame specified in the protocol)
- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, or failure to obtain IRB/IEC approvals for the protocol and ICF revisions

Major deviations are any deviations that impact subject eligibility (ie, protocol inclusion/exclusion violations), subject safety, or a subject's ability to continue in the study.

At the outset of the study, a process for defining and handling protocol deviations will be established with the Contract Research Organization (CRO). This will include determining which deviations will be designated major; thus, requiring immediate notification to the medical monitor and PTC. Prospective deviations (eg, protocol waivers) are prohibited by PTC policy. The investigator is responsible for seeing that any known protocol deviations are recorded as agreed.

12. ETHICS

12.1. Ethics Review

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the investigator and made available for inspection.

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to PTC before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. PTC will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

12.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

12.3. Written Informed Consent

By signing the protocol, the investigator assures that informed consent will be obtained from each subject/subject's caregiver prior to study entry and that the informed consent will be obtained in accordance with current regulations.

The investigator or sub-investigator will give each subject full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent document will be provided to each subject in a language in which they are fluent. This information must be provided to the subject prior to undertaking any study-related procedure. Adequate time should be provided for the subject to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the subject may have about the study. The subject's signature on the ICF should be obtained at the investigator site in the presence of the investigator or a qualified representative (eg, sub-investigator).

The original signed ICFs will be retained by the investigator with the study records. The written subject information must not be changed without prior approval by PTC and the IRB/IEC.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to

refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement or refusal to allow any remaining specimens to be used for exploratory research.

13. DATA HANDLING AND RECORDKEEPING

To enable evaluations and/or audits from regulatory authorities or PTC, the investigator agrees to keep accurate and complete records, including the identity of all participating subjects (sufficient information to link eCRFs and clinic records/source documents), all original signed ICFs, electronic copies (ie, CD-ROM, USB, etc) or paper copies of the data that have been captured in the EDC for each subject (eCRFs), and detailed records of study drug disposition.

The investigator agrees to keep all information provided by PTC in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by PTC will be stored appropriately to ensure their confidentiality. The information provided by PTC to the investigator may not be disclosed to others without direct written authorization from PTC, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

All records and documents pertaining to the study will be maintained by the investigator until notification is received from PTC that the records no longer need to be retained. The investigator must obtain written permission from PTC before disposing of any records. The investigator will promptly notify PTC in the event of accidental loss or destruction of any study records. If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to PTC as applicable.

13.1. Inspection of Records

PTC will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, Drug Accountability Records, subject charts and study source documents, and other records relative to study conduct.

13.2. Retention of Records

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into 2 different categories: investigator's file, and subject clinical source documents.

The investigator's file will contain the protocol/amendments, eCRFs, IEC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per ICH/GCP and local regulations.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory, ECG, pathology and special assessment reports, consultant letters, etc.

These 2 categories of documents must be kept on file by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval or 25 years, whichever is longest). No study document should be destroyed without prior written approval from PTC. Should the investigator wish to assign the study records to another party, or move them to another location, PTC must be notified in advance.

When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

The handling of personal data will comply with local regulations.

13.3. Future Use of Stored Specimens and Data

As part of the current study, blood, plasma, urine, and CSF will be collected. Sample processing will be performed by a laboratory under the direction of PTC. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy. Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of PTC will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. PTC will not sell the samples to a third party.

PTC may store blood and CSF samples for up to 5 years after the end of the study, in accordance with local regulations, to achieve study objectives. Additionally, with subjects' consent, samples may be used for further research by PTC to contribute to the understanding of HD. A separate section of the ICF will address the use of remaining samples for optional exploratory research, as described in Section 12.3.

- Further research may include mutant HTT quantification in the CSF using a more sensitive and robust assay, if one is developed in the future.
- If more robust longitudinal and cross-sectional data are available on the following biomarkers, they may be evaluated:

At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed. No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with any of the biologic samples. All samples will be single coded.

PTC will take steps to ensure that data are protected accordingly, and confidentiality is maintained as far as possible.

Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection. PTC and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include the following:

- CROs retained by PTC
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed. Given the research nature of the laboratory analysis, it will not be possible to return individual data to subjects. The

results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

13.4. Data Protection

- Each clinical study subject will receive a unique identifier that is assigned to them via a web-integrated IRT system. Unique identifiers do not contain any personally identifiable information. Any subject records or datasets that are transferred or accessible to PTC will contain the unique identifier only. Directly identifiable personal information will not be transferred or accessible to PTC.
- In the implementation of the study, PTC and the investigator will comply with all applicable privacy and data protection laws and any additional requirements as may be requested by the local data protection authorities (such as the CNIL Methodology MR001 in France) in order to perform the study.
- The subject will be informed of the purposes and conditions under which his/her personal study-related data will be used by PTC in accordance with local data protection law.
- The subject will be informed that his/her medical records related to the study may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by PTC to monitor the study, or by appropriate IRB/IEC members, or by inspectors from other regulatory authorities, as applicable under the local regulatory framework.

14. PUBLICATION POLICY

The information developed during the conduct of this clinical study is considered confidential by PTC. This information may be disclosed as deemed necessary by PTC.

PTC intends that the data from this study will be presented and published. The PTC staff under the direction of the PTC Chief Development Officer or designee in collaboration with the investigator will be responsible for writing presentations and manuscripts for publication. Investigators will not be allowed to publish or present the data from this study without prior agreement with PTC.

The investigator is obliged to provide PTC with complete test results and all data derived by the investigator from the study. During the study, only PTC may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the Clinical Study Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of PTC.

PTC may publish any data and information from the study (including data and information generated by the investigator) jointly with the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Data from all sites participating in the study will be pooled and analyzed by PTC or PTC's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the investigator may publish or present the results generated at his or her site.

The investigator will provide PTC with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. PTC shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect PTC's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless PTC has notified the institution or the investigator in writing that such proposed publication or presentation discloses PTC's confidential and proprietary technical information. Furthermore, upon the request of PTC, the investigator will delay the publication or presentation for an additional 90 days to permit PTC to take necessary actions to protect its intellectual property interests.

15. PROTOCOL AMENDMENT HISTORY

Version 1.0: 21 September 2021

Version 2.0: 09 December 2021

Version 3.0: 03 February 2022

Version 4.0: 03 June 2022

Version 5.0: 15 December 2022

Version 6.0: 05 October 2023

15.1. Version 6.0: 05 October 2023

The overall reason for Version 6.0 of the protocol was to add reference to the Phase 2 long-term extension study (PTC518-CNS-004-HD).

Section #	Version 6.0/Description of Change	Reason/Rationale
Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical errors, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis and Schedule of Assessments were updated to be consistent with changes in the protocol.	Update
Section 1.1 Table 4 Section 8.2.2 Section 8.2.4	The Safety Follow-Up Period was revised to be 6 months throughout the protocol for consistency with the Schedule of Assessments	Update
Section 1.2	Added that subjects will have the option to enroll into the Phase 2 long-term extension study upon completion of Visit 8 of this study.	Update
Section 3.7	Added a section to outline unscheduled visits and added that subjects may continue within this study attending unscheduled visits approximately every 3 months prior to the end of study visit if they intend on enrolling in the Phase 2 long-term extension study, but that study is not yet locally approved for conduct.	Update
Table 4	Corrected terminology in the notes for clarity. Extended the visit window to be 7 days where applicable. Divided the UHDRS assessment into its individual parts for clarity.	Update
Section 4.2	Extended the definition of exclusion criterion 6 to be specific of what entails [redacted]. Added any known hypersensitivity to PTC518 or its excipients to exclusion criterion 16.	Update
Section 7.2.2	The description of UHDRS was updated to more accurately match the assessment questionnaire.	Update
Section 8.2.10.1	Clarified that if progression of underlying disease is greater than that normally expected and meets expected criteria, or if the investigator considers that there may be a causal relationship between the study drug or protocol design/procedures and the disease progression, and meets the seriousness criteria, then it must be reported to PTC Pharmacovigilance Department within 24 hours of awareness.	Update

15.2. Version 5.0: 15 December 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Protocol Section	Version 5/Update	Reason/Rationale
Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) and minor updates to the text were incorporated to provide clarity. The synopsis and Schedule of Assessments were updated to be consistent with changes in the protocol.	Update
Section 1	Details outlining the HD-ISS staging system of HD were added.	Update
Section 1 Section 1.1 Figure 2	The protocol was updated to define the population to be enrolled in the study as Stage 2 or Mild Stage 3 HD based on the HD-ISS staging criteria.	The enrollment in the study was expanded to enroll those who either have not yet experienced functional decline or who only have very limited features of functional decline as this population is determined to be the most likely to benefit from stabilization of disease from treatment with PTC518.
Section 1.1 Section 4.5 Section 5.4	Specified that the UHDRS TFC and IS scores will be utilized for screening subjects. Specified that PIN_{HD} score will be utilized for stratification of the Stage 2 group only, and that the Mild Stage 3 group will be stratified by TFC score.	Update
Section 1.1 Section 7.2.4 Table 4	Corrected the assessment of early motor changes to be via Opal wearable devices.	Update
Section 1.2 Figure 2	Specified that those with Mild Stage 3 disease will participate in Parts D, E, and F of the study.	Update
Section 1.2 Figure 1	Added an additional Follow-Up Safety Visit on Month 18.	For a final evaluation of adverse events and pregnancy testing 6 months after the last dose of study drug.
Section 1.3.1	Added a section detailing the summary of safety risks, aligning content with the Investigator's Brochure.	Update
Section 2.2 Section 2.7	Added the change in cUHDRS as a secondary objective and endpoint, previously an exploratory objective and endpoint. Specified the secondary objective of mHTT protein in CSF and blood mHTT levels to be at Month 12.	Update

Protocol Section	Version 5/Update	Reason/Rationale
Section 2.3 Section 2.8	Added the change from Baseline in CSF and blood mHTT protein at Month 3 as exploratory objectives and endpoints. Changed the endpoints of change from Baseline in whole brain, putamen, and ventricular volume, UHDRS sub-scores, PBA-s, and TUG, 2-minute walk distance, and postural sway, and FuRST 2.0 questionnaire from over time to at Month 12. Specified the UHDRS sub-scores being evaluated as an exploratory endpoint.	Update
Section 3.1 Section 4 Section 9.2	Updated the number of subjects being enrolled in the study to be up to 252 to correspond with the addition of Mild Stage 3 subjects in the study.	To broaden learning in this Phase 2 study to include more of HD early disease, adding Mild Stage 3 (per HD-ISS staging). Enrollment numbers were also adjusted due to increased power for the primary and key secondary endpoints with larger overall subject numbers.
Table 4	The Baseline period was extended to span from Days -22 to -1.	To reduce the burden on subjects of performing multiple long baseline assessments in a relatively short timeframe.
Table 4	Specified that the safety follow-up visits must be performed for all subjects following either the EOS or ET visits.	Update
Table 4 Table 5 Section 8.1.10.2	Modified the pregnancy testing to be monthly from Day 1 through the last Safety Follow-up Visit. Stated that for when no in-person visit is scheduled, a home pregnancy test will be taken by the subject and reported to the investigator.	Update
Table 4 Section 8.1.7	Transpupillary photographs were removed from the study.	To reduce the burden on subjects, as nonclinical toxicology data (as shared in the IB) indicate that it is safe to remove this assessment from the clinical study
Table 4	PBA-s assessment was removed from Visits 5, 6, and 7 as it will only be conducted in place of Part III of the UHDRS on applicable visits (ie, Visits 2 and 8).	Update
Table 4 Section 4.2 Section 8.1.10	Updated language surrounding the C-SSRS versioning that will be utilized in the study for consistency among study documentation.	Update

Protocol Section	Version 5/Update	Reason/Rationale
Section 4.1	Modified the CAG repeat length to qualify for enrollment to be from 40 to 50, inclusive. Inclusion criteria has been added to delineate Stage 2 and Mild Stage 3 HD.	Update
Section 4.1 Section 8.2.11.3	Bilateral tubal ligation was removed as an acceptable method of permanent sterilization.	Update
Section 4.2	Specified that participation in observational studies is not exclusionary for the study.	Update
Section 4.2	A diagnosis of Juvenile-Onset HD will be excluded from the study.	To keep the subject population as homogenous as possible, as Juvenile-Onset HD is considered a different disease.
Section 5.3	Specified that treatment compliance is defined as taking ≥80% of the medication over the course of the study.	Update
Section 6.1	Modified the description of the study drug for clarity. Removed information on the composition of the drug product as this is provided in other study documents.	Update
Section 6.3	Modified to refer to the pharmacy manual or clinical label for storage conditions of the active and placebo.	Update
Section 6.4 Section 6.4.1	Removed the requirement to take the study drug prior to the first meal of the day.	Update
Section 9.3.1 Section 9.3.3.1 Section 9.3.3.2 Section 9.3.3.3	Modified the statistical methods in accordance with the added group of subjects being evaluated and the change in study endpoints.	Update
Section 9.4	Added in details regarding planned interim analyses.	Update
Section 9.6	Expanded on missing data methodology.	Update
Section 12.3 Section 13.3	Modified the use of remaining mandatory samples for optional exploratory research, and consent required for such activities.	Update

15.3. Version 4.0: 03 June 2022

Protocol Section	Version 4/Update	Reason/ Rationale
Protocol	The protocol was updated throughout to extend the study to be 12 months of treatment duration, followed by 2 Safety Follow-Up Visits 1 and 4 months after the last dose of study drug. The Schedule of Assessments was updated accordingly to account for the additional visits and the planned assessments for each visit. The Schedule of Assessments was also revised for clarity. The protocol was updated throughout to refer to Months rather than Days The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) and minor updates to the text were incorporated to provide clarity. The synopsis and Schedule of Assessments were updated to be consistent with changes in the protocol.	Update

Protocol Section	Version 4/Update	Reason/ Rationale
Section 2.1 Section 2.2 Section 2.3 Section 2.5 Section 2.7 Section 2.8 Section 2.9	The primary pharmacodynamic objective was more clearly defined. Assessing the effects of PTC518 on change in caudate volume via vMRI was moved from an exploratory objective to the key secondary objective and endpoint of the study. [redacted]. A secondary endpoint for blood tHTT protein at Month 12 was added to coincide with the primary endpoint of blood tHTT protein at Month 3. An exploratory endpoint for the cUHDRS score at Month 12 was added. The effect of PTC518 on blood *HTT* mRNA was changed to be an exploratory objective and endpoint. Plasma and CSF NfL were added as exploratory endpoints, in addition to the safety endpoints. The endpoints' timepoints were updated throughout to be consistent with the change in treatment duration to 12 months.	Update
Section 3.3	The dose justification section was revised to include updated nonclinical toxicology information from recently completed studies.	Update
Section 4.1	Removed reference to legally authorized representative throughout the protocol. Specified that CAG repeat length may be determined analytically through amplification. Added that female partners of enrolled males who are of childbearing potential should consider use of highly effective methods of contraception. Added definitions for acceptable use of abstinence as a form of contraception. Added bilateral tubal ligation as a form of permanent sterilization.	Update
Section 4.2	Specified that the inability to fast would preclude inclusion from the study. Added that antipsychotic use is not permitted unless receiving stable doses at least 6 weeks prior to Screening and with a dose regimen that is not anticipated to change during the study. Added that benzodiazepine use for sedation for study-related procedures during the course of the study is permitted.	Update
Section 7.1	Specified the total volumes of blood and CSF to be collected during the study and added reference that individual volumes to be collected are documented in a separate instruction laboratory manual.	Update
Section 8.1.5	[redacted]	Update
Section 8.1.9 Table 5	Uric acid added to the list of clinical laboratory assessments, and clarification provided about local laboratory assessment of CSF WBC, RBC, protein, and glucose.	Update
Section 8.2	Entirety of the safety reporting section was revised to align with updated safety reporting language in accordance with PTC Pharmacovigilance.	Update
Section 9	Updated the definitions of the ITT and Safety Populations for clarity. A Per Protocol Population was added. Updated the statistical methodology throughout to be in line with the extension of study duration and revisions to study endpoints. Revised so that an interim analysis may be performed at any time. Methods of missing data handling was revised.	Update

Protocol Section	Version 4/Update	Reason/ Rationale
Section 13.4	Added a section on Data Protection to outline the methods used.	Update

15.4. Version 3.0: 03 February 2022

Protocol Section	Version 3/Update	Reason/ Rationale
Protocol	The protocol was updated throughout to reflect a 3-part design with a DSMB recommendation occurring prior to the initiation of Part C. The nature of the objectives and associated endpoints was clarified, and the descriptions of assessments were simplified. The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) and minor updates to the text were incorporated to provide clarity. The synopsis and Schedule of Assessments were updated to be consistent with changes in the protocol.	Update/ Clarification
Section 1.1	Study rationale updated to reflect 3-part design	Update
Section 1.2	Study description updated to a 3-part design, behavioral scale on UHDRS replaced with the PBA-s, and CGI-C is eliminated.	Update
Section 2.3	Behavioral scale on UHDRS replaced with the PBA-s in list of exploratory objectives, CGI-C eliminated.	Update
Section 2.8	Description of endpoints edited to reflect that the PBA-s will replace the behavioral scale on the UHDRS and the elimination of the CGI-C.	Update
Section 3.1	Number of subjects updated to reflect 54 per Study Part	Update
Section 3.2	Description of randomization updated to reflect 3-part design	Update
Section 4	Description of sample size updated to reflect 3-part design	
Section 4.2	Glomerular filtration rate unit corrected and reference to LOCSIII grading scale deleted	Clarification
Table 4	Schedule of Assessments updated for clarification and to reflect changes to assessments indicated throughout the protocol.	Update/ Clarification
Section 5.4	Description of randomization updated to reflect 3-part design	Update
Section 7.2	Description of clinical scales revised to replace UHDRS Behavioral Examination with PBA-s, eliminate CGI-C, and clarify use of assessments.	Update
Section 7.2.1	Description of UHDRS revised to reflect that the PBA-s will replace the behavioral scale on the UHDRS	Update
Section 7.2.2	Description of the PBA-s added to reflect that the PBA-s will replace the behavioral scale on the UHDRS, Section devoted to CGI-C was deleted	Update
Section 7.2.3	Language added to reflect that each gait and motor assessment test will be conducted twice.	Update
Section 8.1.4	Text updated to delete reference to abbreviated physical examination, which is not be used in this study	Update
Section 8.1.7	Text updated to delete reference to LOCSIII grading scale, which will not be used in this study	Update
Section 8.1.9	Text updated to reflect that NfL will be assessed in plasma, rather than serum.	Update
Section 9.2	Description of sample size updated to reflect 3-part design	Update
Section 9.3.3.3	Description of analysis edited to reflect that the PBA-s will replace the behavioral scale on the UHDRS and the elimination of the CGI-C.	Update

15.5. Version 2.0: 09 December 2021

Overall reason for Version 2.0: The overall reason for Version 2.0 of the protocol was to incorporate Health Authority feedback.

Protocol Section	Version 2/Update	Reason/ Rationale
Protocol	The protocol was updated throughout to add a third PTC518 dose and to make the study a 2-part design. The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) and minor updates to the text were incorporated to provide clarity. The synopsis and Schedule of Assessments were updated to be consistent with changes in the protocol.	Update
Section 1.2	The study design section was moved here and updated to reflect the 2-part, 3 dose (plus placebo) design and to introduce the DSMB role in moving to Part B of the study.	Update
Section 1.3	Rationale for the doses selected was added together with DSMB details.	Update
Section 2 Section 7	NfL plasma and CSF levels, [redacted], and FuRST 2.0 assessments were added as objectives and the HD Quality of Life questionnaire was removed. The endpoints and clinical assessments were updated accordingly.	Update
Section 3	The Study Design section was removed and included instead in Section 1	Clarification
Section 3.1, Section 4, Section 9.2	The number of subjects was increased to reflect the added dose level.	Update
Section 3.2 Section 5.4	Randomization and treatment details were updated to reflect the new study design. Stratification was also added.	Update
Section 3.3	Model predictions were added as rationale of the dose selection.	Clarification
Section 3.6	Clarification of possible home care assessments was added.	Clarification
Section 4.2	Exclusion criterion #15 was updated to clarify use of illicit drugs or alcohol and #19 was updated to specify that subjects should not become pregnant within 6 months of end of treatment.	Clarification
Section 8	NfL levels were added to the safety parameters and vital signs, ECGs and laboratory test abnormalities were specified, rather than changes from baseline. Neurological examinations were removed.	Update and clarification

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17. APPENDICES

APPENDIX 1. RESTRICTED AND PROHIBITED MEDICATIONS

Drug Name	CYP3A4 Inhibitor	CYP3A4 Inducer	Strength
Aprepitant	X		Moderate
Boceprevir	X		Strong
Bosentan		X	Moderate
Carbamazepine		X	Strong
Cimetidine	X		Moderate
Ciprofloxacin	X		Moderate
Clarithromycin	X		Strong
Clotrimazole	X		Moderate
Cobicstat	X		Strong
Conivaptan	X		Strong
Crizotinib	X		Moderate
Cyclosporine	X		Moderate
Danoprevir/Ritonavir	X		Strong
Diltiazem	X		Strong
Dronedarone	X		Moderate
Efavirenz		X	Moderate
Elvitegravir/Ritonavir	X		Strong
Enzalutamide		X	Strong
Erythromycin	X		Moderate
Etravirine		X	Moderate
Fluconazole	X		Moderate
Fluvoxamine	X		Moderate
Grapefruit Juice	X		Strong
Idelalisib	X		Strong
Imatinib	X		Moderate
Indinavir/Ritonavir	X		Strong
Itraconazole Ketoconazole	X		Strong
Lopinavir/Ritonavir	X		Strong
Mitotane		X	Strong
Modafinil		X	Moderate
Nefazodone	X		Strong
Nelfinavir	X		Strong
Paritaprevir/Ritonavir/Ombitasvir	X		Strong
Phenytoin		X	Strong
Posaconazole	X		Strong
Rifampin		X	Strong
Ritonavir	X		Strong
Saquinavir/Ritonavir	X		Strong
St. John's Wort		X	Strong
Telaprevir	X		Strong
Tipranavir/Ritonavir	X		Strong
Tofisopam	X		Moderate
Troleandomycin	X		Strong
Verapamil	X		Moderate
Voriconazole	X		Strong

Abbreviations: CYP, cytochrome P450

APPENDIX 2. WORLD HEALTH ORGANIZATION RISK DRINKING LEVELS

Risk Level	Definition of Each Level (in grams and US Standard Drinks)
Very High	>100 g (>7.1 drinks) for men; >60 g (>4.3 drinks) for women
High	60-100 g (4.3-7.1 drinks) for men; 40-60 g (2.9-4.3 drinks) for women
Moderate	40-60 g (2.9-4.3 drinks) for men; 20-40 g (1.4-2.9 drinks) for women
Low	1-40 g (<2.9 drinks) for men; 1-20 g (<1.4 drinks) for women

Abbreviations: US, United States
Source: A Reduction in the World Health Organization Risk Levels of Alcohol Consumption as an Efficacy Outcome in Alcohol Use Disorder Clinical Trials

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Clinical Approval	[redacted]	
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Clinical Pharmacology Approval	[redacted]	
Statistics Approval	[redacted]	

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