STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER:

PTC518-CNS-002-HD

STUDY TITLE:

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

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VERSION 1.0

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
BMI	Body mass index
BSI	Boundary shift integral
CAG	Cytosine-adenine-guanine
CI	Confidence interval
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Plasma trough concentration
cUHDRS	Composite Unified Huntington's Disease Rating Scale
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiograms
eCRF	Electronic case report form
FuRST	Functional Rating Scale
HD	Huntington's disease
HD-ISS	Huntington's Disease Integrated Staging System
HTT	Huntingtin (protein)
HTT mRNA	Huntingtin (gene) mRNA
ICF	Informed consent form
IRT	Interactive Response Technology
IS	Independence Scale
LS	Least squares
ITT	Intent-to-Treat
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mHTT	Mutant huntingtin (protein)
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing not at random
NfL	Neurofilament light chain
PINHD	Normed version of the Huntington's disease prognostic index
PBA-s	Problem Behaviors Assessment (short form)
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred term
PTC	PTC Therapeutics
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fredericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
SOC	System organ class
SWR	Stroop Word Reading Test
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TFC	Total Functional Capacity
tHTT	Total huntingtin (protein)
TMS	Total Motor Score
[redacted]	[redacted]
TUG	Timed Up and Go
UHDRS	Unified Huntington's Disease Rating Scale
vMRI	Volumetric magnetic resonance imaging
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION AND OVERVIEW

The objective of this Statistical Analysis Plan (SAP) is to outline the procedures and statistical methods that will be employed to support the final reporting of Study PTC518-CNS-002-HD (PIVOT-HD) after the database lock for the double-blind treatment period. The statistical methods described here are based on Final Protocol Version 6.0, dated 05 October 2023. All decisions concerning the final analysis will be made before the database lock for the double-blind treatment period and the treatment unblinding and will be documented in this SAP.

This study will include a database lock for the double-blind treatment period and a final database lock. The database lock for the double-blind treatment period will occur after all subjects complete 12 months of treatment (Visit 8). The data collected during the double-blind treatment period will be included in the analysis and reported in the Clinical Study Report (CSR). Specifically, the study assessments up to 30 days (i.e., 1-month safety follow-up) after 12 months of treatment (Visit 8) will be included in the double-blind treatment period. The final database lock will take place after all subjects have completed the study. Listings for the additional data collected beyond the double-blind treatment period will be provided and reported after the final database lock.

1.1. Study Design

PIVOT-HD is a Phase 2a, randomized, placebo-controlled, dose-ranging study designed to evaluate the safety and efficacy of PTC518 and to determine the Huntingtin (HTT) protein-lowering effect of three PTC518 doses after 12 months of treatment in subjects with Huntington's disease (HD) who qualify as either Stage 2 or Mild Stage 3 disease based on the Huntington's Disease Integrated Staging System (HD-ISS) criteria.

The HD-ISS was 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.

The study consists of two groups: the Stage 2 Group and the Mild Stage 3 Group, further divided into six parts (Parts A, B, and C for the Stage 2 Group; Parts D, E, and F for the Mild Stage 3 Group). Each part includes an active treatment arm and a placebo arm. In the respective parts, subjects will be randomized to treatment arms (Parts A & D: 5 mg or matching placebo; Parts B & E: 10 mg or matching placebo; Parts C & F: 20 mg or matching placebo).

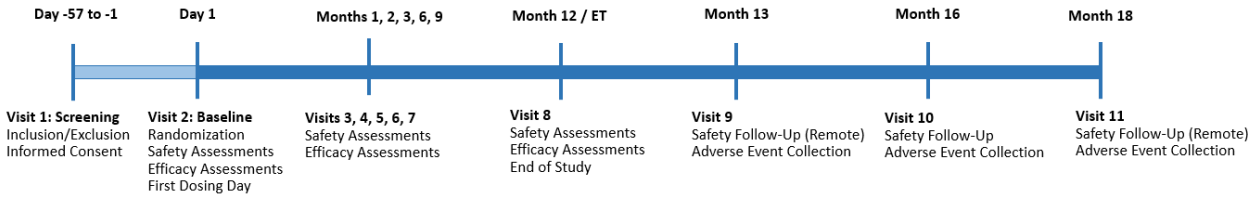
A Data and Safety Monitoring Board (DSMB) will closely monitor the safety of subjects. This study includes a provision for the potential use of a 20 mg dose based on recommendations from the DSMB. Specifically, Part C and F, which include the 20 mg dose, will not be initiated without DSMB recommendation to mitigate potential risks to subjects.

Approximately 144 subjects who satisfy all enrollment criteria at Screening will be randomized into Parts A, B, D, or E, depending on their stage of disease. Following this initial randomization, subjects in Parts A and D will be further randomized to treatment arms receiving either 5 mg PTC518 or matching placebo, while subjects in Parts B and E will be randomized to treatment arms receiving either 10 mg PTC518 or matching placebo, in a 2:1 ratio. Consequently, the combined number of participants in the placebo groups of Parts A and D/Parts B and E will be equal to the number of participants in the treatment groups of Parts A and D/Parts B and E.

Randomization will be stratified based on the normed version of the Huntington's Disease Prognostic Index (PIN_{HD}) score for the Stage 2 Group and the Total Functional Capacity (TFC) score for the Mild Stage 3 Group. Subjects will be treated for 12 months in a double-blind fashion. 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 (Month 12) 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 (i.e., approximately 4 months after the last dose of study drug) to collect adverse events and to perform [redacted]. A final Follow-Up Safety Visit will occur on Month 18 via telephone/telehealth to collect adverse event data.

The study design and the randomization plan are shown below in Figure 1 and Figure 2, respectively.

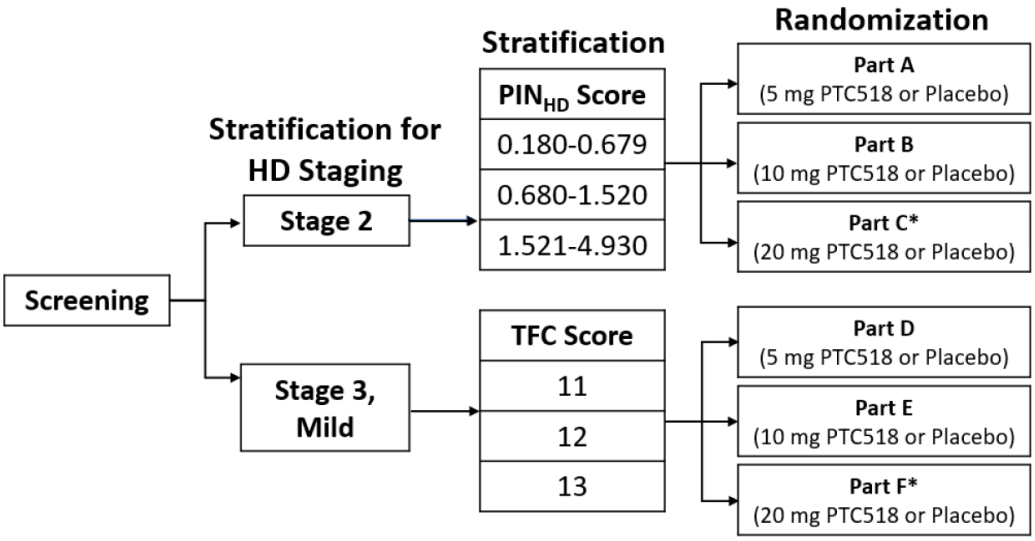
Figure 1: Study Design



Abbreviations: ET, Early Termination

Note: The Baseline period has been extended to encompass Days -22 to -1, as per the most recent protocol amendment to reduce the burden on subjects of performing multiple long baseline assessments in a relatively short timeframe.

Figure 2: Randomization Plan



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.

1.2. Study Objectives

1.2.1. Primary Objectives

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

1.2.2. 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

1.2.3. 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

1.2.4. Pharmacokinetic Objective

- Evaluate the concentration of PTC518 in subjects with HD

1.3. Study Endpoints

1.3.1. Primary Efficacy Endpoint

- Change from Baseline in blood tHTT protein at Month 3

1.3.2. 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

1.3.3. 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) 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 neurofilament light chain (NfL)

1.3.4. Pharmacokinetic Endpoints

- 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

1.3.5. Safety Endpoints

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

1.4. Sample Size

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 (i.e., the magnitude of treatment difference is 85% of one standard deviation [SD]), 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. Up to 252 adult male and female subjects (126 per disease stage) will be enrolled.

1.5. Randomization and Blinding

After subjects complete all baseline procedures on Day 1 and are eligible to be randomized, the site staff will utilize an Interactive Response Technology (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 after which they will be randomized to active treatment or placebo within each part in a 2:1 ratio of active to matching 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 recommendations 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 the staff of PTC Therapeutics (PTC) will remain blinded to the treatment until after the database is locked.

2. SUBJECT POPULATIONS FOR ANALYSIS

2.1. Intent-to-Treat (ITT) Population

The ITT population will include all randomized subjects who take at least one dose of the study drug. This ITT Population will be utilized for all efficacy analyses, with subjects analyzed according to their assigned randomized treatment.

2.2. Per Protocol (PP) Population

The PP population will include 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 primary efficacy endpoint. The criteria for inclusion in the PP population will be finalized prior to the database lock for the double-blind treatment period and the study unblinding. Subjects who meet the following criteria, but not limited to, will be excluded from the PP population:

- Had significant inclusion or exclusion criteria violations
- Received study treatment different from the randomized treatment throughout the first 3 months of study
- Had major protocol deviations which may impact the assessment for efficacy of study treatment
- Unblinded due to the partial clinical hold by the FDA

A separate documentation containing the final exclusion criteria and a list of subjects in this population will be finalized before the database lock for the double-blind treatment period and the treatment unblinding.

2.3. Safety Population

The safety population will include all randomized subjects who receive at least 1 dose of the study drug, with subjects grouped according to the treatment they receive. This population will be used in all safety analyses with subjects analyzed according to the actual treatment they receive. If subjects receive a different treatment from the one they were randomized to throughout the entire study, they will be analyzed according to the different treatment received. However, subjects who receive mixed treatments due to dosing errors will be analyzed according to their randomized treatment.

2.4. Pharmacokinetic Population

The Pharmacokinetic (PK) population will be a subset of the safety population, which includes all randomized subjects who take at least 1 dose of the study drug and do not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the PK assessment (i.e., without major protocol violations or deviations). The subjects who receive placebo will be excluded from the PK population.

A separate documentation containing the final exclusion criteria and a list of subjects in this population will be finalized before the database lock for the double-blind treatment period and the treatment unblinding.

3. GENERAL CONSIDERATIONS

3.1. Definition of Estimand

The primary estimand of the study is intended to provide a population level estimate of treatment effect in terms of the change from baseline in blood tHTT protein at Month 3, by a hypothetical strategy. The primary analysis will be based on ITT population, aiming to answer the research question: what is the change from baseline in blood tHTT protein at Month 3 for all randomized subjects during their treatment period, defined as the time from randomization until 30 days after they stop the treatment. Table 1 lists all estimands in the study.

Table 1: Study Endpoints and Estimands

Endpoint	Population	Variable	Intercurrent events	Population level summary	Analysis
Blood tHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Change from baseline in blood tHTT protein at Month 3	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Treatment difference and corresponding 95% confidence interval (CI) between each PTC518 dose group and placebo group in the change from baseline in blood tHTT protein at Month 3 will be estimated using a mixed model repeated measures (MMRM).	Primary analysis for primary endpoint
Blood tHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria, with no major protocol deviations which may affect treatment efficacy measurements (PP Population)	Change from baseline in blood tHTT protein at Month 3	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Same as primary analysis for primary efficacy endpoint	Sensitivity analysis for primary endpoint
Blood tHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Change from baseline in blood tHTT protein at Month 3 based on the results from	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Same as primary analysis for primary efficacy endpoint	Sensitivity analysis for primary endpoint

Endpoint	Population	Variable	Intercurrent events	Population level summary	Analysis
		complete run (see definition in Section 5.2.3)			
Blood tHTT protein	Completers of Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population completers)	Change from baseline in blood tHTT protein at Month 3	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Same as primary analysis for primary efficacy endpoint	Sensitivity analysis for primary endpoint
Blood tHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Change from baseline in blood tHTT protein at Month 3	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Treatment difference and corresponding 95% CI between each PTC518 dose group and placebo group in the change from baseline in blood tHTT protein at Month 3 will be estimated using a MMRM model, with missing data imputed using a control-based method.	Sensitivity analysis for primary endpoint
Caudate volume via vMRI	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Percent change from baseline in caudate volume as assessed via vMRI at Month 12	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Treatment difference and corresponding 95% CI between each PTC518 dose group and placebo group in the percent change from baseline in caudate volume at Month 12 will be estimated using a MMRM model.	Analysis of key secondary endpoint
cUHDRS	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Change from baseline in cUHDRS scores at Month 12	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Treatment difference and corresponding 95% CI between each PTC518 dose group and placebo group in the change from baseline in cUHDRS scores at Month 12 will be	Analysis of secondary endpoint

Endpoint	Population	Variable	Intercurrent events	Population level summary	Analysis
				estimated using an analysis of covariance (ANCOVA) model.	
Blood tHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Change from baseline in blood tHTT protein at Month 12	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Same as primary analysis for primary efficacy endpoint	Analysis of secondary endpoint
CSF mHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria; outliers will be excluded (ITT Population excluding outliers)	Change from baseline in CSF mHTT protein at Month 12	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Same as primary analysis for primary efficacy endpoint	Analysis of secondary endpoint
CSF mHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Change from baseline in CSF mHTT protein at Month 12	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Same as primary analysis for primary efficacy endpoint	Sensitivity analysis of secondary endpoint
Blood mHTT protein	Stage 2 and Mild Stage 3 HD subjects aged 25 years and older as defined by the protocol I/E criteria (ITT Population)	Change from baseline in blood mHTT protein at Month 12	Discontinuation of study treatment (due to any reason); data after the last dose of study drug + 30 days will be excluded.	Same as primary analysis for primary efficacy endpoint	Analysis of secondary endpoint

3.2. General Considerations

Continuous data will be summarized using the number of observations (n), arithmetic mean (mean), SD, median, minimum value (min), and maximum value (max) by treatment group. Categorical variables will be summarized using the frequency count (n) and percentage (%) by treatment group. For all percentage calculations, the denominator will be the number of subjects in the population for the treatment group, unless otherwise stated. An overall/total group (i.e., a sum of all treatment groups) will generally be presented additionally for summaries of disposition, demography, and baseline characteristics. Biomarker and PK endpoints will be summarized using geometric means and SDs as appropriate.

The data from Stage 2 and Mild Stage 3 groups will be analyzed overall and separately for the Stage 2 and Mild Stage 3 groups, which aims to provide a comprehensive understanding of the study outcomes for each group.

In instances where unscheduled or early termination visits occur, these visits will be mapped into the corresponding scheduled visits when appropriate. This approach ensures that all relevant data is included in the analysis and provides a comprehensive evaluation of the study parameters.

3.3. Interim Analysis

An interim analysis was conducted in June 2023 to confirm the PK and PD expectations and to evaluate safety after approximately 36 subjects in Stage 2 have completed 12 weeks of treatment. Subsequently, in June 2024, an update of interim analysis was conducted when these subjects completed 12 months of treatment. The interim analyses included only descriptive summaries of PK, PD, clinical efficacy and safety endpoints. Since the interim analyses followed the same procedures as the DSMB, the analysis details were outlined in the DSMB SAP.

An independent analysis team conducted the unblinded analysis. Only summary level results were shared with the PTC study team. The study has maintained double-blinding for investigators and the sponsor study team at a subject level until after the database is locked.

3.4. Data Definitions and Analysis Issues

3.4.1. Study Day

The study day will be defined as the number of days since the randomization day, which is assigned as Day 1 of the study. The study day is calculated using the formula if the assessment date is on or after the date of randomization:

Study day = (Date of assessment – Date of randomization) + 1

Otherwise, if the assessment date is before the date of randomization, then the study day will be calculated as follows:

Study day = Date of assessment – Date of randomization

3.4.2. Baseline Definitions and Change from Baseline

For all efficacy and PD endpoints, unless otherwise specified, the assessments collected at the randomization date will serve as the baseline value. If the randomization visit value is not available, then the last non-missing assessment collected prior to randomization will serve as the baseline. For safety endpoints, the baseline value is defined as the last non-missing assessment prior to the first study drug administration.

For the analysis purposes, change from baseline and percent change from baseline will be derived as follows:

Change from baseline = Post-baseline value – Baseline value

Percent change from baseline =100 × (Post-baseline value – Baseline value)/Baseline value

For the vMRI assessments, where the change is directly measured using the Boundary Shift Integral (BSI) for multiple brain areas, the change will not be calculated. For more details, please refer to Section 3.4.3.

3.4.3. Volumetric Magnetic Resonance Imaging

The loss of brain tissue is a continuous variable of disease progression in HD. Volumetric Magnetic Resonance Imaging (vMRI) will be used to effectively assess potential changes in brain volume (whole brain, lateral ventricles, caudate, and putamen volumes) to help determine if the treatment affects the rate of volume loss.

The vMRI images will be used to detect changes in brain volume in different areas over time using the boundary shift integral (BSI) technique. The BSI technique uses the shift in intensity differences on a pair of registered intensity-normalized images to quantify the difference between the 2 images (i.e., to quantify the amount of change in those selected brain regions). This technique is considered the gold standard to measure global brain or regional atrophy (tissue loss) and the output of BSI method is the change from baseline in volume (atrophy or expansion) over time.

The following regional brain volumes and measurements of volume change over time will be assessed at Visit 2 (Baseline) and Visits 5 (Month 3) and 8 (Month 12) in the six brain regions listed below:

- Whole Brain
- Lateral Ventricles
- Left Caudate
- Right Caudate
- Left Putamen
- Right Putamen

For regions including the whole brain, lateral ventricles, left caudate, and right caudate, the vendor will supply the absolute baseline volume and the change in volume from baseline using baseline as a reference timepoint. To estimate volume at Visits 5 (Month 3) and 8 (Month 12), BSI volume change will be subtracted or added to the baseline volume depending on the region.

For the whole brain and caudate areas, a positive BSI value means a decrease in volume (also known as atrophy), thus, the estimated volume at follow-up will be calculated as follows:

$$\text{Volume}_{\text{Follow-up}} = \text{Volume}_{\text{baseline}} - \text{Volume Change}_{\text{Follow-up}}$$

In addition, volume and volume change for the left and right caudate volume will be reported separately. To estimate total caudate volume, the left and right volume and volume change estimates will be summed.

For the lateral ventricles, a positive BSI value means an increase in volume (also known as expansion), thus, the estimated volume at follow-up will be calculated as follows:

$$\text{Volume}_{\text{Follow-up}} = \text{Volume}_{\text{baseline}} + \text{Volume Change}_{\text{Follow-up}}$$

The BSI is unsuitable for use with the putamen because it lacks a distinct boundary. For the left and right putamen, absolute volumes at baseline and post-baseline time points will be provided directly by the vendor. To estimate total putamen volume, the left and right volume estimates will be summed. To estimate volume change from baseline over time volume at follow-up will be subtracted from the baseline volume, as follows:

$$\text{Volume Change}_{\text{Follow-up}} = \text{Volume}_{\text{baseline}} - \text{Volume}_{\text{Follow-up}}$$

A positive putamen volume change will indicate a volume decrease at follow-up, i.e. atrophy, and vice versa.

Additionally, the striatum volume, which is the sum of the total caudate and total putamen volumes, and the change in striatum volume over time will be reported.

Endpoint QC is performed by trained image analysts for all vMRI endpoints. A Pass/Fail grade is assigned after the QC. Only data with a QC flag equal to 'Pass' will be used in the analysis.

3.4.4. Composite Unified Huntington's Disease Rating Scale

The composite Unified Huntington Disease Rating Scale (cUHDRS) is a comprehensive clinical outcome measure specifically designed to assess the progression of HD. It integrates multiple aspects affected by the disease, including motor, cognitive function, and global functional declines, into a single composite score (Schobel et al. 2017). This cUHDRS aims to provide a more accurate and sensitive evaluation of disease progression compared to individual assessments. The composite score is calculated by combining the individual scores from the above domains into a single metric. This approach aims to provide a more holistic view of the patient's clinical status and disease progression. It involves integrating the following components from the UHDRS (Huntington Study Group, 1996):

- Total Motor Score (TMS): Assesses motor function.
  - The motor section of the UHDRS assesses motor features of HD with standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability. The total motor impairment score is the sum of all the individual motor ratings, with higher scores indicating more severe motor impairment than lower scores. There are 15 items with 31 motor sub-items (each rated from 0 to 4)/score range 0-124.
- Symbol Digit Modalities Test (SDMT) and Stroop Word Reading (SWR): Evaluate cognitive function.
  - Both SDMT and SWR are used to assess cognitive operations. Results for SDMT are scored on the number of correct responses in 90 seconds; cognitive tasks do not have a set maximum score. The SWR results are reported as the raw number of correct answers given in a 45-second period. Higher scores indicate better cognitive performance.
- Total Functional Capacity (TFC): Measures global functional capacity.
  - The functional capacity portion of the UHDRS consists of 5 items (score range 0-13) assessing how people with HD manage their work, finances, domestic chores, activity of daily living, and their care arrangements. The TFC score is the sum of all the individual functional capacity ratings, with higher scores indicating a better function (0 representing the poorest function).

The cUHDRS score will be calculated as:

$$cUHDRS = \left[\left(\frac{TFC - 10.4}{1.9}\right) - \left(\frac{TMS - 29.7}{14.9}\right) + \left(\frac{SDMT - 28.4}{11.3}\right) + \left(\frac{SWR - 66.1}{20.1}\right)\right] + 10$$

where cUHDRS decreases as the disease progresses.

3.4.5. Multicenter Study

No adjustment or stratification for site will be performed. Data from all centers will be pooled for all analyses.

3.4.6. Study Analysis Visit

Study analysis visits during the study will be derived as listed in Table 2, based on study days from the randomization date. This window applies to scheduled, unscheduled, or early termination visits. The analysis visit number for each visit, including scheduled, unscheduled, repeat, and early termination/end of study visits, will be re-mapped. Study analysis visits will be used in all by-visit summaries for both efficacy and safety assessments wherever appropriate.

Table 2: Analysis Visit Windows

Analysis Visit	Target Study Day	Analysis Window (Study Day Range)
Visit 3 (Month 1)	30	16-45
Visit 4 (Month 2)	60	46-75
Visit 5 (Month 3)	90	76-120
Visit 6 (Month 6)	180	151-210
Visit 7 (Month 9)	270	241-300
Visit 8 (Month 12)	360	331- (last dose of study drug + 30 days)

For a given subject, if multiple assessments are within the same analysis window, the assessment at the scheduled visit will be used for the analysis; if the scheduled assessment is not available, the one closest to the scheduled study day and with non-missing value will be used for the analysis at that visit. In case of equal number of days to the scheduled visit date, the later assessment with non-missing value will be used for the analysis at that visit. In summary, the assessment to be used for the analysis is determined by the following order:

1) The assessment at the scheduled visit
2) The assessment closest to the target study day
3) The latter assessment, if >=2 observations are equally close to the target study day

Any assessments occurring beyond the last dose of study drug + 30 days will be excluded from the analysis.

3.4.7. Multiplicity Control

For the primary efficacy analysis, to control the family-wise Type I error at the 0.05 level, a fixed sequence (hierarchical) testing procedure will be employed, where the treatment effect between PTC518 10 mg versus placebo will be tested first at the significance level of 0.05 (2-sided) and if p-value <0.05, the treatment effect between PTC518 5 mg versus placebo will be tested at the significance level of 0.05 (2-sided).

The secondary and exploratory efficacy endpoints will be analyzed at the significance level of

0.05 (2-sided) without multiplicity adjustment.

3.4.8. Missing Data

All available data will be included in the data analysis and presented in data listings and tabulations. Missing data will not be imputed for summaries of all safety endpoints and by-visit summaries of all the PD parameters.

For the primary analysis and secondary analyses, where a mixed model repeated measures (MMRM) model will be used, the missing data will be implicitly imputed assuming the missing assessments are missing at random (MAR).

To further assess the influence of missing data for the primary analysis, missing primary endpoint will be imputed using a controlled-based multiple imputation (MI) (Rubin 1987, Ouyang 2017) method under an assumption of missing not at random (MNAR).

3.5. Changes to Protocol Specified Analysis

There are no changes to the planned analysis.

4. SUBJECT DATA

4.1. Subject Disposition

The disposition of subjects will be summarized by treatment group and overall for all randomized subjects, including the number of subjects who were randomized, randomized but not treated, and randomized and treated. The summary will also cover the number of subjects who completed the 12-month treatment, those who prematurely discontinued the treatment, and those who prematurely discontinued the study, along with the reasons for discontinuation. The number of subjects randomized will also be summarized by country and site.

All screened subjects (i.e., subjects who have signed the informed consent form [ICF]) will be summarized along with the reason for not continuing the study.

A by-subject listing of all screened subjects including inclusion/exclusion criteria that subjects do not meet and a by-subject listing of disposition will be provided.

4.2. Data Sets Analyzed

A summary of the number of subjects for each analysis population will be provided by treatment groups and overall. A by-subject listing of subjects excluded from analysis populations will be provided.

4.3. Protocol Deviations

Protocol deviations will be documented and finalized separately in a stand-alone document before database lock which includes deviation categories (e.g., violation of inclusion and exclusion criteria at screening, use of excluded concomitant medications, receiving the wrong treatment or incorrect dose, COVID-19 related or not, etc.), deviation description, classification (minor/major), visit/time point for each deviation. The number of subjects with major protocol deviations will be summarized by treatment and overall. A by-subject listing of major protocol deviations will also be provided.

4.4. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics by treatment group and overall on the ITT population. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables will include mean, SD, minimum, median, and maximum.

Demographics and baseline characteristics variables include:

- Age at screening (year)
- Age groups (≤62, and >62 years)
- Sex (Male, Female [Childbearing Potential, Post-Menopausal, and Surgically Sterile])
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Australian Aboriginal or Torres Strait Islander, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)

- Baseline height
- Baseline weight
- Baseline body mass index (BMI) calculated from weight and height

4.5. Disease Characteristics

Disease characteristics collected at baseline will be summarized with descriptive statistics by treatment group and overall on the ITT population. Summary statistics for categorical variables will include frequency counts and percentages and for continuous variables will include mean, SD, minimum, median, and maximum.

Those characteristics variables include:

- Cytosine-adenine-guanine (CAG) length
- TFC score
- TMS score
- IS score
- SDMT score
- PBA-s score
- PIN_{HD} score
- PIN_{HD} score class (0.180-0.679, 0.680-1.520, and 1.521-4.930)
- HD stage (Stage 2 and Mild Stage 3 groups)

A by-subject data listing of demographics and baseline disease characteristics will also be provided.

4.6. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) Version 25.0. Medical history information will be descriptively summarized by System Organ Class (SOC) and preferred term (PT) by treatment group for the Safety Population. Medical history will be presented in a by-subject data listing.

4.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug-Global-B3 202203). Prior medications are defined as medications that start and end prior to the start of study treatment. Concomitant medications are defined as medications that start before the first dose of study drug and continue during the study treatment or start during study treatment or within 30 days after last dose of the study drug. All prior and concomitant medications will be summarized by WHO ATC level 3 and PT, and by treatment groups for the Safety Population.

All prior and concomitant medications will be presented in a by-subject data listing.

4.8. Extent of Drug Exposure

Duration of exposure (in days) will be calculated as last dose date – first dose date +1 and summarized descriptively by treatment group on Safety Population. It will also be summarized by the following categories:

- < 3 months
- >= 3 to < 6 months
- >= 6 to < 9 months
- >= 9 to < 12 months
- >= 12 months

5. EFFICACY ANALYSIS

The analysis of efficacy and PD endpoints will be performed on ITT Population.

5.1. Primary Endpoint Analysis

The primary efficacy endpoint is the change from baseline in blood tHTT protein at Month 3. The null hypotheses of this study are:

1) the mean change from baseline for blood tHTT protein is the same in the PTC518 5 mg arm and in the placebo arm versus the alternative that they are different, and
2) the mean change from baseline for blood tHTT protein is the same in the PTC518 10 mg arm and in the placebo arm versus the alternative that they are different.

These hypothesis will be tested at the 2-sided 0.05 significance level and adjusted for multiplicity according to Section 3.4.7.

The blood samples for HTT protein (i.e., blood tHTT and mHTT) will be collected pre-dose on Day 1 at Visit 2 (Baseline), and both pre-dose and 4 hours post-dose at subsequent post-baseline visits. The samples will be analyzed by a designated bioanalytic laboratory. In order to reduce within-subject variability (inter-assay variability), samples collected at different time points for a subject will be analyzed in the same batch. In this study, periodical data monitoring activities (i.e., DSMBs) and an interim analysis are planned to review the safety data and/or PK/PD data while the study is ongoing. At each data review, all samples collected up to the time of that data review will be analyzed or re-analyzed. Therefore, a sample may have multiple results from multiple sample analyses (referred thereafter as 'run').

For the purpose of data analysis, a single result at baseline and at each post-baseline visit will be derived according to the following steps:

1. For each post-baseline visit, the averaged value of the pre-dose and post-dose samples will be calculated for each run first. If only one value (pre-dose or post-dose) is available, that value will be used as the averaged value.
2. The change and precent change from baseline will be calculated for the averaged values using the baseline result from the same run.
3. For each subject, the result from the last run will be used for the primary analysis for both baseline and post-baseline visits.

To address the non-normality of the blood tHTT data, log-transformation will be performed. Specifically, the blood tHTT values will be log-transformed and the change from baseline of the log-transformed will be calculated by taking the difference between the log-transformed tHTT values at each post-baseline visits and the log-transformed baseline values.

A mixed model repeated measures (MMRM) model (repeat on visit) will be used to compare each PTC518 dose group with placebo group for the change from baseline in blood tHTT protein levels. Data from Baseline, Visit 5 (Month 3), Visit 6 (Month 6), Visit 7 (Month 9), and Visit 8 (Month 12) will be included in that model.

The MMRM model will be fitted using the change from baseline of log-transformed tHTT as the response variable. The model will include treatment, visit, treatment by-visit interaction as fixed effects, the disease stage (by PIN_{HD} bin for Stage 2 only and by TFC for Mild Stage 3 only) as a

stratification factor (also the fixed effect), and baseline blood tHTT (log-transformed), CAG, age, and CAG by age interaction as covariates. If a subject is mis-stratified, the actual stratification factor based on the data collected in electronic case report form (eCRF) will be used in the model.

An unstructured within-subject covariance structure will be assumed. If the model does not converge under the unstructured covariance matrix, a less complex alternative variance-covariance structures will be considered in the following order until convergence is reached: heterogeneous Toeplitz, heterogeneous Compound Symmetry, heterogeneous first-order autoregressive, Toeplitz, Compound Symmetry, and first-order autoregressive.

The least square (LS) means from the model will be back-transformed to present model-based percent change in geometric means from baseline for each treatment group. The treatment effect (calculated as the difference in model-based percent change in geometric means from baseline between PTC518 and placebo groups) at Visit 5 (Month 3) along with their 95% confidence intervals (CIs), and the normal p-values (2-sided) for each pairwise comparison (PTC518 5 mg vs. placebo/ PTC518 10 mg vs. placebo) will be presented. The delta method will be applied to estimate the treatment differences and standard error.

The blood tHTT protein and precent change from baseline will also be summarized descriptively by treatment group for each visit.

5.2. Sensitivity Analysis

5.2.1. Sensitivity Analysis on PP Population

The above MMRM model for the primary endpoint will also be performed on the PP Population. The blood tHTT protein and percent change from baseline will be summarized descriptively by treatment group for each visit.

5.2.2. Sensitivity Analysis for Missing Data

5.2.2.1. Completer Analysis

The completers analysis will also be performed for the primary efficacy endpoint. It will use all subjects in the ITT population with non-missing the primary endpoint at Visit 5 (Month 3).

5.2.2.2. A Controll-Based Multiple Imputation for Missing Values

For subjects with missing primary endpoint, their primary endpoint will be imputed by MI method using subjects in the placebo arm who completed double-blind period of the study without missing values as reference. The details of MI method and sample SAS code are provided in Appendix I.

5.2.3. Sensitivity Analysis for Complete Run

The primary analysis will be performed using the results from the most recent sample analysis (i.e. last run). During the study, certain samples from Visit 3 (Month 1) and Visit 4 (Month 2) weren't re-analyzed in the last run. To evaluate the consistency of the results, a sensitivity analysis will be conducted. This analysis will include complete data up to Visit 5 (Month 3) from same sample analysis. Specifically, if samples from Visit 3 (Month 1) and Visit 4 (Month 2)

weren't re-analyzed in the last run, the results from previous run that has complete data from Baseline to Visit 5 (Month 3) will be used for the analysis.

The same MMRM model as for the primary analysis will be used, and only the data from Baseline, Visit 3 (Month 1), Visit 4 (Month 2), and Visit 5 (Month 3) will be included in the analysis.

5.3. Secondary Endpoints Analysis

Key Secondary Endpoint Analysis

The percent change from baseline in caudate volume as assessed via vMRI at Month 12 is the key secondary endpoint.

A MMRM model will be used to compare each PTC518 dose group with placebo group for the percent change from baseline in caudate volume as assessed via vMRI at Month 12. The response variable is the percent change from baseline in caudate volume. The model will include fixed effects for treatment, disease stage (by PIN_{HD} bin for Stage 2 only and by TFC for Mild Stage 3 only) with baseline caudate volume as a covariate. The time and time by treatment interactions will be included in the model where time is defined as: date of caudate assessment – date of randomization + 1. 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. If the model does not converge under the unstructured covariance matrix, the Variance Component covariance matrix will be used/. If the model still does not converge, the random effect will be excluded. The treatment effect and treatment difference will be estimated by the LS means and the difference in LS means, along with their SE and with 95% CIs, and the nominal p-values (2-sided) for each pairwise comparison (PTC518 vs. placebo) will be provided.

The caudate volume (left, right, and total [left + right]) and percent change from baseline will be summarized descriptively by treatment group for each visit.

Other Secondary Endpoints Analysis

Other secondary endpoints include:

- Change from baseline in cUHDRS scores at Month 12

  An ANCOVA model will be performed to compare each dose group with placebo group for the change from baseline in cUHDRS at Month 12. The model will include treatment group as the independent variable and baseline cUHDRS, disease stage, CAG, age, CAG by age interaction as covariates. The treatment effect and treatment difference will be estimated by the LS means and the difference in LS means, along with their SE and with 95% CIs, and the nominal p-values (2-sided) for each pairwise comparison (PTC518 vs. placebo) will be provided.

- Change from baseline in blood tHTT protein at Month 12

  The change form baseline at Month 12 will be analyzed using the same model as the primary analysis. The LS means from the model will be back-transformed to present model-based percent change in geometric means from baseline for each treatment group. The treatment effect (calculated as the difference in model-based percent

change in geometric means from baseline between PTC518 and placebo groups) at Visit 8 (Month 12) along with their 95% CIs, and the normal p-values (2-sided) for each pairwise comparison (PTC518 5 mg vs. placebo/ PTC518 10 mg vs. placebo) will be provided. The delta method will be applied to estimate the treatment differences and standard errors.

- Change from baseline in CSF mHTT protein at Month 12

  The CSF samples for mHTT protein will be collected pre-dose at Visit 2 (baseline) and subsequent post-baseline visits. The samples will be analyzed by the same bioanalytic laboratory as blood tHTT protein. For the same reason as blood tHTT protein, a sample may have multiple results. For the analysis purpose, a single result at baseline and at each post-baseline visit will be derived according to the following steps:

  1. The change and precent change from baseline will be calculated for each post-baseline visit using the baseline result from same run.
  2. If the baseline result is ≤2 x the lower limit of quantification (≤3.44 pg/mL), the entire run will not be used for the analysis.
  3. For each subject, the result from the last run will be used for the analysis for both baseline and post-baseline visits.

An MMRM, similar to the analysis model used for blood tHTT protein, will be used to analyze this endpoint. The LS means from the model will be back-transformed to present model-based percent change in geometric means from baseline for each treatment group. The treatment effect (calculated as the difference in model-based percent change in geometric means from baseline between PTC518 and placebo groups) at Visit 8 (Month 12) along with their 95% CIs, and the normal p-values (2-sided) for each pairwise comparison (PTC518 5 mg vs. placebo/ PTC518 10 mg vs. placebo) will be provided. The delta method will be applied to estimate the treatment differences and standard errors.

CSF mHTT levels are generally very low in patients with HD (Wild 2015, Rodrigues 2020). In this study, an ultra-sensitive single molecule counting (SMC) immunoassay on the SMCxPRO platform is utilized to measure mHTT levels in CSF. It has been observed in the interim analysis that the majority of samples were < 3 × the limit of reliable quantification. To address the inherent variability in quantifying protein production at the low level of assay detection, notable outliers will be excluded from the analysis. The notable outliers are defined as follows: if the difference in the percent change from baseline in CSF mHTT levels between Month 12 and the average of Months 6 and 9 exceeds (increases or decreases) 40%, the subject will be excluded from the analysis, because it is highly unlikely to observe such a substantial shift in mHTT levels over a short period of time, especially months after achieving steady state exposure.

In addition, a sensitivity analysis with performed with outliers included.

- Change from baseline in blood mHTT protein at Month 12

  An analysis identical to that performed for blood tHTT at Month 12 will be conducted.

For each secondary PD endpoint, the post-baseline values and percent changes from baseline will be summarized descriptively by treatment group for each visit.

5.4. Exploratory Endpoints Analysis

The exploratory endpoints that will be analyzed include:

- 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, ventricular volume, and striatum (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 11 symptom domains in the short form of the PBA-s at Month 12
- Change from Baseline in the Functional Rating Scale (FuRST) at Month 12
- Change over time in blood *HTT* mRNA
- Change over time in plasma and CSF NfL

- Change from Baseline in wearable accelerometer assessment TUG, 2-minute walk distance, and postural sway at Month 12

These endpoints will be summarized descriptively by treatment group for each visit. The relationship between biomarker endpoints and clinical endpoints will be explored by an association analysis.

5.5. Pharmacokinetic Endpoints Analysis

Descriptive summaries for plasma concentrations at pre-dose and post-dose and for CSF concentrations at pre-dose will be provided for each visit on PK Population. The accumulation ratio of the study drug will be calculated and summarized for both plasma and CSF concentrations. For plasma, the accumulation ratios will be calculated using the C_{trough} (plasma trough concentrations, also known as pre-dose concentrations) at Visits 3 (Month 1) through 8 (Month 12) as the numerator, with the pre-dose concentration at Visit 3 serving as the denominator for all visits. For CSF, the accumulation ratio will be calculated using the pre-dose concentrations at Visits 5 (Month 3) through 8 (Month 12) as the numerator, with the pre-dose concentration at Visit 5 serving as the denominator. Also, the CSF to plasma C_{trough} concentration ratio at each visit will be summarized descriptively.

5.6. Subgroup Analysis

To examine the uniformity of treatment effect in the subgroups, the primary and secondary endpoints will be summarized descriptively for the following subgroups:

- Disease stage (PIN_{HD} score class [0.180-0.679, 0.680-1.520, and 1.521-4.930] for Stage 2 only and by TFC score [11, 12, 13] for Mild Stage 3)

6. SAFETY ANALYSES

The safety analysis will be performed on the Safety Population.

6.1. Adverse Events

All AEs will be coded using the MedDRA Version 25.0. All AEs will be assigned a severity grade using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (refer to the study manual).

A treatment-emergent adverse event (TEAE) will be defined as an AE with onset date, or date of worsening if occurring prior to the first dose of study drug, between the date of first dose of study drug and the date of last dose of study drug + 30 days, inclusive. Only those TEAEs will be included in summary tables.

All AEs, treatment-emergent or otherwise, will be presented in subject data listings. An overview table of TEAEs, including number of subjects with TEAEs, treatment-emergent serious adverse events (TESAEs), TEAEs leading to discontinuation from study treatment, deaths, TEAEs by maximum severity, and treatment-related TEAEs, will be summarized by treatment group. A treatment-related AE will be defined as an AE with a relationship of possibly, probably, or related to the study treatment, as determined by the investigator.

In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. If a subject has the multiple TEAEs in the same SOC or PT, the highest severity (5=fatal, 4=life-threatening, 3=severe, 2=moderate, 1=mild) recorded for the event will be presented and the closest drug relationship (1='Unrelated', 2='Unlikely to be Related', 3='Possibly Related', 4='Probably Related'), reclassified into Related ('Possibly Related', 'Probably Related') or Not Related ('Unrelated', 'Unlikely to be Related'), will be presented on the respective tables.

The following summaries will be produced for the TEAEs and TESAEs by treatment groups:

- TEAEs by SOC and PT
- TEAEs by PT (for cases where the incidence ≥5% in either the 5 mg or 10 mg dose group)
- Treatment-related TEAEs by SOC and PT
- TEAEs by maximum severity
- TEAEs by relationship to study treatment
- TESAEs by SOC and PT
- Treatment-related TESAEs by SOC and PT
- TEAEs leading to discontinuation from study treatment by SOC and PT
- Treatment-related TEAEs leading to discontinuation from study treatment by SOC and PT

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE,

unless the incomplete start date/time or the end date/time indicates an AE started before dosing.

- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.

All AEs, deaths, SAEs and TEAEs leading to discontinuation from study treatment will be presented in by-subject data listings.

6.2. Laboratory Values

Blood samples for hematology, clinical chemistry, and urinalysis will be collected at the visits defined in protocol and the test results will be presented in standard units. The continuous test results and change from baseline will be descriptively summarized by visit and treatment group. Laboratory parameters that will be assessed will include:

- Hematology: hemoglobin, hematocrit, red blood cell count (RBC), platelet count, white blood cell count (WBC), WBC differential, neutrophils, eosinophils, monocytes, basophils, and lymphocytes
- Clinical chemistry: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, total bilirubin, direct bilirubin, indirect bilirubin, calcium, chloride, total cholesterol, creatinine, gamma-glutamyl transpeptidase, glucose, high-density lipoprotein, low-density lipoprotein, lactate dehydrogenase, potassium, sodium, total protein, triglycerides, urea, and uric acid
- Urinalysis: albumin, bilirubin, erythrocytes, glucose, ketones, leukocyte, microscopy, nitrite, pH, specific gravity and urobilinogen
- Coagulation: PT (sec), PT (INR), aPTT

Clinical laboratory test results will be assigned a Low/Normal/High (L/N/H) classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter's reference range. Shifts from baseline to each post-baseline visit will be provided for each laboratory parameter by treatment group.

Abnormal laboratory test results (i.e., results assigned as L/H) will be listed in a by-subject data listing.

CSF assessments, which include WBC, RBC, protein, and glucose, will be gathered locally. These measurements will subsequently be converted to standard units. The test results for WBC and protein will be descriptively summarized by visit and treatment group.

6.3. NfL Levels in Plasma and CSF

For NfL, blood and CSF samples will be collected pre-dose at Visit 2 (baseline) and subsequent post-baseline visits. The samples will be analyzed by the same bioanalytic laboratory as blood tHTT protein. For the same reason as blood tHTT protein, a sample may have multiple results.

For the analysis purpose, a single result at baseline and at each post-baseline visit will be derived according to the following steps:

1. The change and percent change from baseline will be calculated for each post-baseline visit using the baseline result from same run.
2. For each subject, the result from the last run will be used for the analysis for both baseline and post-baseline visits.

These safety exploratory endpoints will be summarized descriptively by treatment group for each visit.

6.4. Vital Signs and Weight

Vital sign measurements (including blood pressure, pulse rate, respiration rate, body temperature and oxygen saturation) and weight (and BMI), and the change from baseline will be summarized descriptively by visit and treatment group.

The vital sign measurements and weight (and BMI) will be presented in a by-subject data listing.

6.5. Physical Examination

Abnormal physical examination results will be listed in a by-subject listing.

6.6. 12-Lead Electrocardiogram (ECG)

The ECGs parameters (including heart rate, RR interval, PR interval, QRS interval, QT interval, Corrected QT interval using Bazett's formula [QTcB] and Corrected QT interval using Fredericia's formula [QTcF]) and the change from baseline will be summarized descriptively by visit and treatment group. The ECGs will be performed in triplicate. For the above ECG parameters, the averaged value of the triplicate will be used for the analysis. For the overall interpretation of ECG (normal, abnormal clinically significant, or abnormal not clinically significant), the value that represents the greatest degree of abnormality will be used for the analysis. In addition, shift from baseline to each post-baseline visit in the overall interpretation will be provided by treatment group.

Categorical analysis of the maximum post-baseline value in QTcF interval will be performed to summarize the number and percentage of subjects meeting the criteria below.

- Absolute QTcF interval prolongation:
  - QTcF interval <= 450 ms
  - QTcF interval > 450 and <= 480 ms
  - QTcF interval > 480 and <= 500 ms
  - QTcF interval > 500 ms
- Change from baseline in QTcF interval:
  - QTcF interval increases from baseline <= 30 ms
  - QTcF interval increases from baseline > 30 and <= 60 ms
  - QTcF interval increases from baseline > 60 ms

A by-subject listing of ECG results will be provided.

[redacted]

6.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a measure used to identify and assess individuals at risk for suicide. The C-SSRS summary will display the number and percentage of subjects who report "Yes" to specific C-SSRS items or categories of items (a category is assigned a "Yes" value if a "Yes" is reported for any item in the category) descriptively by visit and treatment group. These C-SSRS items and categories are as follows:

- Suicidal Ideation Items
  - (1) Wish to be dead
  - (2) Non-specific active suicidal thoughts
  - (3) Active suicidal ideation with any methods (not plan) without intent to act
  - (4) Active suicidal ideation with some intent to act, without specific plan
  - (5) Active suicidal ideation with specific plan and intent
- Suicidal Behavior Items (not reported for the Screening/past 1 year assessment)
  - (6) Preparatory acts or behavior
  - (7) Aborted attempt
  - (8) Interrupted attempt
  - (9) Non-fatal suicide attempt
  - (10) Completed suicide
- Suicidal Behavior Category: Any of items (6) through (10)
- Non-Suicidal Self-Injurious Behavior

In addition to the summaries described above, the shift from baseline to each post-baseline visit in suicidal ideation and behavior (categorized as (1) No Suicidal Ideation or Behavior, (2) Suicidal Ideation only, and (3) Suicidal Behavior will be provided by visit and treatment group.

The C-SSRS results will be provided in by-subject data listings.

7. MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings, and graphs shells will be provided in a separate document.

8. REVISION HISTORY

Version Number	Date	Description
1.0	17MAR2025	Initial release

9. REFERENCES

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10. APPENDIX I

A control-based MI method will be employed to assess the influence of missing data for the primary analysis assuming MNAR. The imputation will be performed on the change from baseline of the log-transformed data using SAS PROC MI. The missing change from baseline of the log-transformed values will be imputed using subjects in the placebo group who completed double-blind period of the study without missing values as reference. One hundred complete data sets will be produced and analyzed using the MMRM model as the primary analysis in Section 5.1.

Sample SAS code for MI is provided as follows.

```
PROC MI DATA=tHTT OUT=tHTTMI SEED=59469 NIMPUTE=100;
    CLASS DiseaseStage;
    FCS REG (base chgM3 chgM6 chgM9 chgM12);
    MNAR MODEL(base chgM3 chgM6 chgM9 chgM12/modelobs= (trtgrp='Placebo'));
    VAR DiseaseStage age cag base chgM3 chgM6 chgM9 chgM12;
RUN;
```

Then the results will be combined by SAS PROC MIANALYZE to produce the final analysis result.