CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease
Short Title:	**PR**idopidine **O**utcome **O**n **F**unction in **H**untington **D**isease (**PROOF-HD**)
Protocol Number:	PL101-HD301
Compound Number (INN/Trademark):	Pridopidine
Study Phase:	Phase 3
Short Title	Efficacy and Safety Study of Pridopidine in Huntington Disease
Sponsor Name:	Prilenia Therapeutics[1]
Legal Registered Address:	10 Hamenofim St. Herzliya, Israel
Regulatory Agency Identifier Number(s):	IND: 77419 EudraCT: 2020-002822-10
Sponsor Representative:	[redacted]
Approval Date:	10 November 2022
Version:	7.0, Amendment 8.0

[1] Applies to both Prilenia Therapeutics BV and Prilenia Neurotherapeutics Ltd.

SPONSOR SIGNATURES

[redacted]

18-Nov-22

Date

[redacted]

17-Nov-22

Date

[redacted]

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease (PROOF-HD)
Protocol Number:	PL101-HD301
Version and Date:	7.0, 10 November 2022
Amendment No.:	8.0
Regulatory Agency Identifier Number(s):	IND: 77419 EudraCT: 2020-002822-10

I, the undersigned, have read this protocol and agree to personally supervise the conduct of this protocol in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, any applicable laws and requirements (including Part 54: Financial Disclosure by Clinical Investigators) and any additional conditions mandated by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I acknowledge that I am responsible for the overall study conduct; I approve of and will comply with all conditions, instructions and restrictions described in this protocol. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved in writing by Prilenia Therapeutics and the respective IRB/IEC.

I also agree that all information provided to me by the Sponsor, including this document, Investigator's Brochure, case report form, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB/IEC. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the Principal Investigator, or in confidence to the IRB/IEC or to the Food and Drug Administration (FDA) or other legally constituted authority.

Site Principal Investigator Signature Date

Printed Name Institution City, Country

COORDINATING INVESTIGATOR AGREEMENT

Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease (PROOF-HD)
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As the coordinating Investigator, I have read this protocol and agree to personally supervise the conduct of this protocol in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, any applicable laws and requirements (including Part 54: Financial Disclosure by Clinical Investigators) and any additional conditions mandated by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

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Coordinating Investigators Signatures

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Protocol V7.0, Amendment 8	10 November 2022
Protocol V6.0, Amendment 7	27 January 2022
Protocol V5.0, Amendment 6	13 May 2021
Protocol V4.2, Amendment 5, France Country-specific	15 March 2021
Protocol V4.1, Amendment 4, France Country-specific	15 February 2021
Protocol V4, Amendment 3	25 October 2020
Protocol V3, Amendment 2	29 September 2020
Protocol V2, Amendment 1	17 July 2020
Original Protocol V1	14 June 2020

Amendment 8, 10 November 2022

Overall Rationale for the Amendment:

The Sponsor has introduced the following modifications to protocol V7.0; these changes are from V6.0 (Amendment 7) and are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Objectives and Endpoints) 3 Objectives and Endpoints	• Hierarchy of secondary endpoints changed (cUHDRS moved up to #1, proportion of participants with improvement or no worsening in UHDRS-TFC moved to #2, TFC at Week 52 and 78 moved up to #3 and #4, Q-Motor lowered to #5, TMS lowered to #6) and change from Baseline to Week 65 in SDMT added to #7 in the hierarchy	• [redacted] • Moved cUHDRS up in the hierarchy as it represents a global measure of HD progression including motor, function, and cognitive components • Moved Q-Motor above TMS to include an objective measure of motor function • Moved SDMT into multiplicity adjusted secondary endpoint in recognition of the importance of cognition in HD

Section # and Name	Description of Change	Brief Rationale
		• TFC at Week 52 elevated in hierarchy to evaluate an earlier onset of response • TFC at Week 78 elevated in hierarchy to evaluate durability of response within the double-blind period
1.1 Synopsis (Objectives and Endpoints) 3 Objectives and Endpoints	• Change from Baseline to Week 26 and 39 are added for some non-multiplicity adjusted efficacy endpoints to better describe the change over time • Sub-scales for some efficacy endpoints as well as OLE and safety endpoints are clarified in endpoint section • Biomarker (NfL) endpoints are added to the OLE endpoints in Section 3 • Pharmacodynamics assessments are not performed therefore removed from the protocol	• Changes are made for clarity
3.1.2 Primary Estimand	• Estimand definitions are further elaborated	• Additional details provided
1.1 Synopsis (Overall Study Design) 1.3.1 Schedule of Activities – Main Study 4.1 Overall Design	• Clarify timing of End of Study visit of the Main study	• For clarity
1.1 Synopsis (Study Duration) 4.4 Study Duration 4.5 End of Study Definition	• Extending the OLE duration by 6 months (to 12 months after the last participant completes the double-blind treatment period)	• Ensuring pridopidine treatment continuity for participants
6.1 Study Drug(s) Administered	• Adding Patheon by Thermo Fisher Scientific as a manufacturer of pridopidine drug product	• Adding a new manufacturing site for pridopidine drug product
9 Statistical Considerations	• Sensitivity analyses for multiplicity-adjusted secondary endpoints, the details of missing	• To provide additional details

Section # and Name	Description of Change	Brief Rationale
	data handling, and OLE analyses are added	
9.4.2 Analysis of Primary Endpoint	• Only in-clinic UHDRS-TFC assessments will be used in the primary analysis and secondary analyses	• To include only in clinic data as <2% of participants are missing in-clinic visits
9.6 Safety Monitoring Committee	• It was clarified that the SMC monitoring will only be performed during the double-blind period of the Main Study	• Clarification added
General	• Update version and date • Update table of contents • Update for consistency throughout protocol (including terminology) • Update cross reference / linking throughout • Minor corrections/updates throughout (punctuation, formatting, style, etc.)	• For consistency and accuracy

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease.

Short Title: Pridopidine Outcome On Function in Huntington Disease (PROOF-HD)

Rationale

Huntington Disease (HD) is an autosomal dominant, progressive fatal neurodegenerative disorder characterized by motor, cognitive, and behavioral abnormalities. While medications to treat chorea and some behavioral symptoms are available, no therapy has yet proven able to modify the progressive and inexorable functional decline of the disease. A therapy that maintains functional capacity and prevents or delays the development of disability represents a critically unmet clinical need.

The purpose of this Phase 3 study is to further evaluate the effect of pridopidine 45 mg bid on functional capacity, as well as motor and behavioral features of HD in early-stage participants (TFC 7-13).

Objectives and Endpoints (Primary, Secondary and Safety)

Main Study

Objectives	Endpoints
Primary	
• To assess the effect of pridopidine on functional capacity in participants with Stage 1-2 HD	• Change from Baseline to Week 65 in the UHDRS-TFC score
Multiplicity Adjusted Secondary Endpoints	
Key Secondary (secondary endpoints are listed by order of hierarchy)	
• To assess the effect of pridopidine on a composite measure of disease progression in participants with HD	1. Change from Baseline to Week 65 in composite UHDRS (cUHDRS) total score
Secondary (secondary endpoints are listed by order of hierarchy)	
• To evaluate the effect of pridopidine on functional capacity, motor function, cognition, and other measures of efficacy over time in participants with HD	2. Proportion of participants with improvement or no worsening (change from Baseline ≥ 0 point) at Week 65 in UHDRS-TFC 3. Change from Baseline to Week 52 in UHDRS-TFC score 4. Change from Baseline to Week 78 in UHDRS-TFC score 5. Change from Baseline to Week 65 in Quantitative motor (Q-Motor) [redacted] 6. Change from Baseline to Week 65 in UHDRS Total Motor Score (TMS) 7. Change from Baseline to Week 65 in Symbol Digit Modalities Test (SDMT) 8. Change from Baseline to Week 52 in UHDRS-TMS score 9. Proportion of participants with improvement or no worsening in

	Clinical Global Impression of Change (CGI-C) at Week 65
Non-multiplicity Adjusted Secondary Endpoints	
• To evaluate the effects of pridopidine in participants with HD	• Change from Baseline to Week 26 and 39 in the UHDRS-TFC • Proportion of participants with improvement or no worsening in UHDRS-TFC (change from Baseline ≥ 0) at Weeks 26, 39, 52 and 78 • Change from Baseline to Weeks 26, 39, 52 and 78 in cUHDRS • Proportion of participants with change from Baseline ≥ -1 in cUHDRS at Weeks 26, 39, 52, 65 and 78 • Change from Baseline to Week 26, 39 and 78 in the UHDRS-TMS score • Proportion of participants with improvement or no worsening in UHDRS-TMS (change from Baseline ≤ 0) at Weeks 26, 39, 52, 65 and 78 • Change from Baseline to Weeks 26, 39, 52, 65 and 78 in: – UHDRS-TFC Scale sub-items (capacity to undertake domestic chores, activities of daily living, capacity to manage finances, care level and occupation) – UHDRS-TMS sub-scores for: o Gait and balance score (defined as the sum of UHDRS-TMS domains gait, tandem walking, and retropulsion pull test) o Eye movement o Dystonia • Change from Baseline to Weeks 26, 39, 52 and 78 in SDMT • Change from Baseline to Weeks 26, 39, 52, 65 and 78 in Stroop Word Reading (SWR)

	• Change from Baseline to Weeks 26, 39, 52 and 78 in Q-Motor [redacted] • Proportion of participants with improvement or no worsening (change from Baseline ≤ 0 msec) in Q-Motor [redacted] at Weeks 26, 39, 52, 65 and 78 • Change from Baseline to Weeks 26, 39, 52, 65 and 78 in Q-motor [redacted] • Responder analyses on CGI-C using different thresholds at Weeks 26, 39, 52, 65 and 78
Safety and Tolerability	
• To evaluate the safety and tolerability of pridopidine in participants with HD	• Incidence (count and rate) of adverse events (AEs) and serious AEs (SAEs) overall, by severity, by relationship to study drug, and those that led to discontinuation of study drug and/or withdrawal from the study • Incidence and shifts of clinically significant abnormalities in electrocardiogram (ECG)[2], laboratory tests, vital signs, and abnormalities in physical and neurological exam • Analysis of Columbia-Suicide Severity Rating Scale (C-SSRS) throughout the study • Tolerability: – The number (%) of participants who complete the Treatment period – The number (%) of participants who fail to complete the Treatment period due to AEs – The number (%) of participants who fail to complete the Treatment period due to Fridericia-corrected QT

[2] QT Stopping Rules: QTcF >500 ms; QTcF >480 ms AND ΔQTcF >60 ms from baseline.
QT Monitoring Rule: QTcF >480 ms OR ΔQTcF >60 ms from baseline.

	interval (QTcF) change, Creatinine Clearance (CrCl) or Psychiatric Stopping Rules

Open-label Extension (OLE)

Objectives	Endpoints
Efficacy	
• To evaluate the long-term treatment effect of pridopidine in participants with HD who previously completed the Main Study	• Proportion of participants with change from Baseline (Main Study) to each OLE visit in UHDRS-TFC ≥ -1 • Proportion of participants with change from Baseline (Main Study) to each OLE visit in UHDRS-TFC ≥ 0 • Change from Baseline (Main Study) to OLE visits in: – UHDRS-TFC – cUHDRS – UHDRS-TMS – Quantitative motor (Q-Motor): [redacted] – SDMT – SWR • Change from Baseline (Main Study) to OLE visits in: – CGI-C – PBA-s – Huntington Disease Quality of Life Questionnaire (HDQoL)
Safety and Tolerability	
• To evaluate long-term safety and tolerability of pridopidine in	• Incidence (count and rate) of AEs and SAEs overall, by severity, by relationship to study drug, and those that led to

participants with HD who previously completed the Main Study	discontinuation of study drug and/or withdrawal from the study • Incidence and shifts of clinically significant abnormalities in ECG (refer to Section 7.1.1), laboratory tests and vital signs • Analysis of C-SSRS throughout the study • Tolerability: – The number (%) of participants who complete the OLE treatment period – The number (%) of participants who fail to complete the OLE treatment period due to AEs

Inclusion/Exclusion Criteria

Inclusion Criteria – Main Study:

1. Twenty-five years of age (inclusive) and older, at the time of signing the informed consent.
2. Diagnosis of HD based on clinical features and the presence of ≥36 cytosine-adenine-guanine (CAG) repeats in the huntingtin gene (HTT), confirmed by historical laboratory quantified results or by a diagnostic test at Screening.
3. Diagnostic confidence level (DCL) of 4 (unequivocal motor signs, ≥ 99% confidence) on the standardized motor exam UHDRS-TMS.
4. Adult-onset HD with onset of signs and symptoms ≥18 years of age.
5. Stage 1 or Stage 2 HD, defined as a UHDRS-TFC score of ≥7, at Screening.
6. UHDRS-Independence Scale (IS) score ≤90% at Screening.
7. UHDRS-TMS ≥20 at Screening.
8. Must meet all criteria required to move forward with the Randomization Authorization Flow (RAF) and be considered eligible by the RAF Reviewer.
9. Male or female.
10. Female participants of childbearing potential must have a negative β-human chorionic gonadotropin (β-HCG) test at Screening and Baseline, be sterile, or be postmenopausal.
11. Female participants of childbearing potential whose male partners are potentially fertile (e.g., no vasectomy) must use highly effective birth control methods stable for at least 3 months prior to screening, for the duration of the study and for 30 days after discontinuation of the study drug.

12. Male participants must be sterile, or if they are potentially fertile/reproductively competent ((not surgically (e.g., vasectomy) or congenitally sterile)) and their female partners are of childbearing potential, they must use, together with their female partners, effective birth control methods for the duration of the study and for 90 days after study drug discontinuation.
13. For participants taking allowed antipsychotic, antidepressant, or other psychotropic medication, the dosing of medication must be stable for at least 4 weeks before the Baseline visit and throughout the study (unless clinically necessary to change).
14. For participants taking allowed concomitant medications, dosing of medications must be stable for a t least 4 weeks prior to the Baseline visit (note: Amiodarone is not allowed within 6 weeks of Baseline visit).
15. Capable of providing signed informed consent.

Inclusion criteria – OLE

1. Completed the End of Study (EoS) visit of the Main Study on treatment without important protocol deviations impacting efficacy and safety assessments.
2. Capable and willing to provide signed informed consent for the OLE.
3. Must meet all criteria required to move forward with the OLE assessments.

Exclusion Criteria – Main Study

1. Prolonged QTcF interval (defined as a QTcF interval of >450 ms for male and >470 ms for female) at Screening[3].
2. Clinically significant heart disease within 12 weeks before randomization, defined as follows:
    a. Participants with clinically significant heart disease, a clinically significant history of arrhythmia, symptomatic or uncontrolled atrial fibrillation despite treatment, or confirmed ventricular tachycardia[2], or presence of left bundle branch block
    b. Participants with a known history of congenital long QT syndrome or a first-degree relative with this condition
    c. Clinically significant bradycardia, sick sinus syndrome, complete atrioventricular block, congestive heart failure, polymorphic ventricular tachycardia, clinically relevant hypocalcemia, hypokalemia or hypomagnesemia
4. History of epilepsy or seizures within the last 5 years.
5. Serious medical illness includes, but not limited to, uncontrolled hypertension; respiratory disease, including severe forms of asthma; severe hepatic disease (confirmed Hepatitis B virus [HBV], Hepatitis C virus [HCV]; confirmed human

[3] If there is evidence of a prolonged QTcF interval at screening from the initial (single) administration, then the ECG will be repeated twice, and the mean of the 3 screening administrations will be used to determine whether or not the participant is suitable for inclusion in the study.

immunodeficiency virus [HIV]); renal disease; acquired immune deficiency syndrome; and unstable psychiatric or other neurologic disorders) and metastatic cancer.
For serious kidney and liver illnesses see also exclusion criterion 12 (laboratory test abnormalities).

6. Known intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage.
7. Female participants who are pregnant, planning to become pregnant or breastfeeding.
8. Medications that prolong QT interval, taken within 4 weeks of the Baseline visit (note, Amiodarone is not allowed within 6 weeks of the Baseline visit) or at any timepoint during the study, including non-allowed antipsychotic medications, tricyclic antidepressants, and/or Class I antiarrhythmics.
9. Use of pridopidine within 12 months before the Baseline visit.
10. Treatment with any investigational product within 6 weeks or 5 half-lives (whichever is longer) before the Screening visit or a plan to participate in another clinical study that assesses any investigational product during the study.
11. Gene therapy at any time.
12. Prior participation in studies with tominersen at any time.
13. Laboratory values that fall outside of the central laboratory's reference range at Screening and are considered clinically significantly abnormal by the Investigator, and affect the participant's suitability to participate in the study or put the participant at risk if he/she enters the study in the Investigator's opinion[4].
14. Have any of the following laboratory test abnormalities at Screening:
    a. Creatinine clearance (CrCl) <30 mL/min at Screening, calculated using the Cockcroft-Gault equation: (140–age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL)[5]
    b. Aspartate aminotransferase (AST) ≥2.5 × upper limit of normal (ULN)
    c. Alanine aminotransferase (ALT) ≥2.5 × ULN
    d. Gamma glutamyl transferase (GGT) ≥3.0 × ULN
    e. Total bilirubin >1.5 mg/dL, except participants with unconjugated hyperbilirubinemia without other liver function derangements or other explanations for the elevated bilirubin (consistent with diagnosis of Gilbert's syndrome)
15. Alcohol and/or substance use disorder within the 6 months prior to screening, as defined by the Diagnostic and Statistical Manual–Fifth Edition (DSM-5) Text Revision criteria for substance use.

[4] Repeat testing is allowed (up to a maximum of 3 tests) if required to establish whether values are within the normal range or clinically significantly abnormal.
[5] It is allowed to repeat the test once, if clinically appropriate.

16. Active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the C-SSRS if the ideation occurred within 1 year of Screening, or participants who answered "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior), if the attempt or acts were performed within 1 year of Screening, or participants who, in the opinion of the Investigator, present a serious risk of suicide.
17. Known allergy to any ingredient of the study drug (pridopidine, silicified microcrystalline cellulose, or magnesium stearate).
18. Vulnerable participant (e.g., people kept in detention), or participant unfit to participate in a clinical study due to living circumstances (e.g., without sufficient family or social support, stable residence, sustainable financial and general healthcare and resources).
19. An employee or a family member of an employee of the Sponsor, Investigator or Investigator study site, or otherwise dependent on the Sponsor, the Investigator or the Investigator study site.

Overall Design

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of pridopidine administered orally at a dose of 45 mg bid in participants with early HD defined as Stages 1 and 2 (based on Shoulson and Fahn (Shoulson, 1979)). The study will be conducted at approximately 60 sites in North America and Europe.

The study will consist of a Screening period, a double-blind Treatment period (Main Study), and an optional OLE as described below.

After signing informed consent, participants will undergo screening assessments to determine eligibility over a Screening period of up to 6 weeks[6].

The Screening period will be followed by a 65- to 78-week double-blind Treatment period, composed of a 2-week Titration period, a 63-week double-blind full-dose Maintenance Treatment period followed by a variable double-blind Treatment period of up to 13 weeks (total of up to 78 weeks; Main Study).

On Day 1 (Baseline visit), eligible participants will be randomized in a 1:1 ratio to active (pridopidine 45 mg bid) or control (placebo) arm as shown in Table 1. Randomization will be stratified by Baseline HD stage (HD1 vs. HD2) and baseline Neuroleptic use (Yes/No).

Starting on Day 1, during the Titration period, all participants will self-administer 1 capsule of study drug orally (PO), once daily (QD), in the morning for 2 weeks. Thereafter, the study drug will be taken PO bid in the morning and in the afternoon (7-10 hours apart) for 63 weeks (double-blind full-dose Maintenance Treatment period). Participants who complete the Maintenance period (63 weeks) will continue into a variable double-blind period of up to 13

[6] If there is no need for genetic tests or washout from prohibited medication, the screening period should be completed within 3 weeks.

weeks or until the last participant randomized completes 65 weeks of treatment (2-weeks Titration + 63-weeks full- dose), whichever comes first. Most participants will be followed for 78 weeks. Participants entering the study within 90 days of the last randomized participant will be followed between 65 and 78 weeks. As soon as the last participant reaches Week 65, the Main study EoS visit for all remaining participants who are between Week 65 and Week 78 needs to be conducted within 4 weeks.

For participants who complete their Week 65 visit within 4 weeks of the last participant completing Week 65, the Week 65 visit will be considered the EoS Visit. For participants who are beyond 4 weeks from their Week 65 visit when the last participant reaches Week 65, and have not had a Week 78 visit, the EoS visit will be conducted within 4 weeks.

The double-blinding will be maintained for all participants and Investigators until that time.

For each participant, the last visit will be the Main Study EoS visit scheduled between Week 65 and Week 78, if the participant completes all study visits, or Early Termination (ET) visit if the participant withdraws from the study before Week 65 or Week 78, respectively.

Eligible participants who complete the Main Study, 65- or 78-week double-blind Treatment period, will have the option to enroll into an OLE period, commencing at the Main Study EoS visit, and receive pridopidine. The OLE will consist of a 2-week Titration period and a Maintenance period. During the Titration period, participants will self-administer 1 capsule of pridopidine 45 mg PO, QD, in the morning, for 2 weeks. Thereafter, pridopidine will be taken PO, bid in the morning and in the afternoon (7-10 hours apart).

Participants who are not continuing to the OLE study will be contacted by phone for a safety evaluation 2 weeks after the Main Study EoS/ET visit. AEs will be monitored for these 2 weeks until the safety telephone contact.

Throughout the study, participants will be assessed through on-site clinic visits, virtual visits (via telephone), and safety telephone calls (TCs), as specified in the corresponding Schedule of Activities (SoA) (Table 2 – Main Study, and Table 3 – OLE) and study schema (Figure 1 – Main Study, and Figure 2 – OLE).

During the double-blind Treatment period of the Main Study, an independent Safety Monitoring Committee will oversee the safety and tolerability based on participants' data accrued in the electronic data capture (EDC) system, based on an ongoing review of SAEs and periodical review of the accumulating safety data.

Disclosure Statement: The Main Study is a parallel-group treatment study with 2 arms that is participant- and Investigator-blinded.

Number of Participants and Treatment Groups

Main Study

Table 1: Treatment Groups – Main Study

Treatment	Dose and dose regimen		Number of participants
	Titration Period (2 weeks)	Maintenance Period (65 to 78 weeks)	
Active – pridopidine	45 mg capsule PO, QD	45 mg capsule PO, bid (total daily dose of 90 mg)	240
Control – matching placebo	Capsule, PO, QD	Capsule, PO, bid	240

Abbreviations: twice daily (bid); oral (PO); once daily (QD)

OLE

Pridopidine, 45 mg capsule PO, QD will be taken for the first 2 weeks (Titration period), followed by 45 mg capsule PO, bid (total daily dose of 90 mg, Full-dose period). The number of participants is to be determined, depending on the number of eligible participants.

Study Duration

The Main Study is expected to be conducted from Q3 2020 until Q1 2023. Participant recruitment period is planned from Q3 2020 until approximately Q4 2021 (end date can vary based on actual study performance and enrollment status).

For each participant, the total duration of study participation in the Main Study (Screening and Double–blind period) will be up to 86 weeks.

Main Study:

Screening period:	Up to 6 weeks
Double-Blind Treatment period:	Up to 78 weeks as follows: • 2 weeks Titration period • 63 weeks full-dose treatment • Up to 13 weeks variable double-blind period (until the last randomized participant completes 65 weeks of treatment = 2 weeks Titration + 63 weeks full-dose)
Follow-up period:	2 weeks (only for participants not continuing to OLE)

OLE:

- 2 weeks Titration period
- Full dose treatment until 12 months after the last participant completes the double-blind Treatment period
- OLE duration may be further extended pending emerging data from the double-blind portion of the study

Safety Monitoring Committee: Yes

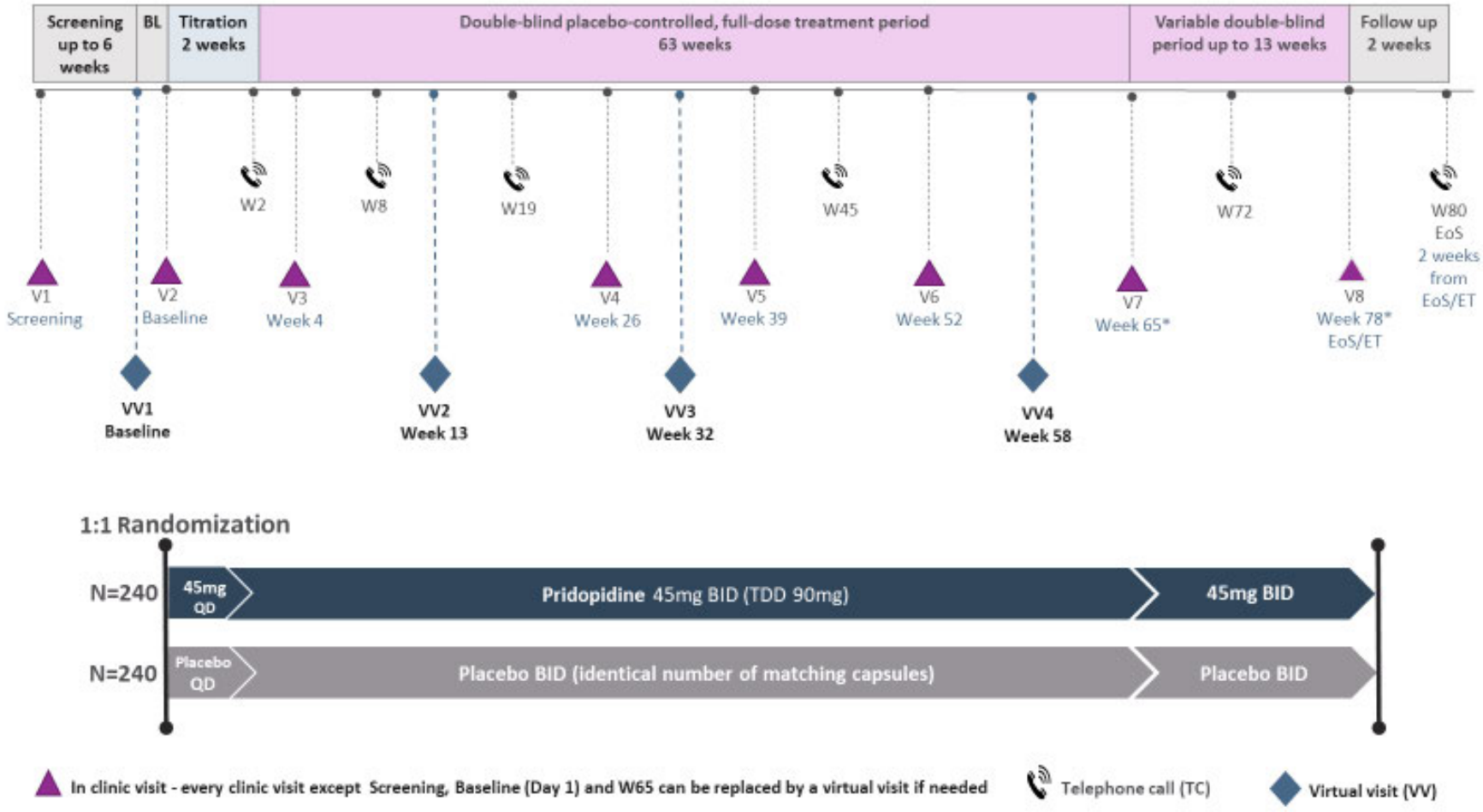
Coronavirus Disease 2019 (COVID-19) Mitigation Plan

Proactive mitigation measures to ensure participants' safety and study integrity during COVID-19 pandemic (or any Public Health Emergency) are included in this study. Four virtual visits are incorporated into the protocol to ensure participant safety and minimize the risk of missing data. In addition, every in-clinic visit, except Screening, Baseline and Week 65 visits, can be converted to a virtual visit if this will be required.

Some of the efficacy and safety measures can be carried out by remote assessments, if required. Raters will be trained and ready to implement these remote safety and efficacy measures. Home visits by health care professionals for safety assessments may be conducted if in-clinic visits will not be possible (including safety laboratories, vital signs, and ECG administration). Drug accountability will also be conducted at home visits by health care professionals.

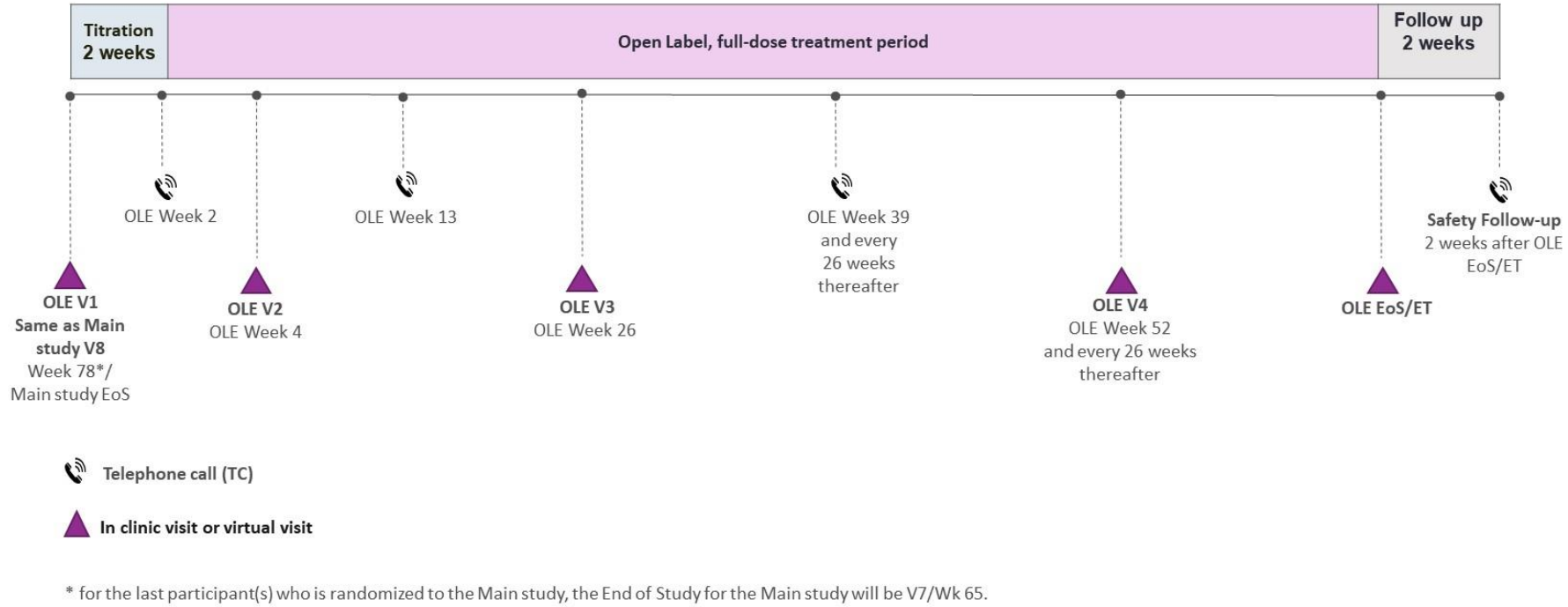
1.2. Study Scheme

Figure 1: Study Scheme – Main Study – Double-blind Placebo-controlled



Abbreviations: twice daily (bid); Baseline (BL); End of Study (EoS); Early Termination (ET); once daily (QD); Visit (V); Virtual Visit (VV); Week (W); Total Daily Dose (TDD).
* For each participant, the last treatment visit will be the EoS at either Week 65 or Week 78 if the participant completes all study visits; or Early Termination (ET) visit if the participant withdraws from the study before Week 65.

Figure 2: Study Scheme – Open-label Extension



* for the last participant(s) who is randomized to the Main study, the End of Study for the Main study will be V7/Wk 65.

Abbreviations: End of Study (EoS); EarlyTermination (ET); Open-label Extension (OLE); Visit (V); Week (Wk).

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities – Main Study – Double-blind, Placebo-Controlled

General note: every clinic visit, except Screening V1, Baseline V2, and V7 can be converted to virtual visits (VV) (e.g., via telephone). Refer to Appendix 10 (Section 10.10) for guidance.

Table 2: Schedule of Activities – Main Study – Double-blind, Placebo-Controlled

Study Period Procedures and Assessments	**Screening[a]**		**Double-blind Titration Period**		**Double-blind, Placebo-controlled, Fulldose Maintenance Treatment Period**											**Double-blind Variable Period[b]**		**Follow-up Safety Assessment[c]**
Study Clinic Visit	**V1**		**V2 BL[d]**		**V3**				**V4**		**V5**		**V6**		**V7[e]**		**V8 (Main Study EoS[e, f] /ET[g])**	**F/U**
Virtual Visit (VV)		**VV1 BL**					**VV 2**			**VV3**				**VV 4**				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			**Day1**	**2**	**4**	**8**	**13**	**19**	**26**	**32**	**39**	**45**	**52**	**58**	**65**	**72**	**78**	**80 (2 weeks after Main Study EoS/ET)**
Visit Windows (days)	**< 42**	**<7**			**±5**	**±5**	**±14**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±5**
Informed consent	X (Main Study)														X (●LE)		X (●LE) if not obtained at V7	
Check willingness to enter ●LE															X[i]			
Demography	X																	
Medical and psychiatric history (including smoking)	X																	
Prior medication and treatment history	X																	
Inclusion and exclusion criteria	X[j]																	

Study Period Procedures and Assessments	Screening[a]		Double-blind Titration Period		Double-blind, Placebo-controlled, Fulldose Maintenance Treatment Period										Double-blind Variable Period[b]		Follow-up Safety Assessment[c]
Study Clinic Visit	**V1**		**V2 BL[d]**		**V3**				**V4**		**V5**		**V6**		**V7[e]**		**V8 (Main Study EoS[e, f] /ET[g])**	**F/U**
Virtual Visit (VV)		**VV1 BL**					**VV 2**			**VV3**				**VV 4**				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			**Day1**	**2**	**4**	**8**	**13**	**19**	**26**	**32**	**39**	**45**	**52**	**58**	**65**	**72**	**78**	**80 (2 weeks after Main Study EoS/ET)**
Visit Windows (days)	**< 42**	**<7**			**±5**	**±5**	**±14**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±14**	**±14[h]**	**±5**
Clinical lab tests (serum chemistry, hematology and urinalysis)[k]	X		X		X				X		X		X		X		X	
Pregnancy test (for WOCBP)[l]	Serum		Urine (U)		U				U		U		U		U		U	
					Monthly urine pregnancy tests (at home)													
Full physical and neurological examination	X		X										X		X		X	
Brief physical examination					X				X		X							
12 lead ECG	X[m]		X[n, o]		X[o]				X[p]						X[p]		X[p, q]	
Vital signs[r]	X		X		X				X		X		X		X		X	
C-SSRS (Baseline version)	X																	
C-SSRS (since last visit version)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
UHDRS-TFC	X	X	X						X	X	X		X	X	X		X	
UHDRS-TMS	X		X						X		X		X		X		X	
UHDRS-IS	X																	

Study Period Procedures and Assessments	Screening[a]		Double-blind Titration Period		Double-blind, Placebo-controlled, Fulldose Maintenance Treatment Period											Double-blind Variable Period[b]		Follow-up Safety Assessment[c]
Study Clinic Visit	V1		V2 BL[d]		V3				V4		V5		V6		V7[e]		V8 (Main Study EoS[e, f] /ET[g])	F/U
Virtual Visit (VV)		VV1 BL					VV 2			VV3				VV 4				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			Day1	2	4	8	13	19	26	32	39	45	52	58	65	72	78	80 (2 weeks after Main Study EoS/ET)
Visit Windows (days)	< 42	<7			±5	±5	±14	±14	±14[h]	±14	±14[h]	±14	±14[h]	±14	±14[h]	±14	±14[h]	±5
SDMT			X						X		X		X		X		X	
SWR			X						X		X		X		X		X	
●-Motor	X[s]		X						X				X		X		X	
PBA-S (Short Form)		X	X				X		X				X	X	X		X	
CGI-S (modified)		X	X															
CGI-C									X		X		X		X		X	
HD●oL-P			X						X				X		X		X	
Benzodiazepines and antidepressants inquiry[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alcohol/illicit drug use inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of tolerability to study drug prior to dose escalation				X														
Randomization			X															
Dispense/collect study drug			X (dispense only)		X				X		X		X		X		X	
Review study compliance and adherence				X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period Procedures and Assessments	Screening[a]		Double-blind Titration Period		Double-blind, Placebo-controlled, Full-dose Maintenance Treatment Period										Double-blind Variable Period[b]		Follow-up Safety Assessment[c]
Study Clinic Visit	V1		V2 BL[d]		V3				V4		V5		V6		V7[e]		V8 (Main Study EoS[e,f] /ET[g])	F/U
Virtual Visit (VV)		VV1 BL					VV 2			VV3				VV 4				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			Day1	2	4	8	13	19	26	32	39	45	52	58	65	72	78	80 (2 weeks after Main Study EoS/ET)
Visit Windows (days)	<42	<7			±5	±5	±14	±14	±14[h]	±14	±14[h]	±14	±14[h]	±14	±14[h]	±14	±14[h]	±5
Study drug administration			<===						X								===>	
Adverse event inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for PK analysis[u]									X				X		X		X	
Plasma sample for biomarkers analysis[v]	X[w]		X[w]						X				X		X		X	
Blood sample for genetic analysis[v,x]	X[w]		X[w]															
Blood sample for CAG repeat analysis[v,y]	X																	

Abbreviations: Baseline (BL); cytosine-adenosine-guanine (CAG); Clinical Global Impression of Change (CGI-C); Clinical Global Impression of Severity (CGI-S); Columbia-Suicide Severity Rating Scale (C-SSRS); electrocardiogram (ECG); End of Study (EoS); Early Termination (ET); Follow-Up (F/U); Huntington Disease Quality of Life Questionnaire-Participant (HDQoL-P); Independence Scale (IS); Problem Behaviors Assessment – Short Form (PBA-s); pharmacokinetic (PK); Quantitative motor (Q-Motor); Symbol Digit Modalities Test (SDMT); Stroop Word Reading (SWR); Total Functional Capacity (TFC); Total Motor Score (TMS); Unified Huntington Disease Rating Scale (UHDRS); Visit (V); Virtual Visit (VV); women of childbearing potential (WOCBP).

Table Footnotes:

a. A participant not meeting all eligibility requirements may be rescreened only once. Screening assessments may be repeated during the screening period if approved and at the discretion of the study Medical Monitor (or designee). After the screening period all screening assessments must be repeated except for Cytosine Adenine Guanine (CAG) repeat (provided the results are available from a prior screening period).

b. This period is variable in duration up to 13 weeks. Participants will continue to receive treatment during the double-blind variable period until they reach Week 78 or until the last participant randomized completes 65 weeks of treatment (2 weeks titration + 63 weeks full-dose), whichever comes first. As soon as the last participant reaches Week 65, the Main Study EoS visit for all remaining participants who are 4 weeks beyond their respective Week 65 visit needs to be conducted within 4 weeks.
c. Follow-up visit in Main Study is only applicable to participants who are not continuing to Open-label Extension.
d. All Baseline assessments should be done pre-dose, except post-dose ECG.
e For the last group of participants whose Week 65 visit is within 4 weeks of last participant's Week 65 visit in the Main Study, the End of Study visit will be V7.
f. After completing the Main Study EoS visit, eligible participants will have the option to continue for an Open-label Extension.
g. When a participant discontinues study drug but continues to be followed in the study, they should first do ET visit and then continue with the follow-up off study treatment as scheduled.
h. Visit window can be expanded any post Week 4 (V3) in-clinic visit window to ±28 days; this applies to V4-8). The expansion of the in-clinic visit window is only in case of a global pandemic.
i. To be done once, as early as Main Study Week 58, or at V7 (Main Study Week 65)/Main Study Week 72 (depending on when the participant is anticipated to transition to OLE).
j. Inclusion/exclusion criteria should be met before Baseline visit.
k. Safety laboratories should not be collected for participants who are off drug and remain in the study, unless there are abnormalities requiring follow-up.
l. **Serum** pregnancy test will be performed at Screening. At Baseline visit, **urine** pregnancy test will be performed before first dose. Both test results must be known before first dosing. **Urine** pregnancy test will be performed at subsequent timepoints. An indeterminate or positive reading for the urine pregnancy test should be followed-up by a serum pregnancy test and the participant should be referred to a gynecologist if required. During the Treatment period, urine pregnancy tests will be performed monthly. Refer to Appendix 4 Section 10.4.
m. Single ECG to assess eligibility.
n. Baseline pre-dose assessment will include triplicate ECG administrations.
o. Single ECG 1-2 hours post-dose.
p. Single ECG pre-dose.
q. Only for participants not continuing to Open-label Extension (single ECG). Participants continuing to OLE, will have triplicate ECG (pre-dose) at V8.
r. Vital signs (body temperature, systolic and diastolic blood pressure, and heart rate) will be measured in a supine position after 5 minutes rest; thereafter, blood pressure should be measured again after standing for 2 minutes.
s. For training purposes only.
t. This information will be collected as part of the concomitant medication inquiry.
u. Blood samples for plasma concentration of study drug will be collected 1-2 hours **after** dosing and **after** the ECG. PK samples should not be collected from participants who are off drug and remain in the study.
v Always collect blood after ECG is administered (not before).
w. Sample analysis will be drawn at Screening **or** Baseline.
x. Sampling analyses for DNA extraction will be performed only once during the study, at Screening or at Baseline, for future genetic analysis related to pridopidine response or HD.
y. Sampling analyses for CAG, only if needed.

1.3.2. Schedule of Activities – Open-label Extension (OLE)

Table 3: Schedule of Activities – Open-label Extension

Study Period Procedures and assessments	Open-Label Titration Period		Open-Label Full-dose Treatment Period					Follow-up Safety Assessment	
Study Clinic Visit	**OLE V1 [a] (same as Main Study V8)**		**OLE V2**		**OLEV3**		**OLEV4+**	**OLE EoS /ET[b]**	**OLEF/U**
Telephone Call Safety Visit		✆		✆		✆			✆
OLE Study Week	**OLE Day 1 (same as Main Study Wk 78/EoS)**	**OLE Wk 2**	**OLE Wk 4**	**OLE Wk 13**	**OLE Wk 26**	**OLE Wk 39 & every 26 wks thereafter**	**OLE Wk 52 & every 26 wks thereafter**	X	**+2 weeks after OLEEoS/ET**
Visit Windows (days)		**±1**	**±5**	**±5**	**±14**	**±14**	**±14**	**±14**	**±5**
OLE Informed consent	X (if not obtained at Main Study V7)								
Re-confirm eligibility to OLE	X								
Clinical laboratory tests (serum chemistry, hematology) [d]	X		X		X		X	X	
Urinalysis[e]	X								
Pregnancy test (for WOCBP)	U		U		U		U	U	
		Monthly urine pregnancy test (at home)							
Brief physical examination	X (full PE)		X		X		X	X	
12 lead ECG	X[f,g]		X[g]		X[h]			X[h]	
Vital signs	X		X		X		X	X	
C-SSRS (since last visit version)	X		X	X	X	X	X	X	X
UHDRS-TFC	X				X		X	X	
UHDRS-TMS	X				X		X	X	
SDMT	X				X		X	X	
SWR	X				X		X	X	
●-Motor	X		X		X		X	X	
PBA-S (Short Form)	X		X		X	X	X	X	X
CGI-C	X				X		X	X	
HD●oL	X				X		X	X	

Study Period Procedures and assessments	Open-Label Titration Period		Open-Label Full-dose Treatment Period					Follow-up Safety Assessment	
Study Clinic Visit	**OLE V1 [a] (same as Main Study V8)**		**OLEV2**		**OLE V3**		**OLEV4+**	**OLE EoS /ET[b]**	**OLEF/U**
Telephone Call Safety Visit		✆		✆		✆			✆
OLE Study Week	**OLE Day 1 (same as Main Study Wk 78/EoS)**	**OLE Wk 2**	**OLE Wk 4**	**OLE Wk 13**	**OLE Wk 26**	**OLE Wk 39 & every 26 wks thereafter**	**OLE Wk 52 & every 26 wks thereafter**	X	**+2 weeks after OLEEoS/ET**
Visit Windows (days)		**±1**	**±5**	**±5**	**±14**	**±14**	**±14**	**±14**	**±5**
Benzodiazepines and antidepressants inquiry	X	X	X	X	X	X	X	X	X
Alcohol/illicit drug use inquiry	X	X	X	X	X	X	X	X	X
Dispense/collect study drug	X		X		X		X	X(collect only)	
Review study compliance and adherence	X	X	X	X	X	X	X	X	X
Study drug administration	<==========X==========						==========>		
Adverse event inquiry	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X
Plasma sample for biomarkers analysis					X[c]		X	X[c]	

Abbreviations: Clinical Global Impression of Change (CGI-C); Columbia-Suicide Severity Rating Scale (C-SSRS); electrocardiogram (ECG); End of Study (EoS); Early Termination (ET); Follow-up (F/U); Huntington Disease Quality of Life Questionnaire (HDQoL); Open-label Extension (OLE); Physical Examination (PE); Problem Behaviors Assessment–Short Form (PBA-s); Symbol Digit Modalities Test (SDMT); Stroop Word Reading (SWR); Total Functional Capacity (TFC); Total Motor Score (TMS); Unified Huntington Disease Rating Scale (UHDRS); Visit (V); women of childbearing potential (WOCBP).

Table Footnotes:

a. The OLE V1 is the same as Main Study V8 (or V7/W65 for the last group of participants in the Main Study). Assessments do not need to be repeated if conducted as part of the Main Study.
b. A participant who discontinues study drug at any point during the OLE, must also be withdrawn from the study and attend an EoS visit.
c. In-clinic visit window can be expanded to ±28 days; this applies to all in-clinic visits including OLE V1-4+ and OLE F/U. The expansion of the in-clinic visit window is only in case of a global pandemic.
d Collect blood **after** ECG is administered (**not** before).
e. Urinalysis will be done as part of Main Study V8, not as part of OLE
f. Triplicate ECG pre-dose.
g. Single ECG 1-2 hours post-dose.
h. Single ECG pre-dose.

2. INTRODUCTION

2.1. Study Rationale

Huntington Disease (HD) is an autosomal dominant, progressive fatal neurodegenerative disorder characterized by motor, cognitive, and behavioral abnormalities. While medications to treat chorea and some behavioral symptoms are available, no therapy has yet proven able to modify the progressive and inexorable functional decline of the disease. A therapy that maintains functional capacity and prevents or delays the development of disability represents a critically unmet clinical need.

Pridopidine, a novel small molecule under development for the treatment of HD has high affinity

[redacted]

[redacted]

The purpose of this Phase 3 study is to further evaluate the effect of pridopidine 45 mg bid on functional capacity, as well as motor and behavioral features of HD in early-stage participants (TFC 7-13).

2.2. Background

HD is a fatal neurodegenerative disorder characterized by progressive deterioration of motor and cognitive functions, as well as behavioral and psychiatric disturbances. The disease has an autosomal dominant inheritance and is caused by an expanded cytosine-adenine-guanine (CAG) repeat in the huntingtin gene (HTT) on chromosome 4, encoding the mutant protein huntingtin (Huntington's Disease Collaborative Research Group, 1993).

The estimated prevalence of HD in North America, North-Western Europe, and Australia ranges from 5.96 to 13.7 cases per 100,000 people (Fisher, 2014; Rawlins, 2016). The age of onset of the signs and symptoms of HD and the rate of disease progression can vary greatly. Adult-onset HD most often begins between 30 and 40 years of age. The illness generally lasts 15 to 20 years and is fatal. Following diagnosis, motor and cognitive functions steadily decline, ultimately leading to a state of immobility, dementia, and premature death (Ross, 2014).

In HD to date, only 2 drugs, tetrabenazine and deutetrabenazine, have been approved for the management of chorea. A number of medications are used off-label to control motor and psychiatric symptoms arising from HD.

[redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of pridopidine is provided in the Iuvestigator's Brochure (IB).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of pridopidine may be found in the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study drug Pridopidine		
QT Prolongation	Known risk identified in pre-clinical and clinical studies as a result of Ikr potassium channel block in ventricular myocardium. Excessive QT prolongation is a recognized surrogate marker for a specific type of ventricular tachycardia, Torsade de Pointes. Exposure-response modeling based on dosing of pridopidine up to 112.5 mg bid suggests a linear response of QTcF to increasing drug exposure (refer to Appendix 9 Section 10.9). At 45 mg bid, the dose evaluated in this trial, the estimated QTcF prolongation is 6.6 ms and not considered clinically meaningful.	Participants will be excluded if they have a clinically significant heart disease, a clinically significant history of arrhythmia, symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia, or presence of left bundle branch block. Participants with known history of congenital long QT syndrome or a first degree relative with this condition will be excluded. Participants with clinically significant bradycardia, sick sinus syndrome, complete atrioventricular block, congestive heart failure, polymorphic ventricular tachycardia, clinically relevant hypocalcemia, hypokalemia or hypomagnesemia will be excluded. ECG parameters will be closely monitored throughout the study (refer to Appendix 8, Section 10.8). Participants will be required to discontinue study drug during the study if they have symptomatic or uncontrolled atrial fibrillation, confirmed ventricular tachycardia, presence of left bundle branch block
Decreased creatinine renal clearance	Identified risk in clinical studies. There have been no serious outcomes relating to the decrease, and discontinuation of the pridopidine treatment results	Participants with a creatinine clearance (CrCl) <30 mL/min will be excluded. Creatinine values will be monitored throughout the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	in the return of creatinine to normal values.	Participants will be discontinued from the study if their CrCl reaches <30 mL/min during the study.

2.3.2. Benefit Assessment

There are currently no disease-modifying drugs for the treatment of HD. The results from completed studies with pridopidine suggest a potential benefit of pridopidine to fulfill a critical unmet need in the treatment of patients with HD, and support further clinical development.

Participants in the study may experience symptomatic improvement and, possibly, the rate of disease progression may be reduced. However, there is no guarantee that participation in the current study will help the participant; the participant may receive a placebo treatment during the Main Study. During the OLE, all participants will receive pridopidine.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants taking part in this study, the potential risks identified in association with pridopidine are justified by the anticipated benefits that may be afforded to participants with HD.

3. OBJECTIVES AND ENDPOINTS

3.1. Main Study Objectives, Endpoints and Primary Estimand

3.1.1. Main Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of pridopidine on functional capacity in participants with Stage 1-2 HD	• Change from Baseline to Week 65 in the UHDRS-TFC score
Multiplicity Adjusted Secondary Endpoints	
Key Secondary (secondary endpoints are listed by order of hierarchy)	
• To assess the effect of pridopidine on a composite measure of disease progression in participants with HD	1. Change from Baseline to Week 65 in composite UHDRS (cUHDRS) total score
Secondary (secondary endpoints are listed by order of hierarchy)	
• To evaluate the effect of pridopidine on functional capacity, motor function, and other measures of efficacy over time in participants with HD	2. Proportion of participants with improvement or no worsening (change from Baseline ≥ 0 point) at Week 65 in UHDRS-TFC 3. Change from Baseline to Week 52 in UHDRS-TFC score 4. Change from Baseline to Week 78 in UHDRS-TFC score 5. Change from Baseline to Week 65 in Quantitative motor (Q-Motor) [redacted] 6. Change from Baseline to Week 65 in UHDRS Total Motor Score (TMS) 7. Change from Baseline to Week 65 in Symbol Digit Modalities Test (SDMT) 8. Change from Baseline to Week 52 in UHDRS-TMS score

	9. Proportion of participants with improvement or no worsening in Clinical Global Impression of Change (CGI-C) at Week 65
Non-multiplicity Adjusted Secondary Endpoints	
• To evaluate the effects of pridopidine in participants with HD	• Change from Baseline to Week 26 and 39 in the UHDRS-TFC • Proportion of participants with improvement or no worsening in UHDRS-TFC (change from Baseline ≥ 0) at Weeks 26, 39, 52 and 78 • Change from Baseline to Weeks 26, 39, 52 and 78 in cUHDRS • Proportion of participants with change from Baseline ≥ -1 in cUHDRS at Weeks 26, 39, 52, 65 and 78 • Change from Baseline to Week 26, 39 and 78 in the UHDRS-TMS score • Proportion of participants with improvement or no worsening in UHDRS-TMS (change from Baseline ≤ 0) at Weeks 26, 39, 52, 65 and 78 • Change from Baseline to Weeks 26, 39, 52, 65 and 78 in: – UHDRS-TFC Scale sub-items (capacity to undertake domestic chores, activities of daily living, capacity to manage finances, care level and occupation) – UHDRS-TMS sub-scores for: o Gait and balance score (defined as the sum of UHDRS-TMS domains gait, tandem walking, and retropulsion pull test) o Eye movement o Dystonia • Change from Baseline to Weeks 26, 39, 52 and 78 in SDMT

	• Change from Baseline to Weeks 26, 39, 52, 65 and 78 in Stroop Word Reading (SWR) • Change from Baseline to Weeks 26, 39, 52 and 78 in Q-Motor [redacted] • Proportion of participants with improvement or no worsening (change from Baseline ≤ 0 msec) in Q-Moto [redacted] at Weeks 26, 39, 52, 65 and 78 • Change from Baseline to Weeks 26, 39, 52, 65 and 78 in Q-motor [redacted] • Responder analyses on CGI-C using different thresholds at Weeks 26, 39, 52, 65 and 78
Safety and Tolerability	
• To evaluate the safety and tolerability of pridopidine in participants with HD	• Incidence (count and rate) of AEs and serious AEs (SAEs) overall, by severity, by relationship to study drug, and those that led to discontinuation of study drug and/or withdrawal from the study • Incidence and shifts of clinically significant abnormalities in electrocardiogram (ECG) (refer to Section 7.1.1), laboratory tests, vital signs, and abnormalities in physical and neurological exam • Analysis of Columbia-Suicide Severity Rating Scale (C-SSRS) throughout the study • Tolerability: – The number (%) of participants who complete the Treatment period – The number (%) of participants who fail to complete the Treatment period due to AEs – The number (%) of participants who fail to complete the Treatment period due to meeting the Fridericia-corrected QT interval (QTcF) change, CrCl or Psychiatric Stopping Rules

Exploratory	
• To evaluate the exploratory efficacy effects of pridopidine in participants with HD	• Change from Baseline to Weeks 26, 52, 65 and 78 in: – Problem Behaviors Assessment - Short Form (PBA-s) total score o PBA-s sub-score for apathy – Measurement of quality of life using HDQoL
• To evaluate changes in disease biomarker plasma neurofilament light chain (NfL) following treatment with pridopidine in participants with HD	• Change from Baseline to Weeks 26, 52, 65 and 78 in plasma NfL protein • Relationship between Baseline NfL and changes from Baseline in select efficacy endpoints • Relationship between changes from Baseline to Weeks 26, 52, 65 and 78 in NfL and selected efficacy endpoints • Proportion of participants with different thresholds for change from Baseline in plasma NFL levels to Weeks 26, 52, 65 and 78
• To evaluate the pharmacokinetics (PK) of pridopidine and its main metabolite in participants with HD	• Plasma concentrations of pridopidine and its main metabolite at Weeks 26, 52, 65, and 78 and at last participants' visit • Relationship between plasma concentration of pridopidine and clinical outcome measures

3.1.2. Primary Estimand

The primary estimand will answer the clinical question of "Whether the intent-to-treat (ITT) population of early HD patients (HD1 and HD2) have a clinically meaningful and statistically significant mean change from Baseline to Week 65 in UHDRS-TFC."

The 5 components of the primary estimand for this study based on the International Council for Harmonization (ICH) E9 R(1) guidance which defines the scientific question of interest are listed below.

The hypothesis testing will be based on the main estimand separately defined for European Medicines Agency (EMA) and non-EMA regions.:

For non-EMA regions, the main estimand is defined as **non-EMA-Estimand**:

- Treatment of interest: Pridopidine 45 mg bid vs placebo (on background of standard of care) that participants are randomized to

- Population of interest: Early HD Participants (HD1 & HD2) defined through the study inclusion/exclusion criteria. The modified intent to treat (mITT) dataset will be used in analyzing this estimand
- Variable of interest measured on each participant: Change from Baseline to Week 65 in UHDRS-TFC
- Population level summary: Least squares (LS) mean difference between pridopidine and placebo from Mixed Model for Repeated Measurements (MMRM) in change of UHDRS-TFC from Baseline to Week 65
- Handling of Intercurrent Events (ICEs): ICE include treatment discontinuation or death. Treatment policy strategy will be used to handle the ICE, where occurrence of an ICE is irrelevant. All observed values will be used regardless of occurrence of an ICE. No imputation is performed.

For EMA regions, the main estimand is defined as **EMA-Estimand**:

- Treatment: Pridopidine 45 mg bid or placebo (on background of standard of care) that participants are randomized to
- Population: Early HD Participants (HD1 & HD2) defined through the study inclusion/exclusion criteria. The ITT population will be used in analyzing this estimand
- Variable: Change from Baseline to Week 65 in UHDRS-TFC
- Population Level Summary: LS-Mean difference between pridopidine 45 mg bid and placebo from MMRM model in change of UHDRS-TFC from Baseline to Week 65
- ICE and Strategies for Addressing ICE:

  ICE include treatment discontinuation or death and will be handled by a composite of treatment policy and hypothetical strategies.

  - Treatment policy strategy will apply to all observed values including those collected after treatment discontinuation as these values reflect the remaining off-drug treatment effect in reality
  - Hypothetical strategy will apply to missing values after the last observed values. The method of multiple imputation will be applied to impute the missing data using Pattern Mixture Model (PMM) with control-based pattern imputation under Missing Not at Random (MNAR) assumptions

Additional details are included in Statistical Section of this protocol (Section 9) and in the statistical analysis plan.

3.2. OLE Objectives and Endpoints

Objectives	Endpoints
Efficacy	

• To evaluate the long-term treatment effect of pridopidine in participants with HD who previously completed the Main Study	• Proportion of participants with change from Baseline (Main Study) to each OLE visit in UHDRS-TFC ≥ -1 • Proportion of participants with change from Baseline (Main Study) to each OLE visit in UHDRS-TFC ≥ 0 • Change from Baseline (Main Study) to OLE visits in: – UHDRS-TFC – cUHDRS – UHDRS-TMS – Quantitative motor (Q-Motor): [redacted] – SDMT – SWR • Change from Baseline (Main Study) to OLE visits in: – CGI-C – PBA-s – HDQoL
Safety and Tolerability	
• To evaluate long-term safety and tolerability of pridopidine in participants with HD who previously completed the Main Study	• Incidence (count and rate) of AEs and SAEs overall, by severity, by relationship to study drug, and those that led to discontinuation of study drug and/or withdrawal from the study • Incidence and shifts of clinically significant abnormalities in ECG (refer to Section 7.1.1), laboratory tests, and vital signs • Analysis of C-SSRS throughout the study • Tolerability: – The number (%) of participants who complete the OLE treatment period

	– The number (%) of participants who fail to complete the OLE treatment period due to AEs
Biomarker	
• To evaluate long-term efficacy effects of pridopidine on NfL in participants with HD who previously completed the Main Study	• Change from Baseline (Main Study) in NfL protein level to each OLE visit • Relationship between changes from baseline in NfL and selected efficacy endpoints in the OLE period

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of pridopidine administered orally at a dose of 45 mg bid in participants with early HD defined as Stages 1 and 2 (based on Shoulson and Fahn (Shoulson, 1979)). Approximately 480 participants will be enrolled (240 per arm) at approximately 60 sites in North America and Europe.

The study will consist of a Screening period, a double-blind Treatment period (Main Study), and an OLE as described below.

After signing informed consent, participants will undergo screening assessments to determine eligibility over a Screening period of up to 6 weeks[7].

The Screening period will be followed by a 65- to 78-week double-blind Treatment period, composed of a 2-week Titration period, a 63-week double-blind full-dose Maintenance Treatment period followed by a variable double-blind Treatment period of up to 13 weeks (total of up to 78 weeks: Main Study).

On Day 1 (Baseline visit), eligible participants will be randomized in a 1:1 ratio to active (pridopidine 45 mg bid) or control (placebo) arm as shown in Table 1. Randomization will be stratified by Baseline HD stage (HD1 vs. HD2) and Baseline Neuroleptic use (Yes/No).

Starting on Day 1, during the Titration period, all participants will self-administer 1 capsule of study drug orally (PO), once daily (QD), in the morning for 2 weeks. Thereafter, the study drug will be taken PO, bid in the morning and in the afternoon (7-10 hours apart) for 63 weeks (double-blind full-dose Maintenance Treatment period). Participants who complete the Maintenance period (63 weeks) will continue into a variable double-blind period of up to 13 weeks or until the last participant randomized completes 65 weeks of treatment (2 weeks titration + 63 weeks full-dose), whichever comes first. Most participants will be followed for 78 weeks. Participants entering the study within 90 days of the last randomized participant will be followed between 65 and 78 weeks. As soon as the last participant reaches Week 65, the Main Study EoS visits for the remaining participants who are between Week 65 and Week 78 needs to be conducted within 4 weeks. For the group of participants who will not be able to reach Week 78 within these 4 weeks, Week 65 will be considered their EoS visit. The double-blinding will be maintained for all participants and Investigators until that time.

For each participant, the last visit will be the Main Study EoS or Early Termination (ET) visit. For participants who stay on study drug and complete all scheduled visits during the double-blind study period, their EoS visit will be either Week 65 visit or Week 78. Participants who discontinue early from study drug will be encouraged to remain in the study and complete all other visits as scheduled for the full course of the study. Participants who withdraw from the study before Week 65 visit and are not willing to continue with the study visits and procedures for the full course of the study, will be asked to undergo an ET visit that will include evaluations as specified in the SoA (Table 2 – Main Study). Participants withdrawing from the Main Study will be encouraged to complete the same final evaluations as participants

[7] If there is no need for genetic tests or washout from prohibited medication, the screening period should be completed within 3 weeks.

completing the study according to this protocol (EoS visit of the Main Study), particularly safety and primary and secondary efficacy evaluations.

Eligible participants who complete the Main Study, 65- or 78-week double-blind Treatment period, will have the option to enroll into an OLE period, commencing at the Main Study EoS visit, and receive pridopidine. The OLE will consist of a 2-week Titration period and a Maintenance period. During the Titration period, participants will self-administer 1 capsule of pridopidine 45 mg PO, QD, in the morning for 2 weeks. Thereafter, pridopidine will be taken PO, bid, in the morning and in the afternoon (7-10 hours apart) until 12 months after the last participant completes the double-blind Treatment period.

Participants who are not continuing to the OLE study will be contacted by phone for a safety evaluation 2 weeks after the Main Study EoS/ET visit. AEs will be monitored for these 2 weeks until the safety telephone contact.

Throughout the study, participants will be assessed through on-site clinic visits, virtual visits (via telephone), and safety telephone calls (TCs), as specified in the corresponding SoAs (Table 2 – Main Study, and Table 3 – OLE) and study schemas (Figure 1 – Main Study, and Figure 2 – OLE).

During the double-blind Treatment period of the Main Study, an independent Safety Monitoring Committee will oversee the safety and tolerability based on participants' data accrued in the electronic data capture (EDC) system, based on an ongoing review of SAEs and periodical review of the accumulating safety data. Further details are provided in Section 9.6.

4.2. Scientific Rationale for Study Design

[redacted]

There are currently no available HD therapies that maintain function capacity or core clinical features of the disease. Tetrabenazine and deutetrabenazine are the only currently approved treatments for HD, but they are indicated for symptomatic treatment of chorea, and not for maintenance of functional capacity (Shen, 2013; Frank, 2016).

4.3. Justification for Dose

[redacted]

[redacted]

4.4. Study Duration

The Main Study is expected to be conducted from Q3 2020 until Q1 2023. Participant recruitment period is planned from Q3 2020 until approximately Q4 2021 (end date can vary based on actual study performance and enrollment status).

For each participant, the total duration of study participation in the Main Study (Screening and Double-blind period) will be up to 86 weeks.

Main Study:

Screening period:	Up to 6 weeks
Double-blind Treatment period:	Up to 78 weeks as follows: • 2 weeks Titration period • 63 weeks full-dose treatment • Up to 13 weeks variable double-blind period (until the last randomized participant completes 65 weeks of treatment = 2 weeks titration + 63 weeks full-dose)
Follow-up period:	2 weeks

OLE:

- 2 weeks Titration period
- Full dose treatment until 12 months after the last participant completes the double-blind Treatment period. OLE duration may be further extended pending emerging data from the double-blind portion of the study.

4.5. End of Study Definition

A participant is considered to have completed the Main Study if he/she has completed the Week 65 assessments without discontinuing early. The Main Study will be considered completed when all participants either complete the study through Week 65 (EoS visit) or discontinue earlier (ET visit).

The OLE study will be considered completed 12 months after the last participant completes the double-blind Treatment period. OLE duration may be further extended pending emerging data from the double-blind portion of the study. The Sponsor intends to submit a substantial protocol amendment for the extension of the OLE after ensuring a remaining positive benefit-risk ratio after analysis of the data from the Main Study.

4.6. Coronavirus Disease 2019 (COVID-19) Mitigation Plan

Proactive mitigation measures to ensure participant's safety and study integrity during COVID-19 pandemic (or any Public Health Emergency) are included in this study. Four virtual visits are incorporated into the protocol to ensure participant safety and minimize the risk of

missing data. In addition, every in-clinic visit, except Screening, Baseline and Week 65 visits, can be converted to a virtual visit if this will be required.

Some of the efficacy and safety measures can be carried out by remote assessments, if required. Raters will be trained and ready to implement these remote safety and efficacy measures. Home visits by health care professionals for safety assessments may be provided if in-clinic visits will not be possible (including safety laboratories, vital signs and ECG administration). Drug accountability will also be conducted at home visits by health care professionals. For additional information refer to Appendix 10 (Section 10.10).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria – Main Study

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Twenty-five years of age (inclusive) and older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Diagnosis of HD based on clinical features and the presence of ≥36 CAG repeats in the HTT, confirmed by historical laboratory quantified results or by a diagnostic test at Screening.
2. Diagnostic confidence level (DCL) of 4 (unequivocal motor signs, ≥99% confidence) on the standardized motor exam UHDRS-TMS.
3. Adult-onset HD with onset of signs and symptoms ≥18 years of age.
4. Stage 1 or Stage 2 HD, defined as a UHDRS-TFC score of ≥7, at Screening.
5. UHDRS-Independence Scale (IS) score ≤90% at Screening.
6. UHDRS-TMS ≥20 at Screening.
7. Must meet all criteria required to move forward with the Randomization Authorization Flow (RAF) and be considered eligible by the RAF Reviewer.

Sex

8. Male or female.

Pregnancy and Contraception

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (refer to Appendix 4, Section 10.4).

9. Female participants of childbearing potential must have a negative β-human chorionic gonadotropin (β-HCG) test at Screening and Baseline, be sterile, or be postmenopausal.
10. Female participants of childbearing potential whose male partners are potentially fertile (i.e., no vasectomy) must use highly effective birth control methods stable for at least 3 months prior to Screening, for the duration of the study and for 30 days after discontinuation of the study drug.
11. Male participants must be sterile, or if they are potentially fertile/reproductively competent (not surgically [e.g., vasectomy] or congenitally sterile) and their female partners are of childbearing potential, they must use, together with their female partners, effective birth control methods for the duration of the study and for 90 days after study drug discontinuation.

Concomitant Therapy

12. For participants taking allowed antipsychotic, antidepressant, or other psychotropic medication, the dosing of medication as listed in Appendix 6 (Section 10.6), must be stable for at least 4 weeks before the Baseline visit. and throughout the study (unless clinically necessary to change).
13. For participants taking allowed concomitant medications, dosing of medications must be stable for a t least 4 weeks prior to the Baseline visit (note: Amiodarone is not allowed within 6 weeks of Baseline visit).

Informed Consent

14. Capable of providing signed informed consent for the Main Study as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Inclusion Criteria – OLE

1. Completed the EoS visit of the Main Study on treatment without important protocol deviations impacting efficacy and safety assessments.
2. Capable and willing to provide signed informed consent for the OLE.
3. Must meet all criteria required to move forward with the OLE assessments.

5.3. Exclusion Criteria – Main Study

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Prolonged QTcF interval (defined as a QTcF interval of >450 ms for male and >470 ms for female) at Screening[8].
2. Clinically significant heart disease within 12 weeks before randomization, defined as follows:
    a. Participants with clinically significant heart disease, a clinically significant history of arrhythmia, symptomatic or uncontrolled atrial fibrillation despite treatment, or confirmed ventricular tachycardia, or presence of left bundle branch block.
    b. Participants with a known history of congenital long QT syndrome or a first degree relative with this condition.
    c. Clinically significant bradycardia, sick sinus syndrome, complete atrioventricular block, congestive heart failure, polymorphic ventricular tachycardia, clinically relevant hypocalcemia, hypokalemia or hypomagnesemia.

2. History of epilepsy or seizures within the last 5 years.
3. Serious medical illness includes, but not limited to, uncontrolled hypertension; respiratory disease, including severe forms of asthma; severe hepatic disease (confirmed Hepatitis B virus [HBV], Hepatitis C virus [HCV]; confirmed human immunodeficiency

[8] If there is evidence of a prolonged QTcF interval at screening from the initial (single) administration, then the ECG will be repeated twice, and the mean of the 3 screening administrations will be used to determine whether or not the participant is suitable for inclusion in the study.

virus [HIV]); renal disease; acquired immune deficiency syndrome; and unstable psychiatric or other neurologic disorders) and metastatic cancer.
For serious kidney and liver and liver illnesses see also exclusion criterion 12 (laboratory test abnormalities).

4. Known intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage.
5. Female participants who are pregnant, planning to become pregnant or breastfeeding.

Prior/Concomitant Prohibited Therapy

6. Medications that prolong QT interval, taken within 4 weeks of the Baseline visit (note, Amiodarone is not allowed within 6 weeks of the Baseline visit) or at any timepoint during the study, including non-allowed antipsychotic medications, tricyclic antidepressants, and/or Class I antiarrhythmics as listed in Appendix 7 (Section 10.7).
7. Use of pridopidine within 12 months before the Baseline visit.
8. Treatment with any investigational product within 6 weeks or 5 half-lives (whichever is longer) before the Screening visit or a plan to participate in another clinical study that assesses any investigational product during the study.
9. Gene therapy at any time.
10. Prior participation in studies with tominersen at any time.

Diagnostic Assessments

11. Laboratory values that fall outside of the central laboratory's reference range at Screening and are considered clinically significantly abnormal by the Investigator and affect the participant's suitability to participate in the study or put the participant at risk if he/she enters the study in the Investigator's opinion[9].
12. Have any of the following laboratory test abnormalities at Screening:
    a. CrCl <30 mL/min at Screening, calculated using the Cockcroft-Gault equation: (140–age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL)[10]
    b. Aspartate aminotransferase (AST) ≥2.5 × upper limit of normal (ULN)
    c. Alanine aminotransferase (ALT) ≥2.5 × ULN
    d. Gamma-glutamyl transferase (GGT) ≥3.0 × ULN
    e. Total bilirubin >1.5 mg/dL, except participants with unconjugated hyperbilirubinemia without other liver function derangements or other explanations for the elevated bilirubin (consistent with diagnosis of Gilbert's syndrome)

Other Exclusions

13. Alcohol and/or substance use disorder within the 6 months prior to Screening, as defined by the Diagnostic and Statistical Manual–Fifth Edition (DSM-5) Text Revision criteria for substance use.

[9] Repeat testing is allowed (up to a maximum of 3 tests) if required to establish whether values are within the normal range or clinically significantly abnormal.
[10] It is allowed to repeat the test once, if clinically appropriate.

14. Active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the C-SSRS if the ideation occurred within 1 year of Screening, or participants who answered "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior), if the attempt or acts were performed within 1 year of Screening, or participants who, in the opinion of the Investigator, present a serious risk of suicide.
15. Known allergy to any ingredient of the study drug (pridopidine, silicified microcrystalline cellulose, or magnesium stearate).
16. Vulnerable participant (e.g., people kept in detention), or participant unfit to participate in a clinical study due to living circumstances (e.g., without sufficient family or social support, stable residence, sustainable financial and general healthcare and resources).
17. An employee or a family member of an employee of the Sponsor, Investigator or Investigator study site, or otherwise dependent on the Sponsor, the Investigator or the Investigator study site.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria not met, and any serious adverse event (SAE).

Potential candidates who do not meet the criteria for participation in this study (screen failure) may be rescreened only once.

Screening assessments may be repeated during the screening period if approved and at the discretion of the study Medical Monitor (or designee). After the screening period, all screening assessments must be repeated except for Cytosine Adenine Guanine (CAG) repeat (providing the results are available from a prior screening period).

6. STUDY DRUG

The study drug is defined as investigational intervention(s) and intended to be administered to a study participant according to the study protocol.

6.1. Study Drug(s) Administered

ARM Name	**Active**	**Control**
Study Part	Main Study and OLE	Main Study only
Study Drug Name (INN)	Pridopidine	Placebo
Type	Drug (small molecule)	-
Dose Formulation	Hard gelatin capsules	Hard gelatin capsules
Unit Dose Strength(s)	45 mg	NA
Dosage Level(s) **Titration period** **Main full-dose Treatment period**	 45 mg capsule QD (morning dose) for 2 weeks 45 mg capsule bid (1 capsule in the morning and 1 capsule in the afternoon, 7 to 10 hours after morning dose); total daily dose of 90 mg	 Placebo capsule QD (morning dose) for 2 weeks Placebo capsule bid (1 capsule in the morning and 1 capsule in the afternoon, 7 to 10 hours after morning dose)
Route of Administration	Oral	Oral
Use	Experimental	Placebo-comparator
Sourcing	Pridopidine drug product, manufactured by Teva Pharmaceutical Industries, Ltd or by Apotek Production & Laboratories AB (APL) or Patheon, by Thermo Fisher Scientific and provided centrally by the Sponsor or subsidiary, or designee	Placebo, manufactured by Teva Pharmaceutical Industries, Ltd or by Apotek Production & Laboratories AB (APL) and provided centrally by the Sponsor or subsidiary, or designee
Packaging and Labeling	Study drug will be provided in high-density polyethylene bottle with a child-resistant cap, labeled as required per country requirement. The secondary packaging and labeling of the study drug will be performed by Fisher Clinical Services. All packaging and labeling operations for the study drug will be performed according to current Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.	
Prior Code Name	PL101 (formerly TV7820, ACR16 and ASP2314)	-

6.2. Handling Missed Doses

If a participant misses the morning dose, he/she can still take the missed morning dose as long as there is a minimum of 7 hours before the planned afternoon dose.

If there are less than 7 hours until the planned afternoon dose, the participant should skip the morning dose and administer only the afternoon dose.

If a participant misses the afternoon dose, he/she can take that dose until 7:00 pm.

After 7:00 pm the participant should skip the dose and continue the next day with the planned morning dose.

6.3. Preparation/Handling/Storage/Accountability

- Capsules will be swallowed whole with water. The study drug can be taken irrespective of meals.
- The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all the study drug received and that any discrepancies are reported and resolved before the use of the study drug.
- Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled (15 to 25 ºC), and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Study drug will be dispensed at the study visits summarized in SoA (Table 2 – Main Study, and Table 3 – OLE). Returned study drug (which was previously dispensed) should not be re-dispensed to participants.
- Further guidance and information for the final disposition of unused study drugs are provided in the Study Reference Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally randomized on a 1:1 basis to receive either pridopidine or placebo using an Interactive Response Technology (IRT), based upon the stratification variables of whether they are HD1 or HD2 and whether they are taking neuroleptics or not.

All participants, site staff, Sponsor, CRO and vendors involved with the study will remain blinded to treatment assignments until the database is locked and the study unblinded. The CRO(s) creating the randomization assignments, implementing the IRT and drug packaging groups will follow their standard operating procedures to ensure no one, involved in the conduct of the study or review and analysis of data, is unblinded except as indicated below for emergency unblinding. Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's study drug assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's study drug assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blinding. The date and reason that the blinding was broken must be recorded in the source documentation and case report form, as applicable.

Appropriate personnel at the Sponsor or sponsor designee will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose of regulatory reporting. The Sponsor will submit SUSARs to regulatory agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

6.5. Study Drug Compliance

When participants self-administer study drug(s) at home, compliance with study drug will be assessed at each visit. Participants will be instructed to bring the used and unused study drug bottles at every site visit. Compliance will be assessed by counting returned unused capsules during the site visits and documented in the source documents and electronic case report form (eCRF). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Compliance for each clinic visit and overall for the Main Study period and for the OLE period will be calculated using the following formulation:

> Compliance (%) = [Total number of administered doses/Total number of scheduled doses] x 100

The total number of scheduled doses will be calculated based on the extent (days) of exposure of each participant. A range between 80% to 120% will be taken as reference limits for a satisfactory level of compliance.

A record of the number of pridopidine capsules dispensed to and taken by each participant must be maintained and reconciled with study drug and compliance records. Study drug start and stop dates, including dates for study drug delays and/or dose reductions, will also be recorded in the eCRF.

6.6. Dosing Regimen and Modifications

All participants receiving the study drug are intended to receive the same fixed-dose regimen, in terms of dose and daily (bid) frequency, according to the study schedule.

After the Titration period, participants who are unable to tolerate bid schedule will be allowed to stay in the study at the lower study drug dose QD schedule for 1 week. After 1 week of study drug at QD schedule, the dose will be increased to bid dose schedule. If participants cannot tolerate the second increase to bid dose schedule, they will be discontinued from treatment with the study drug (refer to Section 7.2).

6.7. Concomitant Therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The study Medical Monitor (or designee) should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1. Permitted Medication

For participants taking allowed antipsychotic, antidepressant, antiarrhythmic, or other medication, the dosing of medication must be stable for at least 4 weeks before the Baseline visit and must be kept constant during the study (unless clinically indicated to change the dose). Please refer to Appendix 6, Section 10.6 for the list of permitted medications.

6.7.2. Prohibited Medication

Medications specifically prohibited in the exclusion criteria are not allowed during the study. If there is a clinical indication for any medication specifically prohibited during the study, discontinuation from the investigational product may be required. The Investigator should discuss any questions regarding this with the study Medical Monitor (or designee), prior, if possible, to the administration of prohibited medications and treatments. The final decision on any supportive therapy rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on investigational product requires the mutual agreement of the Investigator and the study Medical Monitor (or designee).

Please refer to Appendix 7, Section 10.7 for a summary of prohibited medications and substitution alternatives (note, the list of medications in Appendix 7 is not exhaustive). Any investigational agent, other than study drug, is also prohibited.

Caution should be exercised with medications that are mainly eliminated via the CYP2D6 -dependent pathway.

6.8. Treatment of Overdose

For this study, any dose of pridopidine greater than 180 mg within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the study Medical Monitor (or designee) immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities (at least 3 days).
2. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the study Medical Monitor (or designee) based on the clinical evaluation of the participant.

6.9. OLE

Eligible participants who complete the Main Study will have the option to enroll into an OLE study and receive pridopidine 45 mg orally bid (total daily dose of 90 mg) for 12 months after the last participant completes the double-blind Treatment period. OLE duration may be extended pending emerging data from the double-blind portion of the study.

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Individual Participant Stopping Rules from Study Drug

7.1.1. QT Stopping and Monitoring Rules

Refer to Appendix 8, Section 10.8 for ECG Monitoring Plan during the study.

QT Stopping Rules:

- QTcF >500 ms
- QTcF >480 ms **AND** ΔQTcF >60 ms from Baseline

If the local ECG reading results at the site match the above Stopping Rules, the participant will discontinue study drug until the central ECG reader's report is received. If the central reader does not report a QTcF interval that leads to discontinuation according to the above, then the participant can restart the study drug.

QT Monitoring Rule:

- QTcF >480 ms OR ΔQTcF >60 ms from Baseline

If the local ECG reading results at the site meet the Monitoring Rule, the participant can continue the study drug per protocol until the central ECG reader's report is received. If the central reader confirms meeting Monitoring Rule, the participant will stay on study drug (per protocol) and will return for a follow-up ECG after 3-14 days.

If after 3 days QTcF change is confirmed (meets Monitoring Rule) then the participant will be discontinued from study drug.

7.1.2. Creatinine Clearance Stopping Rules

Participants with CrCl <30 mL/min, calculated using the Cockcroft-Gault equation [(140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/dL)], at any timepoint after the Baseline visit 2 will be requested to return to the clinic for an unscheduled visit 1 week later, to repeat the CrCl test one more time for confirmation. If the repeated CrCl value is confirmed to be <30 mL/min, the participant will be discontinued from the study drug.

7.1.3. Psychiatric Stopping Rules

Participants with C-SSRS suicidal ideation ≥4 or PBA-s suicidal ideation >3 will be discontinued from treatment with study drug.

7.1.4. Seizures

Participants will discontinue study drug if they experience a seizure or convulsions.

7.1.5. Other Excluded Conditions during Study

Participants will discontinue study drug in case of occurrence of the following exclusion criteria after initiation of treatment:

- Symptomatic or uncontrolled atrial fibrillation, confirmed ventricular tachycardia, presence of left bundle branch block

- Intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage
- Alcohol and/or substance use disorder per DSM-5

7.1.6. Pregnancy

A participant must permanently discontinue the investigational product if she becomes pregnant. See Appendix 4 (Section 10.4.3) and Section 8.3.5 for additional details.

7.2. Discontinuation of Study Drug

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study drug. A participant may discontinue study drug for reasons including but not limited to:

- AE
- Death
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant
- Loss of capability to consent

The reason for participant discontinuation from the study drug will be recorded in the eCRF.

Participants who are **discontinued from study drug** during the Main Study will be encouraged to continue their participation in the study and perform all the scheduled visits and assessments, while off study drug. If participants are unable/unwilling to attend in-clinic visits, these visits can be replaced with virtual phone visits except for the following: Main Study Week 65, Week 78/EoS and ET visits. If a clinic visit is replaced by a virtual visit at Week 4, Week 26, Week 39, and Week 52, the UHDRS-TFC, clinical laboratories, and vital signs should not be assessed (refer to Appendix 10, Section 10.10). They will continue to be closely monitored by the Investigator and will be referred for psychiatric evaluation per the Investigator's medical judgment. Participants who are discontinued from study drug during the OLE will be withdrawn from the study and will be requested to return to an EoS visit.

See the SoA (Table 2 – Main Study, and Table 3 – OLE) for data to be collected at the time of study drug discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be discontinued by the Investigator. Participants may be withdrawn from the study for any of the following reasons:

- Death
- Withdrawal by participant
- Lost to follow-up
- Study terminated by Sponsor

The reason for participant withdrawal from the study will be recorded on the eCRF. At the time of withdrawal, ET visit procedures outlined in the SoA (Table 2 – Main Study, and Table 3 – OLE) should be completed, if possible.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected, based on local regulations, before such a withdrawal of consent. Participants withdrawing consent may request destruction of any samples taken and not tested, and the Investigator must document this request and proof of destruction in the site study records.

If a participant withdraws from the study, he/she may request the destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to engage for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit (for exceptions refer to Appendix 10 in Section 10.10):

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 TCs and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1 (Section 10.1.8).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 2 – Main Study, and Table 3 – OLE). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the study Medical Monitor (or designee) immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the relevant SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 2 – Main Study, and Table 3 – OLE).

8.1. Efficacy Assessments

Planned timepoints for efficacy assessments are provided in the SoA (Table 2 – Main Study, and Table 3 – OLE). Some efficacy measures can be done by remote assessments, if required. Study personnel will be trained to implement these measures remotely by virtual visit (via telephone): UHDRS-TFC, PBA-s, and CGI-C. Completion of the applicable eCRF pages should be performed at each visit.

All effort should be made to ensure that the same rater conducts a given rating scale for a given participant at all study visits, including virtual visits, to ensure consistency across the study.

8.1.1. United Huntington Disease Rating Scale – Total Functional Capacity (UHDRS-TFC)

The UHDRS-TFC is the standard and well-accepted clinical scale for staging and tracking the progression of HD using functional capacity (Shoulson, 1979; Marder, 2000). Scores range from 0 to 13, with 13 as the least affected and 0 as complete incapacity. The scale assesses the participant's capacity to maintain their domestic chores, activities of daily living, finances, care level (home, chronic care, skilled nursing required) and occupation. As described below, the scale is designed to detect changes in the early stages of HD (HD1 and HD2), and it has an obvious floor effect in advanced HD.

Functional capacity declines inexorably throughout the course of the disease, but the steepest rate of decline occurs in the earlier stages of HD manifestation, corresponding to TFC scores of 7 to 13, or HD Stages 1 and 2. Functional decline, as measured by TFC, correlates with advancing pathology (as assessed by computerized tomography and more recently, with magnetic resonance volumes in TRACK-HD) (Tabrizi, 2012). Natural history studies demonstrate that TFC decline parallels the progressive disability in other measures, including motor, cognitive, neuropsychiatric, and functional (Tabrizi, 2012; Dorsey, 2013).

As participants advance beyond Stage 2 into Stage 3, the annual rate of functional decline in TFC lessens, consistent with the known floor effect of this widely used HD assessment tool. Observational studies demonstrate an annual decline of approximately 0.8 to 1.2 units per year for participants with TFC scores 7 to 13 (Stages 1 and 2), compared to only 0.2 to 0.3 units per year for participants with TFC scores of 3 to 6 (Stage 3), and less than 0.1 units per year for participants with a TFC score under 3 (Stages 4 and 5) (Marder, 2000).

8.1.2. United Huntington Disease Rating Scale – Total Motor Score (UHDRS-TMS)

The UHDRS comprises a broad assessment of features associated with HD. It is a research tool which has been developed to provide a uniform assessment of the clinical features and course of HD (HSG, 1996).

The UHDRS-TMS is the standard and well-accepted clinical tool for tracking the progression of motor symptoms in patients with HD (HSG, 1996). 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 UHDRS-TMS is the sum of 31 individual motor ratings from the 15 items of the UHDRS, with each assessment rated on a 5-point scale from 0 (normal) to 4 (maximally abnormal). Higher scores indicate more severe motor impairment.

8.1.3. Quantitative Motor (Q-Motor)

8.1.4. Clinical Global Impression

8.1.4.1. Modified Clinical Global Impression of Severity (modified CGI-S)

The Clinical Global Impression of Severity (CGI-S) is a modified 7-point scale that requires the clinician to rate the overall severity of the participant's HD symptoms at the time of assessment, relative to the clinician's past experience with participants who have the same diagnosis. Considering total clinical experience, a participant is assessed on the severity of illness at the time of rating (Table 6).

Table 6: Modified CGI-S Score

Description	Score
Normal, not at all ill	1
Borderline ill	2
Mildly ill	3
Moderately ill	4
Markedly ill	5
Severely ill	6
Extremely ill	7

8.1.4.2. Clinical Global Impression - Change (CGI-C)

Global improvement will also be rated by the Investigator or designee separately using the CGI-C.

CGI-C Score:

0 = Not assessed

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

8.1.5. Exploratory Assessments

8.1.5.1. Stroop Word Reading (SWR)

The SWR is a neuropsychological test commonly used to measure the participant's attention and mental flexibility. It takes advantage of the Stroop effect to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second, conflicting stimulus attribute (Stroop, 1935; Scarpina, 2017). The words in the Stroop Word Reading are in Black print. The participants read the name of the colors ("red" "green" "blue") that appear in black ink/print ("participants are required to read names of colors (henceforth referred to as color-words) printed in black ink"). The participant's accuracy and speed at the SWR can be recorded and used to track the progression of cognitive deterioration. Scores reflect the number of correct responses in 45 seconds. Higher scores indicate better performance.

8.1.5.2. Symbol Digit Modalities Test (SDMT)

The SDMT is a paper-and-pencil test of psychomotor speed and working memory. Participants view a 'key' at the top of the page containing symbols paired with numbers. The remainder of the page displays rows of symbols, and the participant has 90 seconds to write the corresponding number that matches each symbol.

8.1.5.3. Problem Behaviors Assessment – Short Form (including apathy sub-item)

Because of the prominence of psychiatric symptoms in HD, it is recommended that the PBA-s form be used in all HD studies with any need for behavioral assessment as a comprehensive screen for the most common psychiatric symptoms in HD (Craufurd, 2001; Kingma, 2008). The PBA-s also includes questions concerning suicidal behavior, a particular concern in HD. The PBA-s is based on the same set of core behavioral symptoms as the UHDRS behavioral questions, which were used previously as the global psychiatric measure in most HD studies. The PBA-s has more detailed questions and more specific guidance on administration and scoring.

The PBA-s is a brief semi-structured interview covering the most common behavioral and psychiatric manifestations of HD. The interview is not restricted to a single construct, but rather covers several broad symptom domains relevant to HD, comprising 11 items: low mood, suicidal ideation, anxiety, irritability, anger/aggressive behavior, loss of motivation, perseverative thinking or behavior, obsessive-compulsive behaviors, paranoid thinking, hallucinations, behavior suggestive of disorientation. Each symptom is rated for severity on a 5-point scale according to detailed scoring criteria which roughly correspond to the following: 0 = “not at all”; 1 = trivial; 2 = mild; 3 = moderate (disrupting everyday activities) and 4 = severe or intolerable. Each symptom is also scored for frequency on a 5-point scale as follows: 0 = symptom absent; 1= less than once weekly; 2 = at least once a week; 3 = most days (up to and including some part of each day); and 4 = all day, every day. Severity and frequency scores are multiplied to produce an overall ‘PBA score’ for each symptom.

If the participant has a positive score 1 and 2 on the suicidal ideation item or depressed mood item of the PBA-s, the participant will be monitored more closely and treated according to the Investigator's medical judgment. Participants’ PBA-s suicidality scores 1 and 2 may be handled by study Investigator/neurologist with a consultancy with psychiatrists, where necessary, per Investigator’s medical judgment.

Appropriate clinical care is required for AE/SAE of suicidal ideation/suicidal attempt or a significant increase in the suicidality scale from Baseline (e.g., 2-point increase or higher) or C-SSRS or PBA-s suicidality score 3 and above. All participants with PBA-s suicidal ideation item score >3 will be discontinued from treatment with study drug. Participants who are discontinued from treatment may continue their participation in the study and perform the scheduled visits and assessments, while off study drug. They will continue to be closely monitored by the Investigator and will be referred for psychiatric evaluation per the Investigator's medical judgment.

Assessment can be done by virtual visits or phone calls (via telephone), if required.

8.1.5.4. The Huntington Disease Quality of Life Questionnaire (HDQoL)

The HD-QoL is a standardized instrument for measuring health-related QoL (Hocaoglu, 2012). It is a validated disease-specific measure designed for HD, and can provide a summary score of overall health-related QoL, as well as scores on several discrete scales. HD-QoL is for people who are living with HD; this includes people who are at risk for HD, people who have tested positive for the HTT but do not have symptoms, and also for people at early to late stages of disease. HD-QoL can be used across the full spectrum of HD.

HD-QoL will be completed by the participant.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 2 – Main Study, and Table 3 – OLE). Safety evaluations can be done by remote assessments, if required. Study personnel will be trained to perform remote safety assessments of C-SSRS, AE, and concomitant medication inquiry by virtual visits (via telephone), and safety TCs. Home visits by health care professionals for safety assessment may be provided if in-clinic visits are not possible, including safety laboratories, vital signs, and ECG administration. Study procedures should be completed within the windows provided in the corresponding SoA and as specified in this section.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Vital signs will be measured in a supine position after 5 minutes rest in a quiet setting without distractions (e.g., television, cell phones) and will include body temperature, systolic and diastolic blood pressure, and heart rate. Thereafter, blood pressure should be measured again after standing for 2 minutes.
- Vital signs will be measured prior to any blood draw that occurs at the same timepoint.
- Home health care professionals may be used to measure vital signs for safety if clinic visits will not be possible. Note, this will only occur if the nursing service is activated during COVID-19 and the participant is on treatment.

8.2.3. Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (Table 2 – Main Study, and Table 3 – OLE) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Home ECG administration may be carried out by health care professionals, if in-clinic visits are not possible.
- In case QTcF prolongation is observed, monitoring procedures and criteria for discontinuation of individual participants from treatment with the study drug are outlined in Section 7.1 and Appendix 8 (Section 10.8).

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Table 2 – Main Study, and Table 3 – OLE) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or study Medical Monitor (or designee).
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Medical Monitor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments, performed at the institution's local laboratory, require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.
- Home visits by health care professionals may be provided for safety blood draws if clinic visits will not be possible. Note, this will only occur if the nursing service is activated during COVID-19 and the participant is on treatment.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

The study population should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing study drug in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

Baseline assessment of suicidal ideation and behavior and/or treatment-emergent suicidal ideation and behavior will be assessed during the study using the PBA-s (see Section 8.1.4.2) and the C-SSRS.

The C-SSRS will be used to rate the participant's degree of suicidal ideation on a scale ranging from "no suicidal ideation" to "active suicidal ideation with specific plan and intent" (Posner, 2011). The C-SSRS Baseline version will be completed at Screening (Visit

0), while the C-SSRS Since Last Visit version will be completed at all other visits as specified in the SoA. Participants with active suicidal ideation, as measured by a score of 4 or 5 on the C-SSRS at the Screening visit, will not be eligible for the study.

Assessment should be done through on-site clinic visits, virtual visits (via telephone), and safety TCs. Rater consistency should be maintained in all visits, including virtual visits. As much as possible, there should be one rater for a participant throughout the study in-clinic, safety TCs, and virtual visits.

In any event of suspected active suicidality (e.g., active suicidal ideation or intent, significant suicidal behavior) or clinical findings suggesting that the participant is dangerous to himself or herself, the participant should be referred for **immediate** psychiatric evaluation.

Participants with a positive C-SSRS suicidal ideation score of 1 and 2 will be monitored more closely and treated according to the Investigator's medical judgment. Participants with C-SSRS or PBA-s suicidality scores 1 and 2 may be handled by study Investigator/ neurologist with a consultancy with psychiatrists, where necessary per Investigator's medical judgment.

8.3. Adverse Events and Serious Adverse Events

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, etc.).

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 for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue the study drug (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AE and SAEs will be collected from the signing of the ICF until the last Follow-up visit at the timepoints specified in the SoA (Table 2 – Main Study, and Table 3 – OLE). Assessment should be done through on-site clinic visits, safety TCs, and virtual visits (via telephone).

An event that emerged during or after treatment or worsened relative to the pretreatment state will be recorded as a treatment-emergent adverse event (TEAE).

All SAEs will be recorded and reported to the Sponsor or designee immediately upon any site study staff becoming aware and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including death, at any time after a participant has been discharged from the hospital, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- For all studies of therapeutic agents, Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected as outlined in Appendix 4 (Section 10.4).
- If pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Death Events

Timelines for reporting of death events are identical to the requirements for SAE reporting. (Appendix 3, Section 10.3).

8.4. Pharmacokinetics

Blood samples will be collected at the timepoints detailed in the SoA (Table 2 – Main Study) for measurements of plasma concentration of pridopidine and its main metabolite (TV45065).

In case of an SAE, the aim will be to collect an additional PK sample at the closest time possible to the event. Instructions for the collection and handling of the plasma samples will be provided in the Laboratory Manual. The dates and times of pridopidine administration and the date and timepoint (24-hour clock time) of each pharmacokinetic sample will be recorded both on the source documentation and the eCRF.

Samples will be analyzed for the concentration of pridopidine and its main metabolite TV45065 using an appropriate validated method. Incurred sample reanalysis may be performed.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Pharmacodynamic/Biomarkers

Potential exploratory assessments include at least plasma NfL protein.

For biomarkers, blood will be drawn and processed at the timepoints detailed in the SoA (Table 2 – Main Study and Table 3 – OLE).

Details on specimen collection, processing, and handling requirements are provided in the Laboratory Manual.

8.6. Pharmacogenetics

Blood sample will be collected at Screening to examine CAG repeats in the HTT, if historical laboratory quantified results or diagnostic test are not available.

Blood sample for remnant deoxyribonucleic acid (DNA) will also be collected at Screening and saved for future exploratory analysis to examine association of genetic variation with emergent safety or efficacy findings of pridopidine.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

9. STATISTICAL CONSIDERATIONS

This protocol section summarizes the planned statistical analyses. A separate SAP will be finalized prior to database lock and unblinding the data. The SAP will serve as a complement to the study protocol and will supersede the protocol in case of differences. In case of major differences between the study protocol and SAP (e.g., changes in the analysis related to the primary endpoint), a protocol amendment will be considered.

9.1. Statistical Hypotheses

The **null hypothesis** represents no difference between the therapeutic efficacy response in the active treatment group compared to the placebo group:

$H_0: \mu_A = \mu_P$

$H_A: \mu_A \neq \mu_P$

Where μ_A is the mean change from Baseline to Week 65 in UHDRS-TFC for participants randomized to pridopidine (Active) and μ_P is the mean change from Baseline to Week 65 in UHDRS-TFC for participants randomized to the placebo group.

Under the alternative hypothesis, there exists a difference between the therapeutic efficacy response in the pridopidine (Active) group compared to the placebo group.

Testing of the statistical hypothesis will be conducted hierarchically for the primary and secondary endpoints as indicated in Sections 9.4.2 and 9.4.3. Each test will be at a type I error level ≤ 0.05, two-sided to preserve the overall Type I error. As soon as a test yields a p-value >0.05 no further tests following it will be considered statistically significant.

9.2. Sample Size Determination

[redacted]

Under this assumption, a total sample size of 372 participants will provide 94% power using a two-tailed t-test at a significance level of 0.05. Assuming a dropout rate of 22.5%, a total of 480 participants needs to be randomized.

For analysis of UHDRS-TFC under assumption of Missing Not at Random (MNAR) with imputed values for all discontinued participants estimated based on the trajectory of placebo participants with available data, a treatment difference in change from Baseline for imputed values at Week 65 is anticipated to be 0.1 points. The overall difference would then be 0.565 (0.7*0.775+0.1*0.225) or 0.7 points for the 77.5% completers and 0.1 points for the 22.5 % participants who discontinue and have imputed data at Week 65. A difference of 0.565 points with SD of 1.9 with a sample size of 480 participants would provide 90% power (SAS V 9.4 PROC POWER).

9.3. Populations for Analyses

The ITT population is the main analysis population of primary endpoint for EMA region. The mITT population is the main analysis population for primary endpoint in non-EMA regions. For all other efficacy analyses, the mITT population is the main analysis population in both EMA

and non-EMA regions. The ITT and PP populations will also be used as sensitivity analyses to show robustness of results for select secondary endpoints.

9.3.1. Main Study

Population	Description
Intent-to-Treat (ITT) population	The ITT population will include all randomized participants. The participants will be grouped as randomized.
Modified Intent-to-Treat (mITT) population	The mITT set is a subset of the ITT population and will include all randomized participants who receive a dose of study drug and have valid TFC efficacy assessments both at the Baseline visit and at least one post-baseline in-clinic timepoint. The participants will be grouped as randomized.
Per Protocol Week 65 (W65PP) population	The per protocol Week 65 set is a subset of the mITT set and includes all participants who have a valid in-clinic UHDRS-TFC at Week 65, were on study drug with compliance > 80% during the study, and did not have any important protocol deviations impacting efficacy assessment. Per protocol variations will be defined prior to unblinding the data and participants subsequently grouped as treated. The per protocol set will be used for supplementary analysis of the primary and select secondary endpoints.
Per Protocol Week 78 (W78PP) population	The per protocol Week 78 set is a subset of the mITT set and includes all participants who have a valid in-clinic UHDRS-TFC at Week 78, were on study drug with compliance > 80% during the study, and did not have any important protocol deviations impacting efficacy assessment. Per protocol variations will be defined prior to unblinding the data and participants subsequently grouped as treated. The per protocol set will be used for supplementary analysis of the primary and select secondary endpoints.
Safety population	The safety set will include all participants receiving at least one dose of study drug. The participants will be grouped according to the treatment regimen actually received. The safety set will be used for safety analyses.
PK population	The PK population will include all randomized participants who received at least 1 dose of pridopidine and have at least 1 valid PK assessment. The

Population	Description
	participants will be grouped according to the treatment regimen actually received.

9.3.2. OLE

Population	Description
OLE mITT population	The OLE mITT population will include all participants who received at least 1 dose of pridopidine during the OLE period, and have at least 1 valid in-clinic UHDRS-TFC score during the OLE period.
OLE Safety population	The OLE safety population will include all participants who received at least one dose of pridopidine during the OLE period.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis will be performed using SAS software Version 9.4 or higher. Continuous variables will be summarized using the number of participants with available and missing data, the mean, the standard deviation, first quartile, median, third quartile, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. All collected data will be listed in data listings unless agreed to otherwise with regulatory agencies.

Unless otherwise specified, for all efficacy and safety analyses in Main Study (double-blind) Treatment Period, the Baseline will be defined as the last non-missing assessment prior to the first dose of study drug. All analyses of Main Study and OLE data will be fully described in the SAP.

9.4.2. Analysis of Primary Endpoint

The **primary endpoint** is the change from Baseline to Week 65 in the UHDRS-TFC score. Due to <2% missing in-clinic visits during COVID-19 pandemic and lack of validation of virtual UHDRS-TFC assessments, the analyses of primary endpoint and UHDRS-TFC-related secondary endpoints will include only in-clinic UHDRS-TFC assessments.

Based on the feedback from regulatory agencies, the primary analysis is specified separately for the EMA and non-EMA regions based on the primary estimands defined in Section 3.1.2.

For the EMA, the following is considered the primary analysis:

The primary endpoint will be compared between the treatment groups using the MMRM. Before conducting the MMRM analysis, missing data will be imputed using Multiple Imputation (MI)

methods under the assumption of MNAR. For this purpose, Copy-Reference imputation will be used, i.e., the trajectories of the participants are assumed to follow the placebo group after the discontinuation. The Copy-Reference procedure for imputing the missing data is summarized below.

- First, the ITT dataset will be used to generate monotone missing data. For participants with intermittent missing values, before performing MI, a monotone missingness pattern will be generated. After this, intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology, by repeating the MI procedure 100 times. This imputation step is based on the Missing at Random (MAR) assumption.
- After this, the remaining missing data will be imputed sequentially for each in-clinic visit (virtual visits are not included in the analysis) (first Week 26, followed by Week 39, etc.). Only data from the placebo group will be used for the imputation. Patients with the first missing value occurring at Week 26 will have their missing Week 26 value replaced by an imputed value from a regression model with treatment group, stratification variables (baseline HD stage and baseline neuroleptic use) and the baseline UHDRS-TFC value as explanatory variables. In the next step, participants with their Week 39 value missing will have their missing Week 39 value replaced by an imputed value from a regression model with treatment group, stratification variable (baseline HD stage and baseline neuroleptic use), region, baseline UHDRS-TFC value and the Week 26 value as explanatory variables. Similar procedure will be used to replace the missing values at the subsequent in-clinic visits and each regression model includes the data from all previous in-clinic visits as explanatory variables, in addition to the treatment group, stratification variables (baseline HD stage and baseline neuroleptic use), region and baseline UHDRS-TFC value.
- Finally, the imputed datasets generated with the approach described above do contain only non-missing values and are used as input in the model for the primary analysis of the primary endpoint. MMRMs (as described above) will thus be run on each of the 100 generated imputed datasets. The results from these analyses will be combined to derive an overall estimate of the treatment difference at Week 65.
- MMRM on observed data will be performed as a sensitivity analysis in addition to other sensitivity analyses under assumptions of MAR or MNAR.

For non-EMA regions, the following is considered the primary analysis:

The primary endpoint will be compared between the treatment groups using MMRM with observed cases in the mITT population. All scheduled post-Baseline UHDRS-TFC values from in-clinic visits obtained at Weeks 26, 39, 52, and 65 will be used as dependent variables in the MMRM. The variables used to stratify the randomization (baseline HD stage and baseline neuroleptic use), treatment group, region, visit and the interaction between the treatment group and visit will be included as fixed factors and the Baseline UHDRS-TFC value as a covariate in the model. The treatment difference at Week 65 will be estimated from the model using contrasts.

An unstructured covariance structure will be applied for MMRM. In case the model will not converge with the unstructured covariance structure, the heterogeneous autoregressive (1), heterogeneous compound symmetry or the heterogeneous Toeplitz structure, autoregressive (1)

or compound symmetry without heterogenous variances (1) will be used instead. The denominator degrees of freedom will be computed using the Kenward-Roger method.

The method of MI under different assumptions of MAR and MNAR will be used as sensitivity analyses.

Further sensitivity analyses, including sensitivity analyses assessing the impact of the COVID-19 pandemic on study data will be defined in the SAP.

9.4.3. Analyses of Secondary Endpoints

All secondary and exploratory efficacy analyses on endpoints evaluated as change from Baseline, for both EMA and non-EMA regions, will follow treatment policy strategy regardless of treatment discontinuation or death. Binary endpoints indicated for responder analyses will follow an estimand elaborated below for UHDRS-TFC response.

Multiplicity Adjusted Secondary Endpoints:

The key secondary efficacy variable is change from Baseline to Week 65 in cUHDRS and the main estimand is defined similarly to non-EMA-Estimand for primary endpoint as described in Section 3.1.2. Change from Baseline to Week 65 in cUHDRS will be analyzed using the MMRM in mITT population under treatment policy strategy, as described for the primary endpoint in Section 9.4.2. Other multiplicity adjusted secondary endpoints (UHDRS-TMS, Q-Motor [redacted] and SDMT), evaluated as change from Baseline to post-baseline visits, will also be analyzed similarly to cUHDRS.

The binary UHDRS-TFC response at Week 65 is defined as achieving improvement or no worsening in UHDRS-TFC score, i.e., change from Baseline to Week 65 ≥ 0 points. The hypothesis testing is based on the main estimand as follows:

- Treatment: Pridopidine 45 mg bid or placebo (on background of standard of care) that participants are randomized to
- Population: Early HD Participants (HD1 & HD2) defined through the study inclusion/exclusion criteria. The mITT population will be used in analyzing this estimand
- Variable: Improvement or no worsening (change from Baseline ≥ 0 point) at Week 65 in UHDRS-TFC (Defined as responders to treatment)
- Population Level Summary: Proportion of responders, defined as the proportion of participants achieving improvement or no worsening in UHDRS-TFC (change from Baseline ≥ 0 point) at Week 65
- ICEs and Strategies for Addressing ICEs:

  ICEs include treatment discontinuation and will be handled by combining composite strategy and hypothetical strategy as follows:

  - Composite strategy: Observed UHDRS-TFC values will be used to determine if a participant is a responder or not. For treatment discontinuation due to disease-progression-related death, or meeting Stopping Rules, the participant will be considered a non-responder.

Hypothetical strategy: For treatment discontinuation due to other reasons not included in composite strategy and no TFC data collected afterward, all values after ICEs will be imputed

under MAR as if the participants had continued receiving the study treatment. The MAR imputation model will include UHDRS-TFC as a continuous response variable as described in Section 9.4.2. The UHDRS-TFC response at Week 65 (change from Baseline in UHDRS-TFC ≥ 0) will then be derived using the imputed UHDRS-TFC score as well as the non-missing UHDRS-TFC scores.

The proportion of participants with improvement or no worsening based on CGI-C (assessed as ≥ 1 and ≤ 4), will be analyzed using a logistic regression in the mITT population, as described above for binary UHDRS-TFC response.

Non-Multiplicity Adjusted Secondary Efficacy Endpoints:

The continuous non-multiplicity adjusted secondary endpoints (change from Baseline to post-baseline visits in UHDRS-TMS, Q-Motor [redacted] and cUHDRS total score) will be analyzed similarly as described in non-EMA-Estimand for the primary endpoint.

Q-Motor endpoints [redacted]

The binary non-multiplicity adjusted secondary endpoints, evaluated as proportion of participants meeting a given threshold, will be analyzed similarly to UHDRS-TFC response. Different thresholds that are clinically meaningful may be used for the responder analyses.

Further details for secondary analyses will be included in the SAP.

9.4.4. Exploratory Endpoints

The exploratory endpoints will be analyzed with methods similar to the primary and secondary endpoints. Additional details will be provided in the SAP.

9.4.5. Safety Analyses

The safety analysis will be conducted on the safety dataset. The AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The TEAEs will be summarized by treatment group, system organ class and preferred term. Further summaries will be done by seriousness, severity and relationship to study drug.

Vital signs, ECG data and laboratory tests at Baseline at each post-baseline visit, and changes from Baseline to each of the post-baseline visits will be summarized with descriptive statistics. Shift tables for the laboratory tests based on a classification of values as low, normal, or high with respect to the reference range will be summarized.

For ECG data, absolute QTcF of > 450 ms, > 480 ms, and > 500 ms, changes from Baseline in QTcF > 30 ms and ≤ 60 ms, and changes in QTcF > 60 ms throughout the study will be summarized.

All other safety data will be summarized with descriptive statistics.

9.4.6. OLE Analyses

The final analyses of OLE data will be performed at the End of OLE when all participants complete the OLE EoS visit. Interim analyses may be performed as needed.

Proportion of participants with change of UHDRS-TFC ≥ -1 from Baseline by treatment group and the difference between treatment groups at each OLE visit will be provided along with a 2-sided 95% CIs using normal approximation and p-values from a logistic regression similar to that

described for TFC response. This analysis will be repeated using a threshold of 0 for proportion of participants with change of UHDRS-TFC from Baseline ≥ 0.

Summary statistics will be presented for UHDRS-TFC, cUHDRS, UHDRS-TMS, Q-Motor [redacted] and Q-Motor [redacted] by treatment group and visit during the OLE period. An MMRM analysis will be performed on change from Baseline in UHDRS-TFC through the entire study for patients switching from placebo in Main Study to pridopidine in OLE, with fixed effects of treatment at each period, visit, randomization stratification factors, interaction of treatment and visit within the period, and Baseline UHDRS-TFC. The covariance structure for the MMRM model will be used similarly as described in Section 9.4.2.

9.4.7. PK Analysis

Descriptive statistics of plasma concentrations of pridopidine and TV45065 as continuous variables additionally with geometric mean and coefficient of variation will be presented by treatment groups, scheduled visit and timepoint.

An exposure-response correlation between pridopidine plasma concentrations vs change from Baseline in efficacy (e.g., UHDRS-TFC) and safety measures (including QTcF), and additional covariate analysis may be performed and reported separately as applicable.

9.4.8. Biomarker (NfL) Analysis

Descriptive statistics of plasma NfL levels and log2 transformed NfL levels will be presented by treatment group and visit.

An MMRM will be used to analyze treatment and covariate effects on the change from Baseline in log2 transformed NfL levels.

The impact of log2 transformed Baseline NfL on change from Baseline to post-baseline visits in UHDRS-TFC, cUHDRS, Q-Motor [redacted] UHDRS-TMS, SDMT, and SWR accounting for treatment effect and other covariates will also be analyzed using an MMRM.

Furthermore, the change from Baseline to post-baseline visits in above efficacy endpoints in response to change from Baseline in log2 transformed NfL levels will be analyzed using an MMRM model accounting for treatment effects and other covariates.

The proportion of participants with change from Baseline ≤ 0 in log2 NfL levels to post-baseline visits will be presented by treatment group with 95% CI with normal approximation. Other thresholds to dichotomize log2 NfL change will also be explored, and the resulting proportions by treatment group and the difference between treatment groups in the proportions will be presented along with 95% CI.

9.5. Interim Analysis

No interim analyses are planned for this study.

9.6. Safety Monitoring Committee

During the double-blind treatment period of the Main Study, an independent, unblinded Safety Monitoring Committee will assess the safety and if requested efficacy.

It will be composed of an independent neurologist, cardiologist, and a biostatistician.

The conduct and specific details regarding the committee will be outlined in the Safety Monitoring Committee Charter which will be finalized prior to the first participant being randomized.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit a complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21

CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- In case of doubt if a participant is able to sign the ICF, it should be confirmed and documented by an independent specialist that the affected person is in the position to understand the nature, significance, and scope of the interventions in the clinical trial and to express their wishes accordingly.
- A copy of the ICF(s) must be provided to the participant.
- If a participant withdraws consent for the study, no additional data will be collected, and the data processed until the withdrawal of the consent will be used in accordance with the applicable data protection laws.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.
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 participant the objectives of the exploratory research. Participants 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 participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. Any personal data processing and transfer from European Economic Area (EEA) to a non-EEA country will comply with Chapter V General Data Protection Regulation in the EU.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

- A CSR will be developed by the Sponsor at the completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.
- Sponsor will register the study and post-study results regardless of the outcome on a publicly accessible website (e.g., *clinicaltrials.gov*) in accordance with the applicable laws and regulations.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the participant's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for the recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for reasons related to safety and/or tolerability issues, inability to recruit and retain the target population, inability to perform the study due to pandemic related circumstances, decision to discontinue development of the product or insolvency of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory (unless otherwise indicated).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report in participant's source records.

Table 7: Protocol-Required Safety Laboratory Assessments

Laboratory	Parameters – Main Study	Parameters - OLE
Serum Chemistry	Calcium, phosphorus, sodium, potassium, chloride, magnesium, bicarbonate, creatinine, blood urea nitrogen (BUN), creatine kinase, uric acid, glucose, cholesterol, triglycerides, lactate dehydrogenase (LDH), alkaline phosphatase, ALT, AST, indirect bilirubin, total bilirubin and direct bilirubin, GGT, globulin, total protein, albumin	Calcium, phosphorus, sodium, potassium, chloride, magnesium, bicarbonate, creatinine, BUN, glucose, LDH, alkaline phosphatase, ALT, AST, indirect bilirubin, total bilirubin, direct bilirubin, GGT, total protein, albumin
Hematology	Hemoglobin, hematocrit, RBC, MCH, MCHC, MCV, RDW, RBC morphology, platelet, WBC (neutrophils, lymphocytes, eosinophils, monocytes, basophil)	Hemoglobin, hematocrit, RBC, MCH, MCHC, MCV, RDW, RBC morphology, platelet, WBC (neutrophils, lymphocytes, eosinophils, monocytes, basophil)
Urinalysis	Protein, glucose, ketones, bilirubin, urobilinogen, hemoglobin, pH, specific gravity, appearance, color, leukocyte esterase, nitrite, microscopic tests (bacteria, erythrocytes, leucocytes, crystals, casts, epithelial cells, yeast, oval fat bodies, fat, mucous, sperm, trichomonas)	None
Other laboratory assessments	β-HCG pregnancy test (as needed for women of childbearing potential) Urine pregnancy	β-HCG pregnancy test (as needed for women of childbearing potential) Urine pregnancy

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study drug, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to the progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations (Medically important):

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, 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.

10.3.3. Definition of Suspected and Unsuspected Adverse Reaction

Suspected adverse reactions are defined as:

- Any AE for which there is a reasonable possibility that the investigational product caused the AE. For the purposes of Sponsor regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by the investigational product(s).

Unexpected adverse events are defined as:

- AE which is not listed in the IB or approved label of the investigational product or is not listed at the specificity or severity that has been observed.

10.3.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF within 24 hours of Investigator/site awareness of the event.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
  - ***Related*** – The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.
  - ***Not Related*** – There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, 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 SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, ***it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.***
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available and within 24 hours of Investigator/site awareness.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the study Medical Monitor (or designee) by telephone.

- Contacts for SAE reporting are:
  - When the electronic system is not available please submit paper SAE forms to TFS Drug Safety at: **safety.tfs@tfscro.com**

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal, unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

- 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 hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. FSH may be repeated twice, separated by at least a month if the result of the first instance is more than 30 IU/L.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Male Participants

Male participants are eligible to participate if they agree to the following from informed consent through 90 days after the last dose of study drug:

- Refrain from donating sperm, except for the purpose of fertility analysis as part of this protocol

  PLUS, either**:**

  – Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR

  – Must agree to use contraception/barrier (a male condom)

Female Participants

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

  – Is not a WOCBP

  OR

  – Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency (see table below), from consent through 30 days after the last dose of study drug, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relation to the first dose of study drug.

  – A WOCBP must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of β-HCG] at Screening and a negative urine pregnancy test before the first administration of study drug. During the Treatment period, urine pregnancy tests will be performed monthly. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required, and results must be negative.

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

Highly Effective Methods[a] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[b]
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[a] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the investigational product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

[a] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive pridopidine.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug or be withdrawn from the study.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study drug, susceptibility to, and severity and progression of the disease. Variable response to study drug may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to Pridopidine or HD and related diseases. They may also be used to develop tests/assays including diagnostic tests related to study drug and/or interventions of this drug class and HD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- DNA samples will be analyzed for CAG repeat. Additional analysis related to pridopidine response or HD may be conducted if it is hypothesized that this may help further understand the clinical data. The Sponsor will adhere to the National legislation, including on genetic counselling and processing of health and genetic data.
- Remnant DNA will be saved for future exploratory analysis to examine the association of genetic variation with emergent safety or efficacy findings of pridopidine.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study drug or study drugs of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on study drug continues but no longer than 8 years or other period as per local requirements.

10.6. Appendix 6: Permitted Medications

Note: The list of medications below is not exhaustive; please contact the study Medical Monitor (or designee) for any questions.

Medication Class	Permitted Medications	Comments
Antipsychotic	Olanzapine, fluphenazine, clotiapine, quetiapine, thiothixene, acetophenazine, trifluprom azine, loxapine, tiapride, chlorprothixene, bromperidol, tiapride and amilsupride. Aripiprazole, risperidone and perphenazine	Permitted, at no more than usual recommended doses in the approved labeling. If, according to Investigator judgment, a change of usage or dosage of antipsychotic medication is required during the study, this should be recorded in the eCRF and discussed with the study Medical Monitor (or designee).
Antidepressants	SSRIs/SNRIs including fluvoxamine*, venlafaxine, paroxetine, duloxetine, sertraline, as well as omipramol (opipramol), moclobemide, tranylcypromine, buspirone, bupropion#, reboxetine and dibenzepin	*Fluvoxamine is permitted, at no more than usual recommended doses in the approved labeling. #Bupropion dose should not exceed total daily dose of 450 mg where the daily dose is administered 3 times daily (with each single dose not to exceed 150 mg, and the rate of incrementation of dose is very gradual) (Wellbutrin®, 2017).
Antiarrhythmic	Mexiletine and tocainide	Permitted, at no more than usual recommended doses in the approved labeling.
Management of Chorea	Tetrabenazine and deutetrabenazine	Permitted, at no more than usual recommended doses in the approved labeling.
Antiviral	COVID-19 Vaccines	Vaccination (including boosters) should preferably not occur within 1 week of a study visit to ensure possible side effects do not affect the assessments

Medication Class	Permitted Medications	Comments
Other	Baclofen, bupropion*, ciprofloxacin, cyclosporine, isoniazid, lindane, methylphenidate, metronidazole, penicillins, theophylline, amantadine, morphine, buprenorphine, diphenoxylate, alfentanil, fentanyl, remifentanil, meptazinol and pethidine	Only if no PK interactions are expected. *See comment above for bupropion

10.7. Appendix 7: Prohibited Medications and Substitution Alternatives

Note: The list of medications below is not exhaustive. Prohibited medications may include different salts, esters, ethers, isomers, complexes, or derivatives of the medications listed below. In addition, there may be medications which have the potential to prolong the QT interval which are not currently on the list and are not a derivative of a listed medication. In such instances, a decision to exclude such a medication will be taken following a discussion with the study Medical Monitor (or designee) who will provide the final decision as to whether to allow the medication.

Medication Class	**Excluded Medications Within 4 Weeks of the Baseline Visit** **(unless otherwise noted)**	**Substitution Alternatives** **(**dosing of alternative medications must have been stable for at least 4 weeks before the Baseline visit and must be kept constant during the study)
Antipsychotics	Haloperidol, mesoridazine, thioridazine, pimozide, chlorpromazine, sulpiride and levomepromazine	Olanzapine, fluphenazine, clotiapine, quetiapine, thiothixene, acetophenazine, trifluprom azine, loxapine, tiapride, chlorprothixene, bromperidol, tiapride and amilsupride. Aripiprazole, risperidone, and perphenazine are permitted, at no more than usual recommended doses in the approved labelling. If, according to Investigator judgment, a change of usage or dosage of antipsychotic medication is required during the study, this should be recorded in the eCRF and discussed with the study Medical Monitor (or designee).
Antidepressants	Citalopram >20 mg/day, escitalopram >10 mg/day and fluoxetine	Allowed and carefully monitored: amitriptyline, nortriptyline, imipramine, desipramine, doxepin, clomipramine, protriptyline, and amoxapine, the serotonin – norepinephrine reuptake inhibitors, and trazodone (allowed up to 100 mg/day). SSRIs/SNRIs including venlafaxine, paroxetine, duloxetine, sertraline, as well as omipramol (opipramol),

Medication Class	**Excluded Medications Within 4 Weeks of the Baseline Visit** **(unless otherwise noted)**	**Substitution Alternatives** **(**dosing of alternative medications must have been stable for at least 4 weeks before the Baseline visit and must be kept constant during the study)
		moclobemide, tranylcypromine, buspiron, reboxetine, and dibenzepin. Fluvoxamine is permitted, at no more than usual recommended doses in the approved labelling. Bupropion dose should not exceed total daily dose of 450 mg where the daily dose is administered 3 times daily (with each single dose not to exceed 150 mg, and the rate of incrementation of dose is very gradual) (Wellbutrin®, 2017).
Antiarrhythmics	Disopyramide, procainamide, flecainide, propafenone, amiodarone **(within 6 weeks of Baseline visit)**, dofetilide, ibutilide and sotalol	Mexiletine and tocainide At no more than usual recommended doses in the approved labelling.
Other	Astemizole, terfenadine, azithromycin, erythromycin, moxifloxacin, pentamidine, sparfloxacin, clarithromycin, chloroquine, hydroxychloroquine, halofantrine, bepridil, cisapride, domperidone, droperidol, levomethadyl, sevoflurane, anagrelide, budipine, fluconazole, levofloxacin, lidoflazine, ondansetron, probucol, terodiline and vandetanib	Allowed medications with lowering seizure thresholds but for which no PK interactions are expected are baclofen, bupropion, ciprofloxacin, cyclosporine, isoniazid, lindane, methylphenidate, metronidazole, penicillins, theophylline, amantadine, morphine, buprenorphine, diphenoxylate, alfentanil, fentanyl, remifentanil, meptazinol, and pethidine.

10.8. Appendix 8: ECG Monitoring Plan

ECG Monitoring Flow

During in-clinic visits:

For all participants, ECG will be administered at Screening, Baseline, Week 4 (V3), Week 26 (V4) and Week 65 (V7).

At Screening, a single 12-lead ECG will be administered to assess eligibility.

At Baseline (V2) Visit:

- A triplicate 12-lead ECG will be administered BEFORE 1st drug administration to determine the participant baseline QTcF.
- A single 12-lead ECG will also be administered 1-2 hours POST 1st drug administration.

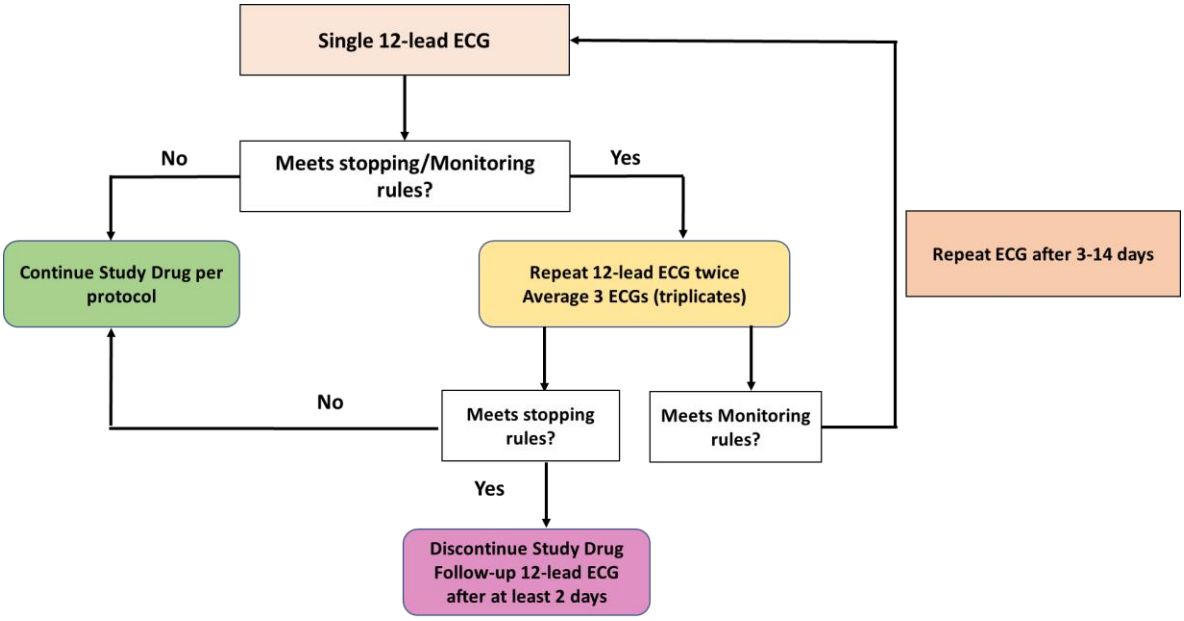
At Week 4 (V3), a single 12-lead ECG will be administered 1-2 hours post-study drug administration.

At Week 26 (V4) and Week 65 (V7), and Week 78 (V8/EoS/ET) for participants not continuing to OLE a single 12-lead ECG will be administered before study-drug administration.

1. Screening Visit (V1)
   - QTcF will be measured by a single12-lead ECG administration
   - If the QTcF is >450 ms for men and >470 ms for women, then ECG will be repeated twice[11] and the QTcF will be determined by the average of the 3 ECGs
   - If mean QTcF is >450 ms for men and >470 ms for women, then the participant will screen fail and will not be randomized
2. Baseline Visit (V2) ECG will be administered **before** first study drug administration:
   - QTcF will be measured by a mean of 3 12-lead ECG administrations (triplicate)
2. Baseline Visit (V2) and Week 4 (V3), single 12-lead ECG will be administered **1-2 hours post-study drug administration** (Figure 3)
3. Week 26 and 65 visits or ET, single 12 lead ECG will be administered **before** study drug administration (Figure 3)

[11] Standard ECG administration for abnormal QTcF readings will be for the ECG to be repeated twice (at least 5 minutes after the 1st ECG, and with an interval of at least 1 minute between each of the 2 additional 10-second recordings), and the mean of the 3 screening administrations will be used to determine final QTcF.

Figure 3: ECG Monitoring Flow



- QTcF will be measured by a single 12-lead ECG
- If QTcF meets Stopping/Monitoring Rules, then ECG will be repeated twice[12] and the QTcF will be determined by the average of the 3 ECGs
- If the average QTcF meets Stopping Rules (confirmed by central read ECG), then the participant is withdrawn from study drug and a follow-up ECG will be performed as soon as practicable (after 2 days) to ensure recovery from QT prolongation
- If the average QTcF meets Monitoring Rule (confirmed by central read ECG), the participant will continue with the study drug per protocol, and will be followed as detailed under Monitoring Rule procedure

Home ECG monitoring

- Home visits by health care professionals for ECG administration may be provided if in-clinic visits are not possible.

Study personnel will confirm that the remote recordings are of sufficient quality to allow for interpretation (participant can record trace without artifact that would impair the ability to measure and interpret the trace).

[12] ECG will be repeated twice (at least 5 minutes after the 1st ECG, and with an interval of at least 1 minute between each of the 2 additional 10-second recordings), and the mean of the 3 screening administrations will be used to determine final QTcF.

10.9. Appendix 9: QT Safety Data

AEs Indicating Proarrhythmic Potential

[redacted]

In accordance with the ICH E14 Guideline, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, the safety database was analyzed for rates of clinical events indicating a proarrhythmic potential, and the rates observed in treated and control participants were compared. An analysis of the full safety database that includes all participants treated with at least one dose of pridopidine found no events of torsade de pointes following treatment with pridopidine at doses of up to 112.5 mg bid. One AE of ventricular arrhythmia was reported.

Exposure-response analysis of QT Prolongation

[redacted]

[redacted]

[redacted]

[redacted]

10.10. Appendix 10: Guidance to Address Global Health Emergencies and Potential Impact on the Clinical Study

As of March 12, 2020, a Coronavirus Disease 2019 (COVID-19) pandemic has been declared by the World Health Organization, leading to the implementation of extensive measures by healthcare systems globally to limit the viral spread, with potential impact on the conduct of clinical studies (because participants/healthcare workers are in self-isolation/quarantine, there is limited access to public places, including hospitals, and health care professionals are committed to critical tasks).

Based on guidelines issued by global regulatory authorities (Health Canada, April 7, 2020; Australian Government, April 9, 2020; EMA, April 2020; MHRA, March 19, 2020; FDA, March 2020), the actions listed below are being implemented in this protocol to address potential disruptions to study conduct secondary to COVID-19 infection or control measures. These actions are to assure the safety of study participants, maintain compliance with good GCP, and minimize the risks to study integrity. Member states within the National Competent Authorities may issue their own guidance requiring country-specific recommendations to be followed.

To the extent feasible, the Sponsor should ensure that the methods and conduct of remote assessments are consistent across sites, participants, and visits.

Informed Consent

- If written consent by the study participant is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given orally by the study participant. Site would record the date and time of discussion.
- Study participants and the person obtaining consent could sign and date separate ICFs.
- In case a written informed consent cannot be obtained at the clinical site informed consent can be obtained remotely. Alternatively, the consent form may be sent to the participant by facsimile or e-mail, and the consent interview may then be conducted remotely by telephone when the participant can read the consent form during the discussion; the participant will be requested to sign and date a blank piece of paper with a written statement affirming that they agree to participate in the study.
- If re-consent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to COVID-19 or important safety issues for other trials), alternative ways of obtaining may include contacting the study participant via telephone and obtaining oral consents, to be documented in the study participants' medical records, supplemented with e-mail confirmation.
- The informed consent procedures to remain compliant with the study protocol as well as local regulatory requirements should be followed. All relevant records should be archived in the Investigator's site master file. A correctly signed and dated ICF should be obtained from the study participants later, as soon as possible.

Study Visits and Procedures

- COVID-19 screening procedures that may be mandated by the health care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits. The Investigator in consultation with the Sponsor will decide if it is in the best interest of COVID-positive participants to remain in the study.
- In the case of missed visits due to COVID-19 (or other health/pandemic) related reasons:
  - The site should make every effort to contact the study participant to confirm and document the reason for the missed visit, and at minimum evaluate AEs/SAEs, and concomitant medications in order to assess participant safety.
- To maintain the integrity of the study, alternative methods of collecting study procedures may be considered where possible and in certain situations, with Sponsor approval:
  - Four Virtual visits have been incorporated as part of the study in addition to on site clinic visits and safety phone visits. Remote study assessments can be completed virtually (via telephone).
  - If on site clinic visits are not possible the visits can be converted to virtual visits (except Screening, Baseline and Week 65) (via telephone).
  - Study assessments will only be conducted in a remote manner if they can be done without affecting the wellbeing of the participant during the study and with the same level of scientific integrity as assessments conducted in a physical study center.
  - According to site operations during public health pandemics, home visits by a health care professional may be used to collect laboratory samples, obtain an ECG, and perform assessments as required by the protocol.
  - A local laboratory may be used to collect laboratory samples as required by the protocol. Local analysis can be used for safety decisions. In addition, a local laboratory can be used for study endpoints if samples drawn at the local laboratory cannot be shipped to the central laboratory. If a local laboratory is used, applicable lab ranges and laboratory certification should be provided to the Sponsor.
  - Data collected from participants participating in remote visits/assessments-may be collected electronically using purpose-built technology, or via traditional paper-based methods. AE/SAE (reporting, assessing and follow-ups) will be handled similarly to a traditional model, with the participant contacting study personnel or engaging local care for public health emergencies.
  - In cases where a participant is continuing to receive study drug but COVID-19 pandemic-related circumstances preclude a visit to the investigative site, remote visits (e.g., virtual visits via telephone) will be allowed for relevant study

procedures while maintaining participant's privacy, as would be done for a clinic visit.

- For missed assessments for primary and secondary endpoints, please discuss these situations with the Sponsor for approval. In certain situations, with prior approval, other options or delayed visits, can be considered.

- The PROOF-HD study is being conducted during the COVID-19 global pandemic and incorporates several mitigation strategies that are included in the protocol and study plans. Table 8 summarizes the Visit Activities according to the Visit Types (in-clinic visits, pre-planned virtual visits and converted virtual visits (home/phone).

Table 8: Study Visit Activities per Visit Type

Study Period Procedures and Assessments	**In-Clinic Visit**	**Pre-planned Virtual Visits (Phone)**	**Converted VV (Home/Phone)**
Informed consent	√		
Demography	√		
Medical and psychiatric history	√		
Prior medication and treatment history	√		
Inclusion and exclusion criteria	√		
Clinical laboratory tests (serum chemistry, hematology, and urinalysis)*	√		√ (Home Nursing Service)
Pregnancy test (for WOCBP)*	√		√ (Home Nursing Service)
Full physical and neurological examination	√		
Brief physical examination	√		
12 lead ECG	√		
Vital signs*	√		√ (Home Nursing Service)
C-SSRS (baseline version)	√		
C-SSRS (since last visit version)	√	√	√ (Phone)
UHDRS-TFC*	√	√	√ (Phone)
UHDRS-TMS	√		
UHDRS-IS	√		
SDMT	√		

Study Period Procedures and Assessments	In-Clinic Visit	Pre-planned Virtual Visits (Phone)	Converted VV (Home/Phone)
SWR	√		
Q-Motor	√		
PBA-S (Short Form)	√	√	√ (Phone)
CGI-S (modified)	√		
CGI-C	√		√ (Phone)
HDQoL-P	√		√
Benzodiazepines and antidepressants inquiry	√	√	√ (Phone)
Alcohol/illicit drug use inquiry	√	√	√ (Phone)
Review of tolerability to study drug prior to dose escalation	√		
Randomization	√		
Dispense/collect study drug*	√		√ (Qualified provider)
Review study compliance and adherence*	√		√ (Home Nursing Service)
Adverse event inquiry	√	√	√ (Phone)
Concomitant medication inquiry	√	√	√ (Phone)
Blood samples for PK analysis	√		
Plasma sample for biomarkers analysis	√		
Blood sample for genetic analysis	√		
ECG	√		

√- Yes, assessment done

* Participants who are off study drug and continue to participate in the study and have their clinic visits converted to virtual visits (by phone) will not be required to undergo UHDRS-TFC assessment or get home nursing services during the converted virtual visits.

Study Drug Supply

- Alternative methods of supplying study drug to enrolled study participants (e.g., direct-to-participant shipment from site) may be considered where possible.
- Additional study drug will not be released to the participant without an evaluation of participant safety, including protocol-required laboratory results (at minimum

hematology, clinical chemistries, pregnancy for WOCBP measurements, and ECG administration), and clearance communicated to the participant.

- In case a participant is unable to attend in-clinic visits or study personnel is not available at the site, where study drug compliance is assessed, accountability for compliance purposes can be done by a home health care professional. In both cases, when possible, the study drug will be return to the site for accountability.
- Drug accountability will also be conducted at home visits by health care professionals.

Monitoring and Audits

- Certain Sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required. On-site audits will be avoided or postponed, and if permitted under local regulations, social distancing restrictions should apply.
- Cancelling or postponing of on-site monitoring visits and extending the period between monitoring visits will be allowed.
- To the extent on-site monitoring remains feasible, it should take into account national, local and/or organizational social distancing restrictions.
- Centralized monitoring can be considered for data acquired by EDC systems (e.g., eCRFs, central laboratory or ECG / imaging data, ePROs etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner.
- Off-site monitoring can be conducted and will include phone calls, video visits, e-mails or other online tools in order to discuss the study with the Investigator and site staff. Remote monitoring should be focused on the review of critical study-site documentation and source data; source documents and ICF with PHI redacted will be sent to the monitor for review. These activities could be used to get information on the clinical study progress, to exchange information on the resolution of problems, review of procedures, study participant status as well as to facilitate remote site selection and Investigator training for critical study procedures.

COVID-19 Vaccination

- Several vaccines for COVID-19 have been approved worldwide.
- The Sponsor does not have specific data regarding any possible interaction between the COVID-19 vaccines and study drug and has no evidence or rationale to suggest that study drug alters the vaccine's efficacy or increases the vaccine's toxicity.
- In the current study COVID-19 vaccines (and boosters) are allowed as concomitant medication per the discretion of the Investigator, based on current standard of care and published guidelines, institutional policies and the participant's values and

preference. The investigator must document participant's receipt of the COVID-19 vaccine as part of concomitant medicine in the eCRF.

- Vaccination should preferably not occur within 1 week of a study visit to ensure possible side effects do not affect the assessments

Risk Mitigation

- The Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to the study participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

10.11. Appendix 11: Abbreviations

Abbreviation Term	Description
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDNF	Brain-derived neurotrophic factor
bid	Twice daily
CAG	Cytosine-adenine-guanine
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity (modified)
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus Disease 2019
CrCl	Creatinine clearance
C-SSRS	Columbia-Suicide Severity Rating Scale
cUHDRS	Composite Unified Huntington's Disease Rating Scale
CYP2D6	Cytochrome P450 2D6
D2	Dopamine 2
D3	Dopamine 3
DCL	Diagnostic confidence level
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual–Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EEA	European Economic Area
EMA	European Medicines Agency
EoS	End of Study
ER	Endoplasmic reticulum
ERK	Extracellular-signal-regulated kinase
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

Abbreviation Term	Description
GGT	Gamma-glutamyl transferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Huntington disease
HDQoL	Huntington Disease Quality of Life Questionnaire
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
HTT	Huntingtin gene
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOI	Inter-onset interval
iPSC	Induced pluripotent stem cells
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	Independence Scale
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
LS	Least squares
MAM	Mitochondria-associated membrane
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mHTT	Mutant huntingtin
MI	Multiple Imputation
mITT	Modified intent-to-treat
MMRM	Mixed Model for Repeated Measurements
MNAR	Missing Not at Random
NfL	Neurofilament light chain

Abbreviation Term	Description
OLE	Open-label Extension
PBA-s	Problem Behaviors Assessment – Short Form
PET	Positron emission tomography
PK	Pharmacokinetics
PMM	Pattern-mixture model
PO	Oral, per os
QD	Once daily
Q-Motor	Quantitative motor
QoL	Quality of life
QTcF	Fridericia-corrected QT interval
RAF	Randomization Authorization Flow
S1R	Sigma-1 receptor
SAE	Serious adverse event
SAP	Statistical analysis plan
SDMT	Symbol Digit Modalities Test
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
SWR	Stroop word reading
TC	Telephone call
TEAE	Treatment-emergent adverse events
TFC	Total functional capacity
TMS	Total Motor Score
UHDRS	Unified Huntington Disease Rating Scale
ULN	Upper limit of normal
V	Visit
VV	Virtual Visit(s)
W65PP	Per Protocol Week 65 Population
W78PP	Per Protocol Week 78 Population
Wk	Week
WOCBP	Woman of childbearing potential
β-HCG	β-human chorionic gonadotropin

10.12. Appendix 12: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Below are summaries of prior amendment(s) in reverse chronological order.

Amendment 7, 27 January 2022

Overall Rationale for the Amendment:

The Sponsor has introduced the following modifications to protocol V6.0; these changes are from V5.0 (Amendment 6.0) and are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (●verall Design) 1.3.1 Schedule of Activities – Main study 4.1 ●verall Design	• Clarify timing of End of Study (EoS) visits after last participant reaches Week 65	• For clarity
1.1 Synopsis (●bjectives and Endpoints) for ●pen-label Extension (●LE) 3.2 ●LE ●bjectives and Endpoints	• Add Q-Motor to efficacy endpoints	• [redacted]
1.2 Study Scheme Figure 2 1.3.2 Schedule of Activities – ●pen-label Extension	• Renumber and rename ●LE visits • Reduce number of phone visits	• For clarity, especially as participants may roll over between Week 65 and 78 • Pridopidine appears to be safe and tolerable, and therefore acceptable to decrease visit frequency and reduce participant burden
1.3.1 Schedule of Activities – Main study	• Add informed consent for ●LE and willingness to enter ●LE • Clarify that at V8, single ECG will be conducted for participants not continuing to ●LE, and triplicate ECG for participants continuing to ●LE • Update to conduct C-SSRS (since last visit) at each visit and delete footnote 'p'	• To ensure study drug availability for participants entering ●LE • For clarity; Safety measure for participants who continue on study drug through the ●LE • As a safety measure; [redacted]

Section # and Name	Description of Change	Brief Rationale
1.3.2 Schedule of Activities ●pen-label Extension	• Add vital signs at ●LE EoS • Update to conduct C-SSRS (since last visit) at each visit and delete footnote 'f' • Add Q-Motor assessment at each in-clinic visit	• ●mitted by error • As a safety measure: [redacted] • To allow evaluation of [redacted]
6.5 Study Drug Compliance	• Clarify procedures for calculating study drug compliance	• For clarity
7.2 Discontinuation of Study Drug 10.10 Appendix 10 Guidance to Address Global Emergencies and Potential Impact on the Clinical Study	• Clarify that participants who discontinue study drug during the Main study can have phone virtual visits (instead of in-clinic visits), except for ET visit, Week 65 and Week 78/EoS. If clinic visits are converted to virtual visits (by phone), UHDRS-TFC, clinical laboratories, and vital signs will not be assessed	• To reduce the burden on participants who are not on study drug
7.2 Discontinuation of Study Drug	• Clarify that participants who discontinue study drug during the ●LE will also be withdrawn from the study and attend ●LE EoS visit	• For clarity
Appendix 2 Clinical Laboratory Tests	• Update laboratory parameters to be done in ●LE	• Pridopidine appears to be safe and tolerable and therefore acceptable to optimize the laboratory tests and reduce participant burden
10.6 Appendix 6 Permitted Medications 10. 7 Appendix 7 Prohibited Medications and Substitution Alternatives	• Align permitted medications (Appendix 6) and Substitution alternatives (Appendix 7)	• For clarity: [redacted]
General	• Update version and date • Update table of contents • Update for consistency throughout protocol (including terminology) • Update cross reference / linking throughout • Minor corrections/updates throughout (punctuation, formatting, style, etc.)	• For consistency and accuracy

Amendment 6, 13 May 2021

Overall Rationale for the Amendment:

The Sponsor has introduced the following modifications to protocol V5.0; these changes are from V4 (Amendment 3) and are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Objectives/Endpoints) 3.2 OLE Objectives and Endpoints	• Add objectives and endpoints for OLE	• Per feedback from ANSM, the French competent authority (this was incorporated in V4.2 Amendment 5.0 – French Country-specific Amendment)
1.1 Synopsis (Overall Design) 4.1 Overall Design	• Add number of clinical sites included in the study	• Per feedback from French Ethics Committee (this was incorporated in V4.1 Amendment 4.0 -French Country-specific Amendment)
1.1 Synopsis (Inclusion/Exclusion Criteria) 5.2 Inclusion Criteria-Main Study	• Add inclusion criterion 14 on concomitant medication use	• For safety purposes, participants should be on stable dosages of concomitant medications at the start of the baseline visit
1.1 Synopsis (Inclusion/Exclusion Criteria) 5.3 Exclusion Criteria-Main Study	• Update exclusion criterion no. 2c (based on clinically significant bradycardia) • Add exclusion criterion no. 11 to exclude participation in studies with tominersen • Clarify exclusion criterion 13e associated with total bilirubin • Correct exclusion criterion no. 14 to read 'Substance Use disorder' • Change exclusion criterion no.14 • Update title of section headings	• To allow inclusion of participants with heart rate lower than 50 bpm if not clinically significant • Avoid interfering with the important ongoing follow-up for these patients • To exclude non- clinically significant cases and benign conditions of elevated bilirubin (such as Gilbert's syndrome) • Per DSM-5 definitions • To add timeframe for suicidal ideations • For clarity

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis (Inclusion/Exclusion Criteria) 5.2 Inclusion Criteria - Open-label Extension	• Add OLE informed consent requirement in synopsis and Section 5.2	• Per feedback from ANSM, the French competent authority (this was incorporated in V4.2 Amendment 5.0 -French Country-specific Amendment)
1.1 Synopsis (Study Duration) 4.4 Study Duration	• Add the expected duration of the overall study and recruitment period	• Per feedback from French Ethics Committee (this was incorporated in V4.1 Amendment 4.0 -French Country-specific Amendment)
1.1 Synopsis (COVID-19 Mitigation plan) 4.6 COVID-19 Mitigation plan 10.10 Appendix 10 - Guidance to Address Global Health Emergencies and Potential Impact on the Clinical Study	• Clarify that drug accountability will be done at home visits by health care professionals	• To ensure compliance with study drug
1.3.1 Schedule of Activities – Main Study	• Expand any post Week 4 (V3) in-clinic visit window to ±28 days. The expansion of the in-clinic visit window is only justified in case of a global pandemic • Clarify the rescreening process • Clarify visit schedule for participants discontinuing study drug but being continued to be followed up in the study • Clarify in a footnote that all baseline assessments except post dose ECG should be done pre-dose	• To ensure participant's safety and study integrity and minimize potential missing data during the pandemic • For clarity • For clarity • To clarify order of study procedures at Baseline
1.3.1 Schedule of Activities – Main Study 10.8 Appendix 8 - ECG Monitoring Plan	• Add ECG assessment at V8 for participant not continuing to OLE	• Safety measure for participants who discontinue study drug
1.3.2 Schedule of Activities (OLE)	• Add plasma sample for biomarkers analysis	• To assess the longitudinal effect of treatment on neurofilament light and other biomarkers
5.4 Screen Failures	• Clarify the rescreening process	• For clarity

Section # and Name	Description of Change	Brief Rationale
6.7.2 Prohibited Medication	• Add a precautionary statement for use with medications eliminated via CYP2D6 dependent pathway	• Per feedback from ANSM, the French competent authority (this was incorporated in V4.2 Amendment 5.0 -French Country-specific Amendment)
7.1.3 Psychiatric Stopping Rules	• Clarify text	• For consistency: to align with exclusion criterion no. 14
7.1.5 Other Excluded Conditions during Study	• Clarify excluded condition	• For consistency: to align with exclusion criterion no. 13 and DSM-5 definition
8.1.5.1 Stroop Word Reading (SWR)	• Clarify procedure	• For accuracy
8.2.2 Vital signs	• Delete requirements to conduct triplicate measurements for blood pressure and heart rate	• Not a safety concern. To ease burden on participants
8.3.1 Time Period and Frequency for Collecting AE and SAE information	• Remove contradictory text about recording AEs occurring before first dose in Medical History page.	• For clarity on the AE recording methodology
9.4 Statistical Analyses	• Indicate that analysis of OLE will be detailed in the Statistical Analysis Plan (SAP)	• The SAP is intended to detail all planned analyses prior to database lock including exploratory endpoints and OLE (this was incorporated in V4.2 Amendment 5.0 -French Country-specific Amendment)
10.4.1 Definitions (Contraceptive Guidance)	• Clarify timing of repeat FSH assessment for postmenopausal women	• For clarity
10.6 Appendix 6 Permitted Medications	• Add fluphenazine as permitted antipsychotic medications • Add permitted medications for management of chorea • Add antiviral (COVID-19 vaccines) as permitted medication	• For clarity • Per Health Canada request • For clarity
10.10 Appendix 10-Guidance to Address Global Health Emergencies and Potential Impact on the Clinical Study	• Add Table 8: tabulated study visit activities per visit type • Add COVID-19 vaccination as permitted medication	• For clarity • For clarity

Section # and Name	Description of Change	Brief Rationale
General	• Update version and date • Update table of contents • Update for consistency throughout protocol • Update cross reference / linking throughout • Minor corrections/updates throughout (punctuation, formatting, style, etc.)	• For consistency and accuracy

Amendments 4 (15 February 2021) and 5 (15 March 2021) are incorporated within Amendment 6 (13 May 2021).

Amendment 3, 25 October 2020

Overall Rationale for the Amendment:

The Sponsor has introduced the following modifications to protocol V4, these changes are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints	• Add text for handling of intercurrent events	• [redacted]
9 Statistical Consideration	• Add statement to reflect that separate analyses of the primary endpoint will be performed for EMA and Non-EMA regions	• [redacted]
General	• Update version and date • Alignment of wording across protocol • Minor clarifications and corrections to various sections • Update glossary	• For consistency and accuracy

Amendment 2, 23 September 2020

Overall Rationale for the Amendment:

The Sponsor has introduced the following modifications to protocol V3, these changes are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 5.3 Exclusion criteria	• Delete footnote in exclusion criterion 2b • Add exclusion criterion 2c • Clarify exclusion criterion 4 about serious medical illness • Add exclusion laboratory test abnormalities to exclusion criterion 12	• [redacted] • To ensure that participants do not have severe illnesses that may put them at risk when participating in the study, influence the results of the study
1.1 Synopsis 4 Study design 6.9 Open-label Extension (OLE)	• Specify OLE duration to be initially for 6 months after the last participant completes Week 65 of the double-blind Treatment period; duration may be extended pending emerging data from the double-blind portion of the study	• [redacted] • To enable Sponsor to analyze emerging data
1.1 Synopsis 1.3 SoA Table 2 Appendix 10 Guidance to Address Global Health Emergencies	• Update that nearly all clinic visits (excepts V1, V2 and V7) can be converted to virtual visits	• Risk mitigation for COVID-19
1.3 SoA (Tables 2 and 3) Appendix 2 Clinical Laboratory Tests Appendix 4 - Contraceptive Guidance and Collection of Pregnancy Information	• Add monthly urine pregnancy test	• [redacted] as a safety precaution
1.3 SoA (Tables 2 and 3) Appendix 8 – ECG Monitoring Plan	• Add ECG at Week 26 (Main study) & Week 78, 104 (OLE)	• [redacted] as a safety precaution
1.3 SoA OLE (Table 3)	• Evaluate C-SSRS and PBAs more frequency during the OLE part of the study	• [redacted] as a safety precaution
2.3.1 Risk assessment 7.1 Individual Stopping Rules	• Update to include additional conditions to trigger study drug discontinuation	• [redacted] as a safety precaution
3 Objectives and endpoints	• Add text around primary estimand • Add exploratory endpoints	• [redacted] • To ensure consistency with the SAP

Section # and Name	Description of Change	Brief Rationale
6.4 Measures to minimize bias: randomization and blinding	• Clarify blinding and unblinding process	• [redacted] to maintain study integrity
7.2 Discontinuation of study drug	• Delete 'progressive disease' as reason for discontinuation	• Due to the slow natural progression of HD, in this trial of patients with early HD, progressive disease is not expected to lead to permanent discontinuation.
	• Add 'loss of capability to consent' as reason for discontinuation	• [redacted] to maintain study integrity
8.2.4 Clinical safety laboratory	• Clarify safety lab should be done per SoA, including home visits if unable to conduct in-clinic visit	• [redacted] as a safety precaution
9 Statistical considerations	• Update sample size to account for attrition rate • Update ITT population analysis definition • Update primary endpoint statistical analysis	• [redacted]
Appendix 1, 10.1.3 Informed Consent Process	• Clarify the informed consent process	• [redacted]
Appendix 1, 10.1.8 Study and Site Start and Closure	• Added study termination criteria	• [redacted]
Appendix 8, 10.8 ECG Monitoring Plan	• Update ECG Monitoring Plan	• [redacted]
General	• Update version and date • Alignment of wording across protocol • Minor clarifications and corrections to various sections • Correct typo, formatting, and style • Update glossary	• For consistency and accuracy

Amendment 1, 17 July 2020

Overall Rationale for the Amendment:

The Sponsor has introduced the following modifications to protocol V2, these changes are presented in order of appearance:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 5.3 Exclusion criteria	• Exclude female participants who are pregnant, planning to become pregnant or breast feeding • Exclude participants with connection to Sponsor or Investigator or investigative site	• To comply with Health Canada requirements • Per ICH E6(R2) and EU requirements
1.1 Synopsis 1.3 Schedule of Activities 3 Objectives and endpoints 8.1 Efficacy Assessments	• Update secondary and exploratory endpoints	• [redacted]
	• Clarified modified CGI-S will be used at Baseline and CGI-C for on-treatment assessment	• Change is more clinically meaningful measure than severity
	• Remove PGI-S	• HDQoL will be used as a Patient Reported Outcome
	• Replace H-QoL with HDQoL (participant)	• HDQoL is the standard quality of life
	• Remove HD-HI	• HD-HI is not available in all languages and cannot be assessed on all study participants
	• Add Q-Motor assessment at Screening	• For training purposes only
1.1 Synopsis 1.2 Study Schema 1.3 Schedule of Activities Table 3 4.1 Overall study design 4.4 Study duration 6.9 OLE	Clarify OLE duration	To allow for flexible OLE duration.

1.3 Schedule of Activities Table 2 (Main study) Table 3 (OLE)	• Update to reflect changes in protocol • Expand visit window (Table 2) • Clarify pregnancy testing (serum / urine) (Table 2)	For clarity
2.1 Rationale	Update study rationale	Additional clarifications and background data
6.2 Handling missed doses	Add section	Additional clarifications
8.4 Pharmacokinetics 8.5 Pharmacodynamics/Biomarkers 8.6 Pharmacogenetics	Clarify and revise text	For clarity, accuracy and consistency with Laboratory Manual
10.1 Appendix 1 Regulatory, Ethical and Study Oversight Considerations	• Clarify data collection when a participant withdraws consent • Clarify procedures for data processing and transfer from EU to non-EU regions.	To comply with EU regulations
10.2	Remove blood draws for coagulation test	No safety concern has been identified
10.5 Genetics	Clarify that Sponsor will comply with relevant regulations for processing genetics data	To comply with EU regulations
10.10 Guidance to address global health emergencies	Update	To comply with latest FDA guidance from 02 July 2020
General	• Add study name PROOF-HD • Update version and date • Add document history and summary of changes • Minor clarifications to various sections • Correct typo, formatting, and style • Update glossary	For consistency and accuracy

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