STATISTICAL ANALYSIS PLAN

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

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

Study No.: PL101-HD301 (PROOF-HD)

Phase: III

IND No.: 77419

EudraCT No.: 2020-002822-10

Based on: Clinical Study Protocol PL101-HD301, Version 7.0, Amendment 8.0, 10 November 2022.

Case Report Forms: Version MSC020, Version Date: 02/06/2023

Study Drug: Pridopidine

Sponsor: Prilenia Neurotherapeutics Ltd.

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SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	7 October 2020		Original
2.0	10 November 2022	(Section 2. 3) Description of study design and endpoint assessments are updated throughout the SAP.	Keep consistency with Protocol Version 7.0, Amendment 8.0.
		(Section 2. 3.2.3, 3.2.4. 3.2.5) 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 endpoints as well as OLE and safety endpoints are clarified in endpoint section. Biomarker (NfL) endpoints are added to the OLE endpoints. Pharmacodynamic assessments are not performed therefore removed from the SAP.	Changes are made for clarity.
		(Section 7.1.1. 7.2, 7.3. 7.4, 5.8) Estimand definitions clarified and sensitivity analyses for multiplicity-adjusted secondary endpoints added. The details of missing data handling added.	Additional details are provided.
		(Section 2. 3.2.2, 7.4) 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.	• Based in part on power assessment using empirical data from prior PRIDE-HD study • 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

SAP Version	Approval Date	Change	Rationale
			importance of cognition in HD • 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
		(Section 7.7, 3.5.3, 3.5.4) Analysis of Open-label extension period was added. and it was clarified that regulatory submission will be based on double-blind treatment period data only.	Additional details are provided.
		(Section 3.3) Sample size consideration for primary endpoint in ITT population under MNAR assumption was supplemented.	Keep consistency with primary analysis for EMA and non-EMA regions.
		(Section 3.2, 3.6.3) It was clarified that only in-clinic assessments would be used in the primary and secondary analyses. The virtual assessments will be analyzed separately as an exploratory analysis. For similar rationale, the previously planned sample size re-estimation to mitigate high dropout rate and COVID-19 impact will not be performed.	Given current study status, where there is <2% missing in-clinic data.
		(Section 7.3.2) Additional pre-specified subgroup analyses have been added.	Additional details are provided.
		(Section 8.4, 8.6, 8.7) The clinically significant criteria are updated with reference to newly issued FDA Medical Queries (FMQ) document [1].	For consistency with guideline document.
		Wording or text rearranged to improve readability.	For consistency and accuracy.
03.0	28 Mar2023	(Section 2 and 3.2.3) Q-Motor analysis at Week 39 removed.	This was a typographical error as Q-Motor was not

[1] FDA – Recent tools publicly available (FMQs, safety analytics TLFs), Sep 2022. https://www.regulations.gov/docket/FDA-2022-N-1961/document

SAP Version	Approval Date	Change	Rationale
			planned nor collected at Week 39.
		(Section 3.1) Text added to indicate following Blinding-Unblinding Plan after database lock.	For statistical validity of OLE data, the Blinding-Unblinding plan outlines maintenance of blind post database lock.
		(Section 3.2.2) For responder analyses if there are fewer that a total of 5 responders the analyses will not be performed.	If there are fewer than 5 responders there is insufficient data to reliably compare responders between treatment groups.
		(Section 3.2.3) CGI of 0 corresponds to CGI not completed so thresholds were updated to account for this.	To exclude 0 as a response threshold.
		(Sections 4.1.3, 4.1.4) Per Protocol Week 65 and Week 78 Population criteria were clarified and efficacy component limited to those impacting UHDRS-TFC.	Criteria for completion through Week 65 or 78 and >80% compliance were kept as is. Additional text was added for clarifying other participants that may be excluded from PP population.
		(Section 5.4) p-values will be presented to 4 instead of 3 decimal places.	To allow for greater precision in presentation of p-values.
		(Section 5.8.1.1) Since there were very few participants (<5) with missing data at baseline their data will not be imputed.	Since the trial randomized 499 participants, missing efficacy data on <5 participant would have minimal to no impact on analyses.
		(Section 5.8.1.3) Details on imputation of Total or Subscale scores on UHDRS-TFC, UHDRS-TMS, HDQoL and their subscales that were partially completed were provided.	This permits use of partially completed scales or subscales for analyses instead of ignoring them.

SAP Version	Approval Date	Change	Rationale
		(Section 5.8.2) Additional detail for imputation for AE missing start date was included	In order to determine if AEs are TEAEs an additional imputation rule was added.
		(Section 6.2) Clarification on selection on CAG repeat assessments analyzed by the laboratory rather than that reported by the participant.	CAG from the laboratory assessment was considered more reliable and hence used rather than the one reported by the participant.
		(Section 6.6) No separate table created for important Protocol Deviations (PDs) due to COVID-19.	Since there were no important PDs due to COVID-19.
		(Section 7.2) Clarification that analyses of Week 65 data will only include data from visits through Week 65 (and not beyond).	The primary endpoint for the study is Week 65. The study was designed to complete when the last participant completed Week 65.
		(Section 7.3.2) Analysis by Region will be for North America vs Europe instead of US vs Europe.	Analysis was intended by region so US and Canada will be combined.
		(Section 7.3.2) An additional subgroup analyses for those participants on Chorea medication was added. The model for subgroup analyses was updated. In addition, if a subgroup had a total of <50 participants the analyses would not be performed.	The subgroup of those participants who were on medication for Chorea Management was deemed important. The primary model for subgroup analyses was deemed more appropriate with select 2-factor interactions as opposed to all of them. Subgroups with <50 participants would not permit a reliable comparison of the effect of Pridopidine vs Placebo.

SAP Version	Approval Date	Change	Rationale
		(Section 7.3.3) Added text to conduct additional exploratory analysis to explore impact of confounding factors. Added sensitivity analysis on neuroleptic use.	Since use of neuroleptics may impact efficacy and was a stratification factor in the study a sensitivity analysis on its use was added.
		(Section 7.4.2) updated that CI's for observed proportions and the difference will be provided using Clopper-Pearson method.	Since it provides the exact CI for observed proportions.
		(Section 7.4.3) Subgroup analyses will be performed on log2-transformed NfL.	To better understand changes in NfL for the different subgroups.
		(Section 7.5) Additional analyses on Q-Motor adjusting for covariates that may impact it were included.	Since Age, Sex and Weight can impact Q-Motor assessments these were added as covariates that may be explored for impact on efficacy.
		(Section 7.5) Added text on robust regression or other analyses.	In order to minimize the impact of outliers that may represent unrealistic changes in key endpoints, text on analyses using robust regression or other methods was added.
		(Section 7.6) Additional analyses may be performed based on subgroups of baseline PIN_{HD} values	In order to understand impact of PIN_{HD} on efficacy.
		(Section 7.6) Additional analyses may be performed on change from baseline in Weight	In order to evaluate changes in weight
		(Section 8.2) Inequality signs updated for analysis of duration of exposure.	Inequality signs were made consistent between interval and cumulative thresholds.
		(Section 8.3) Additional details added on calculation of Compliance and display of relevant data in Listings. Ranges for	Due to participants sometimes not returning bottles additional details

SAP Version	Approval Date	Change	Rationale
		compliance were updated to better reflect range of compliance.	on handling this were added.
		(Section 8.4) Updated to reflect that AEs that start more than 14 days after the end of treatment are not considered TEAEs.	Due to the short half-life of Pridopidine AEs that started more than 14 days after the end of treatment were not considered TEAEs.
		(Section 8.4 and Appendix 12.2) Analyses of Abuse Potential was added.	Analyses of Abuse Potential were deemed important and added.
		(Section 8.6) Criteria for detection of clinically significant laboratory abnormalities were updated.	Updated to be consistent with Laboratory Normal Ranges.
		(Section 8.7) Criteria for detection of vital signs abnormalities were updated.	[redacted]
		(Section 8.8.2) Criteria for the detection of HR, PR and QRS abnormalities were added.	Added to define abnormalities in these ECG parameters.
		(Section 9.1.2) Biomarker (NfL) analyses were updated.	Additional and updated analyses were deemed appropriate.
		Minor updates for clarity.	For improved readability.

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event(s)
AR(1)	Autoregressive (1)
ARH(1)	Heterogeneous autoregressive (1)
bid	Twice daily
BL	Baseline
C-SSRS	Columbia-Suicide Severity Rating Scale
CAG	Cytosine-adenosine-guanine
CAP	CAG-Age-Product
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CrCl	Creatinine clearance
CRF	Case report form
CSR	Clinical Study Report
cUHDRS	Composite Unified Huntington's Disease Rating Scale
DNA	Deoxyribonucleic acid
DSP	Diastolic blood pressure
EDC	Electronic data capture
ECG	Electrocardiogram
EMA	European Medicines Agency
EoS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
HD	Huntington Disease
HDQoL	Huntington Disease Quality of Life Questionnaire
HR	Heartrate
ICC	Intra-class Correlation Coefficient
ICE	Intercurrent event
ICH	International Conference on Harmonisation

IOI	Inter-onset interval
IRT	Interactive Response Technology
IS	Independence scale
ITT	Intent-to-treat
LLOQ	Lower limit of quantification
LSM	Least square mean
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputations
ML	Maximum-Likelihood
MMRM	Mixed Model Repeated Measures
MNAR	Missing not at random
mITT	Modified intent-to-treat
msec	Millisecond(s)
NfL	Neurofilament light chain
OLE	Open-label Extension
OR	Odds ratio
PBA-s	Problem Behaviors Assessment-Short form
PD	Protocol deviation
PIN_{HD}	Prognostic index normed for HD
PK	Pharmacokinetic(s)
PKP	PK Population
PMM	Pattern-mixture model
PP	Per Protocol
PROOF-HD	PRidopidine Outcome On Function in Huntington Disease
PT	Preferred term(s)
Q1	First Quartile
Q3	Third Quartile
QD	Once daily
Q-Motor	Quantitative Motor
QoL	Quality of life

QTcF	Fridericia-corrected QT interval
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard Error
SDMT	Symbol Digit Modalities Test
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SOC	System organ class
SP	Safety Population
SWR	Stroop Word Reading
TC	Telephone call
TEAE	Treatment-emergent adverse event(s)
TFC	Total functional capacity
TFL	Table, Figure, Listing
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
ULN	Upper limit of normal
V	Visit
VV	Virtual Visit(s)
W65PP	Per Protocol Week 65
W78PP	Per Protocol Week 78
Wk	Week
WOCBP	Women of childbearing potential

1. PREFACE

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 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.

The Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Prilenia Therapeutics study PL101-HD301 (A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Participants with Early Stage of Huntington Disease). The study is also referred to as the PRidopidine Outcome On Function in Huntington Disease Participants (PROOF-HD) study. The purpose of this Phase 3 study is to evaluate the efficacy and safety of pridopidine 45 mg twice daily (bid) as compared to placebo. Efficacy will be assessed for HD participants based on functional capacity using the Total Functional Capacity (TFC) score in the Unified Huntington's Disease Rating Scale (UHDRS) as the primary objective.

Some of the analyses in this SAP are included for the Safety Monitoring Committee (SMC). Details of what will be provided to the SMC will be included in the SMC Charter or analysis plan supporting it. Additional details of pharmacokinetics (PK)and pharmacogenomic analyses will be included in SAP addendum, appendix or separate SAPs.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials issued February 1998 as well as the ICH E9(R1) Addendum on Estimands and Sensitivity, November 2019.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol PL101-HD301, Version 7.0, Amendment 8.0, 10 November 2022
- Clinical Study Report (CSR) and subsequent analyses on the Phase 2 Study TV7820-CNS-20002, (PRIDE-HD – Pridopidine Dose Evaluation in Huntington's Disease) study
- Case report form (CRF) for PL101-HD301, V07, 3 May 2022
- ICH E9 Statistical Principles for Clinical Trials
- ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials
- ICH E3 Structure and Content of Clinical Study Reports

- Statistical Considerations for Clinical Trials During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency
- Relevant publications indicated in references related to development of estimands, sensitivity analyses and handling of missing data

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for participant completion in this study. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails, and the differences will be explained in the CSR.

2. STUDY OBJECTIVES AND ENDPOINTS

The purpose of this Phase 3 study is to evaluate the effect of pridopidine 45 mg bid on functional capacity, as well as motor and behavioral features of HD in early-stage participants (HD Stages 1-2, Baseline TFC score of 7-13).

Objectives and Endpoints of the Main Study (Primary, Secondary and Safety):

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 points) 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: ● Gait and balance score (defined as the sum of UHDRS-TMS domains gait, tandem walking, and retropulsion pull test) ● Eye movement ● 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, 52 and 78 in Q-Motor [redacted] • Proportion of participants with improvement or no worsening (change from Baseline ≤0 milliseconds (msec) in Q-Motor [redacted] • Change from Baseline to Weeks 26, 52, 65 and 78 in Q-motor [redacted] • Responder analyses on CGI-C using different thresholds at Weeks 26, 39, 52, 65 and 78
Exploratory Endpoints	
• 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 ● PBA-s sub-score for apathy – Measurement of quality of life (QoL) using the Huntington Disease Quality of Life Questionnaire (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 select efficacy endpoints • Proportion of participants with different thresholds for change from Baseline to Weeks 26, 52, 65 and 78 in plasma NfL levels

• To evaluate the 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
Safety and Tolerability Endpoints	
• 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 withdrawal from the study treatment or study • Incidence and shifts of clinically significant abnormalities in electrocardiogram (ECG), 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 meeting the QTcF-change, Creatinine Clearance (CrCl) or Psychiatric Stopping Rules

Objectives and Endpoints of the Open-Label Extension (OLE) Period:

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 Endpoints	
• 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 withdrawal from the study treatment or study • Incidence and shifts of clinically significant abnormalities in ECG, laboratory tests, and vital signs • Analysis of C-SSRS throughout the study • Tolerability: – The number (%) of participants who completed the OLE treatment period – The number (%) of participants who failed to complete the OLE treatment period due to AEs
Biomarker Endpoints	

• 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

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a multicenter, randomized, parallel group, double-blind, placebo-controlled study to evaluate the efficacy and safety of pridopidine administered orally at a dose of 45 mg bid versus placebo in treatment of functional impairment in participants with early HD, defined as Stages 1 and 2 based on UHDRS-TFC scores (HD1 is UHDRS-TFC 11-13 and HD2 is UHDRS-TFC 7-10). It is planned to enroll a total of 480 participants (240 participants within each treatment arm).

The study will consist of a screening period, a double-blind treatment period (hereafter referred to as the Main Study) and an OLE as described in study schemas Figure 1- Main Study and Figure 2- OLE.

After having signed an informed consent, each participant will be randomized in a 1:1 ratio to the active (pridopidine 45 mg bid) or control (placebo) arm, stratified by Baseline HD stage (HD1 vs. HD2) and Baseline neuroleptic use (Yes/No), for a 65 to 78 weeks double-blinded treatment period as the Main Study.

The Main Study will include an initial 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.

Starting on Day 1, during the titration period, all participants will self-administer 1 capsule of study drug orally, once daily (QD), in the morning for 2 weeks. Thereafter, the study drug will be taken orally bid in the morning and in the afternoon (7-10 hours apart) for 63 weeks (full-dose maintenance double-blind 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.

The reason for the variable length double-blind period is because the study will be considered to have completed when the last participant randomized (and who has not discontinued) completes 65 weeks of double-blind treatment. Participants enrolled prior to that in the study will have the opportunity to complete 78 weeks in the Main Study. Participants enrolled towards the end of the study will have completed between 65 and 78 weeks in the Main Study. The primary endpoint is the change from Baseline to Week 65 in UHDRS-TFC. Change from Baseline to Week 52 and 78 in UHDRS-TFC are secondary endpoints, as indicated in the Section 2.

As soon as the last participant reaches Week 65, the Main Study End of 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-blind will be maintained for all participants and Investigators. Following database lock at the end of Main Study, the treatment assignment will be unblinded for analysis. Details of

personnel unblinded and for those who the blind will be maintained are outlined in the Blinding-Unblinding Plan.

For each participant, the last visit in double-blind treatment period 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.

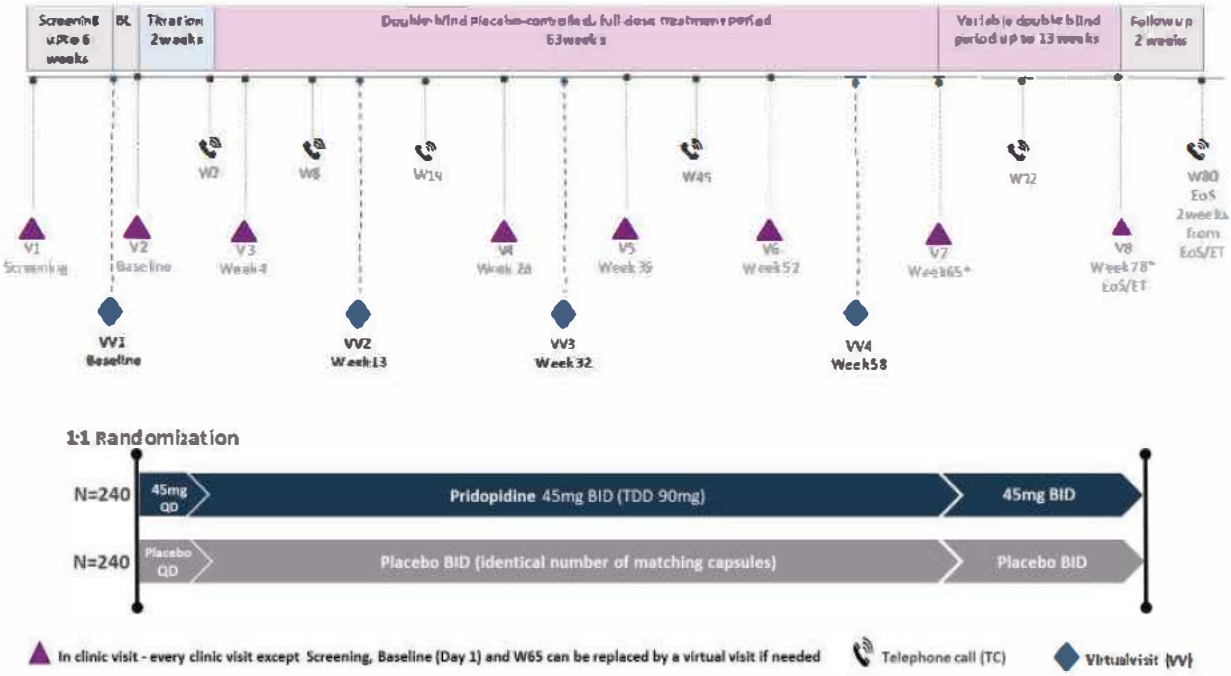
At the Main Study End of Study (EoS) visit, eligible participants will have the option to enroll into an OLE period, commencing at the Main Study EoS visit and consisting of a 2-week up-titration period and a maintenance period, and to receive pridopidine until 12 months after the last participant completes the double-blind treatment period. The OLE duration may be 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 that the benefit-risk ratio remains positive following analysis of the data from the Main Study.

Participants, who are not continuing to the OLE study, will be contacted by phone for a safety evaluation of 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 (VV) (by phone which may be via regular telephone, smart phone, tablet or computer), as specified in the corresponding schedule of activities (SoA) (Table 1 – Main Study, and Table 2 – OLE) and study schema (Figure 1 – Main Study, and Figure 2 – OLE).

During the double-blind treatment period of the Main Study, an independent SMC 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.

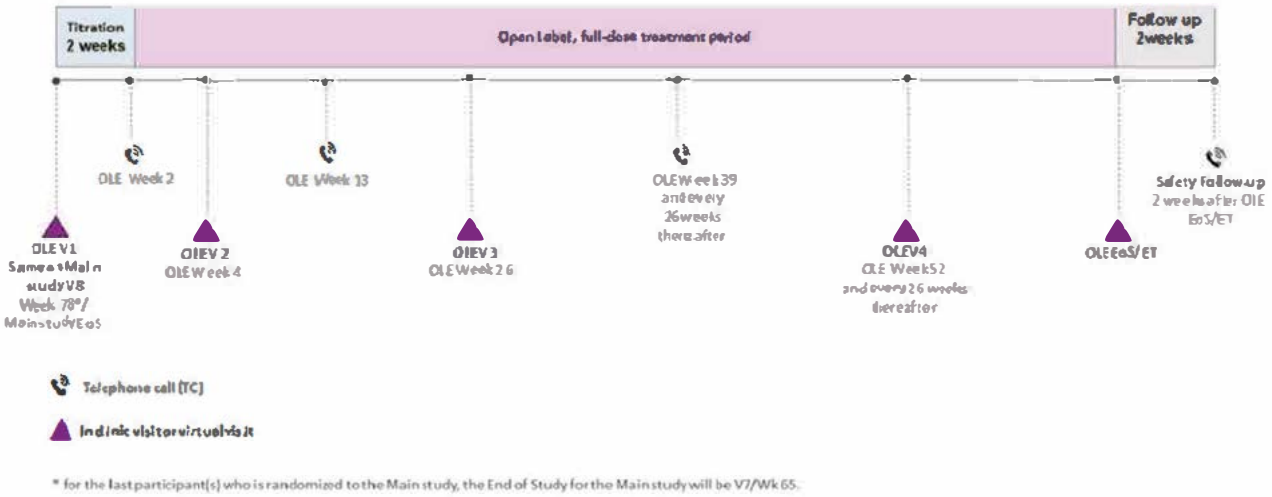
Figure 1: Study Schema – Main Study – Double-blind Placebo-controlled Period



Abbreviations: twice daily (bid); Baseline (BL); End of Study (EoS); Early Termination (ET); once daily (QD); Virtual Visit (VV); 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 Schema – Open-Label Extension



Abbreviations: End of Study (EoS); Early Termination (ET); Open-Label Extension (OLE).

Table 1: Schedule of Activities – Main Study – Double-blind, Placebo-Controlled Period

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					VV2			VV3				VV4				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			Day 1	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]																	
Clinical laboratory tests (serum chemistry, hematology and urinalysis)[k]	X		X		X				X		X		X		X		X	
Pregnancy test (for W●CBP)[l]	Serum		Urine (U)		U				U		U		U		U		U	
					Monthly urine pregnancy tests (at home)													

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					VV2			VV3				VV4				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			Day 1	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
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																	
SDMT			X						X		X		X		X		X	
SWR			X						X		X		X		X		X	
Q-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	
HDQoL-P			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**					**VV2**			**VV3**				**VV4**				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			**Day 1**	**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**
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 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 biomarker analysis[v]	X[w]		X[w]						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					VV2			VV3				VV4				
Telephone Call Safety Visit				✆		✆		✆				✆				✆		✆
Study Week			Day 1	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
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 Protocol 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 deoxyribonucleic acid (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.

Table 2: 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)**		**OLEV2**		**OLEV3**		**OLE V4+**	**OLE EoS/ET[b]**	**OLE F/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	
Q-Motor	X		X		X		X	X	
PBA-s (Short Form)	X		X		X	X	X	X	X
CGI-C	X				X		X	X	
HDQoL	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		OLEV3		OLE V4+	OLE EoS /ET[b]	OLE F/U
Telephone Call Safety Visit		✆		✆		✆			✆
OLE Study Week	OLE Day 1 (same as Main Study Wk 78/EoS)	OLE Wk2	OLE Wk 4	OLE Wk13	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 biomarker analysis					X[c]		X	X[c]	

Abbreviations: Clinical Global hnpression 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); ●pen-label Extension (●LE); 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 Footuotes:

a. The OLE V1 is the same as Main Study V8 (or V7/W65 for the last participant 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 dmg at any point during the OLE, must also be withdrawn from the study and attend an EoS visit.
c. hi-clinic visit window can be expanded to ±28 days; this applies to all in-clinic visits including OLE V1-4+ and ●LE 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.

3.2. Primary, Secondary and Other Efficacy Endpoints and Safety Endpoints

The study endpoints are based on the study objectives listed in the protocol Section 3 and are listed below.

The endpoints described here as the component of the estimand, "variable (or endpoint)" in Section A.3.3 "Estimand Attributes" of ICH E9 R(1)[2], reflect how efficacy is measured for each participant using different assessments (e.g., UHDRS-TFC), timepoints (e.g., Week 65) and methods (e.g., change from Baseline, being a responder). The detailed calculation or derivation for these endpoints is included in Appendix Section 12.1.

In order to preserve Type I error, the multiplicity-adjusted secondary efficacy endpoints will be tested in sequential order as indicated in Section 3.2.2.

In SAP v1.0, it was stated that the combined in-clinic and virtual assessments may be used to define UHDRS-TFC related endpoints in the presence of missing values due to the pandemic impact of COVID-19. As of September 2022, <2% of all scheduled in-clinic visits from all participants were not performed or had UHDRS-TFC assessments missing. Since the proportion of missing in-clinic visits or assessments is very small, and the UHDRS-TFC virtual assessments have not been previously validated, together with the heterogeneity that may exist due to the time interval (6 to 7 weeks) between in-clinic and virtual assessments, the UHDRS-TFC-related endpoints will be defined using in-clinic visits only. Exploratory analysis will be performed by using virtual UHDRS-TFC assessments for primary endpoint (details in Section 7.3).

3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this study is:

- change from Baseline to Week 65 in the UHDRS-TFC (defined as the sum of all UHDRS-TFC 5-items ratings [Domestic Chores, Activities of Daily Living, Finances, Care Level, and Occupation])

3.2.2. Multiplicity-adjusted Secondary Efficacy Endpoints

The **key secondary efficacy endpoint** for this study is:

- change from Baseline to Week 65 in cUHDRS total score

The other **multiplicity-adjusted secondary efficacy endpoints** for this study are to evaluate the efficacy of pridopidine 45 mg bid vs. placebo as measured by:

- the proportion of participants with improvement or no worsening in UHDRS-TFC at Week 65 (change from Baseline ≥0 points) using responder analysis
- change from Baseline to Week 52 in UHDRS-TFC score
- change from Baseline to Week 78 in UHDRS-TFC score
- change from Baseline to Week 65 in Q-Motor [redacted]

- change from Baseline to Week 65 in UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings)
- change from Baseline to Week 65 in SDMT score
- change from Baseline to Week 52 in UHDRS-TMS score
- proportion of participants with no change or improvement in CGI-C at Week 65

For responder analyses where there are fewer than 5 responders (overall between both treatment groups), the analyses will not be performed as too few responders will not allow for comparison of responders between treated and placebo participants.

3.2.3. Non-multiplicity Adjusted Secondary Efficacy Endpoints

The non-multiplicity adjusted secondary efficacy endpoints (listed in Section 2) will evaluate the efficacy of pridopidine 45 mg bid vs. placebo, as measured by change from Baseline to post-baseline scheduled visits in UHDRS-TFC (total score and subscales), cUHDRS, UHDRS-TMS (total score and subscales), dystonia score for those participants with severe dystonia at Baseline (defined as UHDRS-TMS-dystonia score ≥4), SDMT, SWR, Q-Motor measurements [redacted] at Weeks 26, 39, 52, 65 and 78, if not presented as primary or multiplicity-adjusted secondary endpoints.

The proportion of participants with response in cUHDRS, UHDRS-TMS, Q-Motor [redacted], and CGI-C at Weeks 26, 39 (not for Q-Motor assessments), 52, 65 and 78, if not presented as primary and multiplicity-adjusted secondary endpoints, will also be evaluated as non-multiplicity adjusted secondary efficacy endpoints. The response in each endpoint is defined as follows:

- Improvement or no worsening in Q-Motor [redacted] with change from Baseline ≤0 at corresponding post-baseline visit
- Improvement or no worsening in UHDRS-TMS with change from Baseline ≤0 at corresponding post-baseline visits
- Change from Baseline in cUHDRS ≥-1 at corresponding post-baseline visits
- Response in CGI-C defined using different thresholds (i.e., 1, 1 to 2, 1 to 3, 1 to 4) at corresponding post-baseline visits

3.2.4. Other Exploratory Efficacy Endpoints

The other exploratory efficacy endpoints for this study are to evaluate the efficacy of pridopidine 45 mg bid vs. placebo as assessed by:

- Problem Behaviors assessment, as assessed by the change from Baseline to Weeks 26, 52, 65 and 78 in PBA-s total score
- Change from Baseline to Weeks 26, 52, 65 and 78 in PBA-s apathy sub-scores
- Change from Baseline to Weeks 26, 52, 65 and 78 in HDQoL

3.2.5. Biomarker Endpoints

- Evaluate the efficacy of pridopidine 45 mg bid vs. placebo as assessed by the change from Baseline to Weeks 26, 52, 65 and 78 in plasma NfL protein
- Evaluate the relationship between Baseline NfL and changes from Baseline in select efficacy endpoints
- Evaluate the relationship between changes from Baseline to Weeks 26, 52, 65 and 78 in plasma NfL and select efficacy endpoints for pridopidine 45 mg bid vs. placebo
- Proportion of participants with stabilization or improvement in change from Baseline to Week 26, 52, 65 and 78 in plasma NfL levels

3.2.6. Pharmacokinetic Endpoints

- To evaluate plasma concentration of pridopidine and its main metabolite at Weeks 26, 52, 65, and 78. For Week 78 analysis include participants' who had their EoS visit between Week 65 and 78.
- To study the relationship between plasma concentration of pridopidine and clinical outcomes including change from Baseline in UHDRS-TFC, UHDRS-TMS, Q-Motor, cUHDRS, SDMT, and SWR.

3.2.7. Safety Endpoints

Safety endpoints will include the following:

- Incidence of AEs and SAEs throughout the study
- Changes from Baseline and absolute thresholds as per ICH E14 in QTcF and other ECG parameter assessments throughout the study
- Change in clinical safety laboratory tests (serum/blood chemistry, hematology, and urinalysis) and summary of abnormalities throughout the study
- Changes from Baseline C-SSRS throughout the study
- Change in vital signs and summary of abnormalities throughout the study
- Abnormalities in Physical Exam
- Abnormalities in Neurological Exam

3.2.8. Tolerability Endpoints

Tolerability endpoints will include the following:

- The number (%) of participants who complete the treatment period on study drug
- The number (%) of participants who failed to complete the treatment period on study drug due to an AE
- The number (%) of participants who fail to complete the treatment period due to QTcF, CrCl or Psychiatric Stopping Rules

3.3. Sample Size and Power Considerations

Based on experience with early HD participants in the prior Phase 2 PRIDE-HD study, we expect the difference in mean change from Baseline to Week 65 between the 45 mg bid treated and placebo groups to be 0.7 points on the UHDRS-TFC with a standard deviation (SD) of 1.9 points.

A total sample size of 372 participants will provide 94% power to detect a between-group difference of 0.7 points in the mean change from Baseline to 65 weeks in the UHDRS-TFC score, with an SD of 1.9 points, using a two-tailed t-test at a significance level of 0.05. Assuming a drop-out rate of 22.5%, a total of 480 participants will be randomized. The sample size was calculated using SAS version 9.4 PROC POWER.

Based on feedback from Regulatory Authorities, the power assessment was updated as below. Assuming a dropout rate of 22.5 % in each treatment group early in the study, 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, we anticipate a difference in change from Baseline to imputed values at Week 65 for this group 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).

3.4. Randomization and Blinding

Randomization will be used to avoid bias in the treatment assignment, to increase the likelihood that known and unknown attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons.

Participants who meet eligibility criteria will be randomly assigned at Baseline (Visit 2) to receive pridopidine or placebo in a 1:1 randomization using an Interactive Response Technology (IRT), based upon the stratification variables of HD stage (HD1 or HD2) and use of neuroleptics (Yes/No).

This is a double-blind study where all participants, site staff, Sponsor, Clinical Research Organizations (CROs) and vendors involved in the conduct, data management or analysis of the study will remain blinded to treatment assignments. At the End of the Main Study when the last participant has completed the Week 65 visit or has withdrawn from the study, following database lock, the treatment assignment will be unblinded for analysis.

The exceptions to above blinding are the unblinded statistician and programmer who will generate the analyses for the SMC and will not otherwise be involved in the trial, the vendor personnel responsible for configuration of the IRT system, and the drug packaging and labeling team (unblinded personnel) who will distribute the pridopidine or placebo drug. Each of these groups will have standard operating procedures (SOPs) or study specific plans in place for maintaining the treatment blind. 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 system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the responsibility, after consultation with the medical monitor, 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 blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable. The responsible CRO will also be notified immediately of such unblinding without revealing details of the participant's treatment.

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 a blinded or unblinded fashion according to local regulations. The Sponsor will submit SUSARs to Investigators in a blinded fashion. Details of how the blind is maintained during PK analysis will also be included in the blinding/unblinding plan.

3.5. Sequence of Planned Analyses

3.5.1. Interim Analyses

No interim analysis is planned for this study. The analyses after the last participant completes Week 65 will be considered the final analyses of the Main Study. See Section 3.5.3 below.

3.5.2. Analyses for Safety Monitoring Committee Meetings

During the conduct of the Main Study, an independent SMC will be monitoring the safety, tolerability and/or efficacy (if needed).

Details of what data will be reviewed and when during the study will be included in the SMC Charter.

3.5.3. Analyses and Reporting of Main Study Results

All final, planned Main Study analyses specified in this SAP will be performed only after database lock for the Main Study after the last participant has completed the Main Study. The randomization codes will not be unblinded until this SAP has been finalized and the database locked.

The Main Study is considered to be complete when all participants who have signed informed consent, been randomized, and treated have completed at least Week 65 of the study or discontinued from the study earlier.

The regulatory submission will be based on the analyses of Main Study data. OLE analyses as planned in Section 3.5.4 will be provided as update materials after submission.

3.5.4. OLE Analyses

OLE analyses on the data collected during the OLE period will NOT be performed at the database lock for the Main Study. The final analyses for the OLE will be performed after the last participant has completed the EoS Visit and the database has been locked for the OLE period. The analyses will be used to assess the durability of treatment effect, safety and tolerability of pridopidine during the OLE period.

Interim analyses may be performed on OLE data prior to completion of the OLE.

Analyses using external controls such as data collected in ENROLL-HD, a longitudinal, multinational, observational registry study may be performed to contextualize the long-term effect of pridopidine on treating HD in OLE period. These analyses, if required, will be detailed in a separate SAP.

3.5.5. Other Analyses

Additional analyses may be added to this SAP which will be included in an Amendment, Appendix or Addendum.

Any exploratory analyses completed to support study analyses, which were not identified in this SAP or an Amendment, Appendix or Addendum prior to locking the database and unblinding the study, will be documented and reported in changes to the planned analyses section in the CSR.

3.6. COVID-19 Mitigation

The PROOF-HD study is being conducted during the COVID-19 pandemic and incorporates several mitigation strategies that are included in the protocol and study plans. For details, refer to the protocol Section 10.10. A brief summary is included below:

- Four (4) pre-planned virtual visits (VVs) have been incorporated into the protocol at different timepoints (performed via telephone)
- Every in-clinic visit, except Screening, Baseline, and Week 65 visits, can be converted to a VV if required (performed via telephone, smart phone, tablet or computer and home assessments by healthcare professional)
- Raters will be trained and ready to implement pre-identified remote efficacy and safety measures via telephone (see Table 3) during the pre-planned VV and during the converted VV
- Home visit by healthcare professionals will perform essential safety assessments (safety labs, urinalysis, pregnancy test, vital signs, and drug accountability) if clinic visits are converted to VVs

3.6.1. Types of Visits

- **In-Clinic Visits** – Screening, Baseline, W4, W26, W39, W52, W65, W78 (EoS/ET)
- **Pre-Planned VVs** – at Baseline, W13, W32, and W58
  These have been included as a contingency plan for the integrity of the study primary endpoint and several secondary endpoints
- **Converted VVs –** In-Clinic Visits that can be replaced by VV if necessary – W4, W26, W39, and W78

Table 3: Visit Activities According to the Visit Types

Study Period Procedures and Assessments	In- Clinic Visit	Pre-planned Virtual Visits (Phone)	Converted VV (Home/Phone)
Informed consent	√	X	X

Study Period Procedures and Assessments	In- Clinic Visit	Pre-planned Virtual Visits (Phone)	Converted VV (Home/Phone)
Demography	√	X	X
Medical and psychiatric history	√	X	X
Prior medication and treatment history	√	X	X
Inclusion and exclusion criteria		X	X
Clinical laboratory tests (serum chemistry, hematology, and urinalysis)*	√	X	√ (Home Nursing Service)
Pregnancy test (for WOCBP)*	√	X	√ (Home Nursing Service)
Full physical and neurological examination	√	X	X
Brief physical examination	√	X	X
12 lead ECG	√	X	X
Vital signs*	√	X	√ (Home Nursing Service)
C-SSRS (baseline version)	√	X	X
C-SSRS (since last visit version)	√	√	√ (Phone)
UHDRS-TFC*	√	√	√ (Phone)
UHDRS-TMS	√	X	X
UHDRS-IS	√	X	X
SDMT	√	X	X
SWR	√	X	X
Q-Motor	√	X	X
PBA-s (Short Form)	√	√	√ (Phone)
CGI-S (modified)	√	X	X
CGI-C	√	X	√ (Phone)
HDQoL-P	√	X	√
Benzodiazepines and antidepressants inquiry	√	√	√ (Phone)
Alcohol/illicit drug use inquiry	√	√	√ (Phone)
Review of tolerability to study drug prior to dose escalation	√	X	X
Randomization	√	X	X
Dispense/collect study drug*	√	X	√ (Qualified provider)
Review study compliance and adherence*	√	X	√ (Home Nursing Service)
Adverse event inquiry	√	√	√ (Phone)

Study Period Procedures and Assessments	In- Clinic Visit	Pre-planned Virtual Visits (Phone)	Converted VV (Home/Phone)
Concomitant medication inquiry	√	√	√ (Phone)
Blood samples for PK analysis	√	X	X
Plasma sample for biomarker analysis	√	X	X
Blood sample for genetic analysis	√	X	X
ECG	√	X	X

X- assessment not done √- 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.

3.6.2. Other Mitigation Strategies Incorporated

- A customized guidance to address global health emergencies and potential impact on the clinical study is included as an appendix to the protocol Section 10.10. The guidance also covers the following:
  - Consent can be given orally/remotely by the study participant
  - Study participant and person obtaining consent can sign two separate consent forms
  - Local laboratory may be used for safety labs if necessary
  - Monitoring activities may be adjusted (central monitoring, off-site monitoring, remote source data verification)
  - Prilenia and the Huntington Study Group (HSG) will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risk to the study participants and whether it is feasible to mitigate these risks by amending the study protocol and/or procedures

3.6.3. Mitigation Strategies for Analyses of Primary and Important Secondary Efficacy Endpoints

The impact of COVID-19 resulting in treatment discontinuation is described in Section 7.1 and elsewhere in the SAP for estimand and sensitivity analyses under the ICH E9 R(1) framework and related publications[2,3,4] (Akacha et. al., 2020; Meyer et. al., 2020). As of the SAP Version 2.0 update in November 2022, due to the minimal impact of COVID-19 on the efficacy endpoints as detailed in below sections, no additional efficacy analyses will be performed to address COVID-19 impact.

[2] ICH E9 R(1) "Addendum on Estimands and Sensitivity Analysis In Clinical Trials to the Guideline on Statistical Principles For Clinical Trials." May 2021 ICH Revision 1.
[3] FDA Guidance on Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency. Guidance for Industry, August 2021. https://www.fda.gov/media/139145/download.
[4] FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, Guidance for Industry, Investigators, and Institutional Review Boards, March 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

3.6.3.1. Evaluation of the Correlation Between In-clinic UHDRS-TFC Assessment and Phone (virtual) UHDRS-TFC Assessment

In SAP v1.0, it was stated that blinded analyses will be performed to assess reliability of the virtual UHDRS-TFC by computing the intra-class correlation coefficient (ICC) assessed at Baseline in-clinic and virtually over the telephone at VV1, and that if the ICC is shown to be ≥0.80, the last available virtual UHDRS-TFC assessments may be used for participants who discontinue prior to Week 65 or do not have an assessment at Week 65.

However, based on the observed high completion rate (98.9%) of in-clinic UHDRS-TFC assessments as of October 2022, the COVID-19 impact is expected to be minimal. There also may exist some heterogeneity if combining in-clinic and virtual visits as they are conducted in general 6 to 7 weeks apart. Furthermore UHDRS-TFC virtual assessments have not been previously validated. Therefore, only the in-clinic UHDRS-TFC will be used for primary and secondary analyses. Additional exploratory efficacy analyses using virtual UHDRS-TFC will be presented.

It was also stated in SAP v1.0 that if the number of participants who either discontinue from the study or have their Week 65 assessments impacted by COVID-19 was larger than planned, a blinded sample size re-estimation analysis may be conducted. Due to low discontinuation rate and minimal impact of COVID-19 on Week 65 UHDRS-TFC assessments, the blinded sample size re-estimation will not be performed.

3.6.3.2. Impact on Secondary Endpoints

As of October 2022, the completion rate of scheduled assessments is >97% for cUHDRS and TMS. The COVID-19 impact on secondary endpoints is also minimal.

3.6.4. Impact on Protocol Safety Assessments

The impact of COVID-19 on protocol deviations (PDs), medications taken, AEs and other key safety data will be summarized descriptively in corresponding safety analysis.

4. POPULATIONS /ANALYSIS SETS

4.1. Analysis Populations for the Main Study Period

The populations below are defined using the traditional approach as per ICH E9. The exact handling of intercurrent events (ICEs) for each of these are detailed further in Section 7.1 using the estimand framework per ICH E9 R(1).

4.1.1. Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will include all randomized participants. In this population, treatment will be assigned based on the treatment to which participants were randomized, regardless of which treatment they actually received. The ITT population is the main analysis population of primary endpoint for European Medicines Agency (EMA) submission.

4.1.2. Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population is a subset of the ITT population and will include all participants in the ITT population who received at least 1 dose of study drug and have valid in-clinic TFC scores both at Baseline and at least 1 post-baseline timepoint. The mITT population will be analyzed according to the treatment to which the participant was randomized. The mITT population is the main analysis population for primary endpoint in non-EMA submission. For all other efficacy analyses, the mITT population is the main analysis population in both EMA and non-EMA submission.

All participants who received at least 1 dose of pridopidine and have at least 1 valid in-clinic UHDRS-TFC score during the OLE period will be included in the OLE mITT population.

4.1.3. Per Protocol Week 65 (W65PP) Population

The per protocol Week 65 (W65PP) population is a subset of the mITT population and includes all participants who have a valid UHDRS-TFC at Week 65, were on study drug with compliance >80% during the study, and did not have any important PDs (document of PDs resulting in exclusion from PP population) or other events (e.g., receipt of incorrect treatment) impacting the TFC assessment. The W65PP population will be used for sensitivity analysis of the primary and select secondary endpoints at Week 65, and will be analyzed according to the actual treatment received (See Section 4.1.5 for definition of actual treatment). The W65PP population will be finalized prior to locking the database and unblinding the study.

4.1.4. Per Protocol Week 78 (W78PP) Population

The per protocol Week 78 (W78PP) population is a subset of the mITT population and includes all participants who have a valid UHDRS-TFC at Week 78, were on study drug with compliance >80% during the study, and did not have any important PDs (document of PDs resulting in exclusion from PP population) or other events (e.g. receipt of incorrect treatment) impacting the TFC assessment. The W78PP set will be used for sensitivity analysis of secondary endpoints at Week 78, and will be analyzed according to the actual treatment received (See Section 4.1.5 for definition of actual treatment). The W78PP population will be finalized prior to locking the database and unblinding the study.

4.1.5. Safety Population (SP)

The safety population (SP) will include all randomized participants who received at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment participants actually received, regardless of the treatment to which they were randomized. The safety set will be used for safety analyses and biomarker analysis.

All participants who receive at least 1 dose of pridopidine during the OLE period will be included in the OLE safety population.

The actual treatment received in the double-blind period will be pridopidine if a participant receives pridopidine for >10% of total number of doses received; otherwise, the actual treatment will be placebo. The actual treatment received in the OLE will be pridopidine to pridopidine if a participant receives pridopidine for >10% of total number of doses received in the double-blind period; otherwise, the actual treatment will be placebo to pridopidine.

4.1.6. PK Population (PKP)

The PK population (PKP) will include all randomized participants who received at least 1 dose of pridopidine and have at least 1 valid PK assessment. In this population, treatment will be assigned based upon the treatment participants actually received, regardless of the treatment to which they were randomized. This PKP will be used for all PK analyses.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

This section addresses the definitions, algorithms, imputations, and conventions that will apply to the analysis and handling of the data in general. Rules that are data specific will be addressed in the detailed discussions of individual sections below. This SAP and all Tables, Figures and Listings (TFLs) created will use U.S. spelling.

All changes to this SAP prior to locking the database and unblinding the study will be documented in an Addendum.

Any additional analyses performed or changes to the SAP and Addendums after unblinding the study will be described in the CSR under the section "Changes to Planned Analyses".

5.1. General Summary Tables, Figures and Individual Participant Data Listing Considerations

Summary tables and listings (e.g., post text tables and individual participant data listings are prepared according to ICH Guideline E3) will include a "footer" providing explanatory notes that indicate as a minimum (1) Date and time of output generation; (2) SAS program name, including the path that generates the output; (3) Any other output specific details that require further elaboration; (4) Page number in the format of Page X of Y.

Summary tables will include reference(s) to the participant data listing(s) to support the summary data. The data extraction date links the output to the archived database that is frozen to ensure the replication of the results.

For the Main Study, summary tables will display the 2 treatment groups, "Placebo" and "Pridopidine 45 mg bid". An overall total column will be included, where appropriate.

Unless specified, row entries in summary tables are always displayed for every category even if no data exists for any participants (e.g., a row with all zeros will appear). The summary tables will clearly indicate the number of participants to which the data apply along with an indication for the number of participants with missing data.

If no data exist for any participants for a given Table or Listing, a text will be displayed to indicate why there is no data.

In summary tables for medications, medical conditions and AE verbatim (reported) terms are coded to preferred terms (PT) and body/organ systems are coded per standard dictionaries mentioned in Section 5.3.

All relevant data collected in the study will be presented in individual Participant Data Listings (unless agreed to with the agency to not create certain listings, e.g., Laboratory listings, which tend to be very large). All listings will include participant ID and treatment group. Where applicable, listings will also include visit number, visit date, and days relative to the initiation of treatment. Individual participant data listings, at a minimum, are sorted by Treatment, Participant ID, Assessment and Visit (Week), as applicable.

Relevant data derived for analyses will also be included with the raw data in the listings .

Supporting figures may be generated for key tables.

5.2. General Post Text Summary Table and Individual Participant Data Listing Format Considerations

The default convention is to number tables and listings using a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with 2 or more numbers separated by 1 or more decimals digits (e.g., Table WW.XX.YY.ZZ).

1. The first level number will be consistent with the corresponding CSR appendix in which the tables or listings will appear. For example, the post-text tables usually occupy Appendix 14 and the individual participant data listings are in Appendix 16.2. All post-text tables should have a main number level 14 and listings should have a main number level 16.2. The disposition table is usually first in the first section of the report and will be numbered Table 14.1.
2. Participant accounting, final disposition and Baseline and demographic profile should appear as the second level number. Efficacy Tables would be next (14.2 series) followed by safety (Table 14.3 series).
3. The Table/Listings title should be unique, complete, accurate, and concise. The last line of the title should provide the analysis group being summarized (e.g., ITT population, mITT population, or safety population). If possible, the units of measurement for data contained in the table can appear in parentheses to conserve space in the body of the table. For example, the summary of vital signs title could read "Summary of Sitting and Standing Blood Pressure (mmHg) and Heart Rate (HR) (bpm)." Whether in the title, footnotes or body of a table or listing, units must always be specified for all appropriate data unless obvious.
4. If possible, variables being summarized, and statistics reported should appear in the left most column of a table. The next columns would be for the assessment, then the visits followed by treatment groups for the placebo, pridopidine, and (optional) all participants, respectively.
5. The definition of all relevant derived variables and decodes for coded data must appear on the Table and Listings. Tables and Listings should be self-contained and all-relevant information to review the Table or Listing will either be in the titles, column or row headers, or in footnotes.

5.3. Data Management

Data from the study will be entered into the EDC system TrialMaster version 5.0 (https://www.anjusoftware.com/solutions/clinical-trials/trialmaster), a validated electronic 21CFR Part 11 compliant EDC system. Data review, coding, and logic, range, cross-form, and consistency checks will be performed to ensure quality of the data[5]. AEs and medications will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 (or a later version if updated during the study) and the World Health Organization Drug Dictionary version March 2020, B3 (or a later version if updated during the study), respectively.

[5] Guidance on the Management of Clinical Trials During the COVID-19 (coronavirus) Pandemic, Version 5, 2 Oct 2022. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

5.4. Data Presentation Conventions

Continuous variables (e.g., age) are summarized using descriptive statistics (the number of participants with available data, the mean, SD, first quartile (Q1), median, third quartile (Q3), minimum and maximum). Categorical variables (e.g., race) are summarized using counts and percentages. Percentages are calculated using the total participants per treatment group with available data (overall or within relevant subgroup when appropriate). Summaries for discrete variables will include frequencies and percentages. Unless obvious, denominators used for computation of percentages will be indicated in footnotes on tables.

The following conventions will be applied to all data presentations and summaries.

- For continuous variables, all mean, Q1 (25th percentile), median and Q3 (75th percentile) values are formatted to one more decimal place than the measured value. SD values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value. This rule may be modified to fit data in a given table as long as the data displays relevant decimal places for interpretation of results.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses and will be rounded to one decimal place.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- Wherever possible, data will be decimal-centered, or left aligned as appropriate to best display the data and column headers. Parentheses will also be aligned appropriately for best display. This will be detailed in the mock shells.
- P-values, if applicable, will be presented to 4 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.
- Summaries of clinically significant abnormal values will include all post-baseline values (including scheduled, unscheduled, and ET visits).
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

5.5. Derivation and Transformation on Data

5.5.1. Baseline Values

Two baselines (Main Study and OLE baselines) are defined as below. Both baselines can be used to analyze data collected during OLE period. Only Main Study Baseline will be used to analyze data collected during Main Study portion.

5.5.1.1. Main Study Baseline

The Main Study Baseline value for efficacy and safety is the last non-missing observed data prior to the first dose of study drug. Since per SoA all Baseline Visit (V2) assessments (except

post-dose ECGs at V2) are performed and recorded prior to participants taking their first dose of study drug, the baseline value will include observations on or prior to the date of first dose of study drug. For ECGs, the Baseline value is the average of the 3 (triplicates) ECGs performed at Baseline before first drug administration.

5.5.1.2. OLE Baseline

OLE Baseline is defined as the last non-missing observed data prior to the first dose of pridopidine in the OLE period. In general, the OLE Baseline will be the OLE Day 1 assessment. For ECGs, the OLE Baseline value is the average of the 3 (triplicates) ECGs performed at OLE Day 1 visit before first drug administration.

Change from Baseline analysis of ECGs will be performed using Main Study or OLE Baseline as appropriate.

5.5.2. Baseline Age

Due to data protection requirements only year of birth and age at time of signing consent will be captured on the eCRF and no computation of age will be necessary.

5.5.3. Study Day and By-Visit Summaries

If the date of interest (date of visit, date of start of medication, date of AE, etc.) occurs on or after the first dose date then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date, then study day will be calculated as (date of interest – date of first dose). Study Day 1 is the date of first dose and as per CDISC Study Data Tabulation Model Implementation Guide (SDTMIG) 3.2 requirements, there is no Study Day 0.

For by-visit summaries and/or statistical models for efficacy, ET visit for a specific measure will be assigned to the next closest non-missing planned scheduled visit of this measure.

5.5.4. Change and Percent (%) Change from Baseline

Observed change in values from Baseline (i.e., Day 1) is calculated as (post-Baseline result – Baseline result).

Observed % change in values from Baseline is calculated as [100*(post-Baseline result – Baseline result) / (absolute value at Baseline result)].

If either the Baseline or the post-baseline result is missing, the observed change from Baseline is set to missing as well. If the Baseline result is missing or 0, or if the post-baseline result is missing, then observed % Change from Baseline will be set to missing at that visit.

For UHDRS -TFC and other efficacy assessments, change from Baseline will be calculated for scheduled in-clinic visits at Weeks 26, 39, 52, 65, and 78. For other efficacy and safety endpoints, change or % change (where applicable) from baseline to post-baseline visits will be calculated per SoA.

5.5.5. End of Study Definition

End of the Main Study occurs when the last participant has completed the Week 65 visit or has withdrawn from the study. At End of the Main Study, a participant should have either completed the double-blind period between Week 65 and Week 78 or discontinued early from the study.

End of OLE is defined as having occurred when the last participant completes the OLE period of the study or has withdrawn from the study during OLE period.

5.5.6. Last Study Drug Date for the Main Study Analyses

For participants that continue beyond Week 65, the last study drug date for the Main Study analyses will be derived from the last date of study drug administration on the eCRF page, End of Treatment, in the Main Study.

5.5.7. Study Periods

End of Study Day for each participant

End of the Main Study Day (double-blind period) for a participant is defined as the Main Study EoS/ET Visit, or last follow-up safety visit or phone call in the Main Study. **End of OLE Day** for a given participant is defined as the last follow-up safety visit or phone call for final data collection in the OLE period.

A participant is considered as a **Week 65 Completer (Main Study Completer)** if he/she has completed the Week 65 Visit without discontinuing earlier, regardless of whether they were on or off study treatment at Week 65. As per the study design, these participants may have completed visits beyond Week 65.

Treatment periods

Main Study Treatment Period is defined as the period from the first dose to the End of the Main Study Day. **OLE Treatment Period** is defined as the period from 1 day after End of the Main Study Day to End of OLE Day.

5.5.8. Visit Windows

The visit windows for the study are as defined in the protocol. The by-visit analyses will be based on nominal scheduled visits without using the unscheduled visits. Since the evaluation of study drug is for chronic use and using an endpoint that changes over a long term, delayed visits or visits occurring outside of the specified window are likely to have a minimal impact on analyses.

5.6. Multiple Comparisons and Multiplicity

The primary efficacy endpoint, key and other secondary efficacy endpoints will be tested sequentially in the order specified in Section 2 to account for multiplicity and preserve overall Type I error. Each test will be at a type I error level ≤ 0.05, two-sided to preserve the overall Type I error (first test of primary efficacy is conducted at 0.05). As soon as a given test yields a p-value >0.05, all subsequent tests following it will be considered nominal p-values.

No adjustments will be made for multiple comparisons in testing other exploratory efficacy endpoints.

5.7. Analysis by Region and Pooling of Countries with Low Number of Participants

Analyses will be adjusted for region (North America and Europe) as a covariate. Since every country had 9 or more participants, no pooling of subjects is planned for any analyses conducted by country unless otherwise specified. No analyses by center are planned. However, if these are required to be conducted by regulatory authorities, centers with too few participants will be pooled.

5.8. Missing Data and Unscheduled Visits

5.8.1. Missing Efficacy Endpoints

Efficacy variables will be handled using the estimand framework detailed in Section 7.1.

5.8.1.1. Missing Baseline Value

Missing Baseline values for efficacy endpoints will not be imputed for analysis based on observed data since there are only a few participants (<5) missing any baseline efficacy endpoints.

Missing Baseline covariate variables used as covariates in analysis models such as Mixed Model Repeated Measures (MMRM) will be replaced using mean imputation. Since the participants are randomized at Baseline to help ensure balance between treatment groups, the missing values will be imputed by the mean values, as calculated from a regression model with pooled non-missing values for the Baseline variable from both treatment groups as dependent variable adjusting for the randomization stratification factors. For binary variables, coded 0 or 1 for example, the imputed mean will be rounded up to 1 or down to 0, whichever is nearest.

5.8.1.2. Missing Post-baseline Efficacy Data

Missing data will be handled using statistical methods based on National Research Council's *The Prevention and Treatment of Missing Data in Clinical Trials*.

For an analysis with the MMRM model that uses restricted maximum likelihood for estimation, no imputation will be used, and the model will include all observed data to estimate the treatment effect of change from Baseline to Week 65 in UHDRS-TFC, under the assumption of missing at random (MAR).

To evaluate the possible impact of missing values on the primary and select secondary efficacy analyses, the method of multiple imputations (MI) will be used to evaluate the robustness of data assumptions, imputing data under MAR and missing not at random (MNAR), using different assumptions about the treatment effect for the unobserved data. Additional details are provided below.

Missing data are considered monotone if after a certain time point the data are no longer available. This happens when a participant discontinues from the study and there are no assessments after the last visit when the participant was assessed. It is expected that the great majority of missing data will have a monotone pattern. Different assumptions, such as MAR and MNAR, will be made on the monotone missing pattern to show the robustness of estimates. There is also some small amount of non-monotone missing data when there are intermediate time

points of missing data, such as due to missed visits, which will be assumed to follow MAR assumptions. Methods as described below will be adopted to estimate for both non-monotone and monotone missing data patterns.

- Imputation for non-monotone missing data pattern will be based on the initial imputation using Markov Chain Monte Carlo (MCMC) by generating 100 datasets with only monotone missing data. For participants with intermittent missing values, a monotone missingness pattern will be generated in each of the 100 datasets. This imputation step is based on the MAR assumption. In both methods below (under MAR or MNAR) the MI step will generate 100 complete datasets with no missing values.

MAR and MNAR imputation vary at the handling of monotone missing data pattern.

- Under the assumptions of MAR that missingness depends on the observed values and can be predicted based on a participant's observed data, the missing value will be imputed using monotone regression model. The imputation model will include Baseline and all post-baseline values for the efficacy endpoint to be imputed, treatment, randomization strata, and region. Multiple imputations will be performed to assign the response variable at consecutive study visits in a sequential manner for the monotone missing data pattern.
- Under the assumptions of MNAR that missingness depends on unobserved values and cannot be predicted solely based on a participant's observed data, the missing value will be imputed using a pattern-mixture model (PMM). In the PMM, the distribution of a response is modeled as the mixture of a distribution of the observed responses and a distribution of the missing responses. As the missing values for participants in the pridopidine group may imply these participants no longer receive the treatment, it is then reasonable to assume that the conditional distribution of the missing values, given observed data, is similar to that in the placebo group, and impute the missing values in pridopidine group based on the conditional distribution from the placebo group.

  This will be realized by PMM with control-based pattern imputation, a variant of the copy reference method (Little and Wang, 1996; Ratitch and O'Kelly, 2013). In this imputation approach, the model for missing observations is constructed from the observed data in the placebo group only, and then used as the imputation model for missing values in pridopidine and placebo groups. Following the chain-based imputations, multiply imputed datasets will be analyzed using the same MMRM as for primary analysis (Section 7.2).

At the last step, the estimates from all imputed datasets will be combined using Rubin's rule for an overall inference. SAS Procedures, MI, MIXED and MIANALYZE will be used for above steps.

5.8.1.3. Missing Item Scores in Derivation of Total Scale Score

5.8.1.3.1. Missing items on Unified Huntington's Disease Rating Scale – Total Functional Capacity(UHDRS-TFC)

A TFC is considered valid if all 5 domains are scored. If any item is left blank the TFC is considered missing.

5.8.1.3.2. Missing items on Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS)

If at least 16 out of the 31 items on the TMS are scored, the total TMS score will be computed the following way. The observed sum of score from the available items is divided by the total number of the available items, and then multiplied by 31 to get the overall TMS score. For example, if 20 items were completed with a score of 60, then TMS Score will be (60/20) x 31, or 93.

If there are more than 5% of all TMS assessments which required imputation per the above rule, then a sensitivity analysis will be performed excluding those TMS scores that required imputation of partial items.

5.8.1.3.3. Missing items on HDQoL and Other Subscale Scores

A similar approach as above will be used by which the score on missing items will be imputed using the average of the scores on items that were completed.

5.8.2. Missing Start and Stop Dates for Prior / Concomitant Medication, Medical History for HD Diagnosis and Adverse Events

Missing start or stop dates for prior/concomitant medications

The following rules will be used in this study to define concomitant for medications with completely missing start or stop dates:

- If both start and stop dates of a medication or therapy are completely missing, this medication or therapy will be considered both prior and concomitant.
- If the start date of a medication or therapy is completely missing and the stop date is on or after the date of the first dose date of study treatment, that medication or therapy will be considered both prior and concomitant.
- If the stop date of a medication or therapy is completely missing and the start date is after the first dose of study drug, that medication or therapy will be considered concomitant.

For medications with partial missing dates, following imputation rules will be used:

- For partial start dates, missing month will be imputed with January and missing day will be imputed with first day of the month.
- For partial stop dates, missing month will be imputed with December and missing day will be imputed with the last day of the month.

If a medication has a missing or partial missing start/end date or time and cannot be determined whether the medication is taken before first dose or concomitantly, it will be classified as both prior and concomitant.

Missing dates for Medical History for HD Diagnosis

In order to determine onset of symptoms data are collected for who first noticed symptoms (Participant, Family, Rater) and what the symptoms were (Motor, Cognitive, Psychiatric or Other). Since dates are not always exactly known a mid-point of interval rule will be used. If date is missing it will be assumed to be the 15th of the month, if month is missing it will assume

to be June (6th month). To compute the years since onset of HD symptoms the earliest of these dates will be used and subtracted from the screening date.

Missing start date for AEs

The treatment-emergent adverse events (TEAEs) are determined by the start date of the AEs. If the start date of an AE is completely missing, then the AE is considered as treatment-emergent. If the start date of an AE is partially missing, the AE start date will be imputed as follows:

- Missing day – Impute the 1st of the month. If the month and year of AE is same as month and year of the first dose of study drug, then impute first dose date, ensuring the AE is a TEAE.
- Missing day and month – Impute 1st January. If the year is the same as the year of the first dose date, then impute the first dose date, ensuring the AE is a TEAE.
- If AE start date is completely missing it will be set to the treatment start date.

5.8.3. Missing Demographics, Baseline Characteristics, Exposure or Safety Data

Only observed demographics, baseline characteristics, exposure, and safety data will be presented. No imputations will be performed. For efficacy analysis if a baseline covariate is missing it will be imputed as described in Section 5.8.1.

5.8.4. Unscheduled Visits

Summaries of efficacy data will only use data collected at scheduled visits, unless data is not available at the required post-baseline visit and the only available data is from an unscheduled visit close to the scheduled visit within an acceptable time window. If the unscheduled visit efficacy assessment is not within the acceptable window it will be ignored from the efficacy analyses, but will be identified in listings.

For descriptive statistics on continuous safety variables only data collected at scheduled visits will be used. For summary of abnormalities or shift tables all available data from scheduled and unscheduled visits will be used. Abnormality tables and shift tables will display the worst value across all visits, the last available non-missing value, and the values by scheduled visits. For shift tables, if there is more than one abnormality in the time period specified, the worst value will be used. When summarizing "worst" values if the participant had both a low and high value they will be included in both rows.

6. STUDY POPULATION

6.1. Participant Disposition

For Main Study analyses, all references to participant disposition, etc., refer only to the Main Study and exclude the OLE.

The number of participants who signed informed consent, or signed consent but were not randomized along with reason for screening failure will be summarized overall and by region and for select countries.

The number of participants included in each analysis population will be presented by treatment group. The participants who are excluded from each of the analysis population and the reason for exclusion (for example, exclusion from mITT population because they were not treated, or if they were treated but have no post-baseline in-clinic UHDRS-TFC assessment), will be summarized by treatment group. These participants will be identified in the listing of participants with populations in which they are included.

The end of the Main Study is reached when all participants who have signed informed consent, been randomized and treated have either completed through Week 65 or discontinued from the study (defined in Section 5.5.5). At the end of Main Study, the number of participants who completed the Main Study portion as well as those that withdraw from the treatment or study will be summarized along with the reason for withdrawal. The denominator for calculating the percentages will be the number of participants within the treatment group in the population being summarized.

In the OLE analyses, the numbers of participants who have enrolled in the OLE portion, who are included in each analysis population, who have completed the OLE, and who withdraw from the treatment or study along with the reasons will be summarized.

6.2. Demographics and Baseline Characteristics

Participant demographics and baseline characteristics will be examined to assess the comparability of the treatment groups. The continuous variables of participant age, weight, height, body mass index, efficacy and safety scales scores at Baseline will be summarized using descriptive statistics.

The categorical variables of participant sex, race, ethnicity, HD stage (HD1 or HD2) and use of neuroleptics will be summarized using count and percentages for each category.

Other baseline and disease characteristics may also be summarized.

A category will indicate participants with missing data.

Cytosine-adenosine-guanine (CAG) repeat length was reported by participants at Screening and recorded in the EDC. For participants who did not report CAG repeats, a plasma sample was taken and sent to a laboratory to determine the CAG repeat length. For participants whose CAG repeats were reported by both participant and laboratory, the value of CAG repeats as determined by the laboratory test will be used.

6.3. Participant Inclusion and Exclusion Criteria

Reasons for screen failure including inclusion and exclusion criteria not met prior to randomization will be listed for each participant.

6.4. Medical History

All medical history will be coded as per Section 5.3. Participants with a medical history assessment, by system organ class (SOC) and PT will be summarized. Participants are counted only once in each SOC and only once in each PT category. SOC and PT within SOC will be ordered by descending incidence of all participants.

6.5. Prior and Concomitant Medications / Therapies

All medications (both prior and concomitant) will be coded as per Section 5.3.

Prior medications will include all medications which had a start date prior to the first day of study drug treatment regardless of when it ended. This includes medications taken and stopped prior to V2 Baseline Visit (day of first study drug treatment) or started prior to V2 and continued to be taken on or after V2. Any medication given at least once after V2 will be defined as a concomitant medication.

Concomitant medications are defined as medications continued or newly received by the participants during Main Study Treatment Period or OLE Treatment Period (see definition in Section 5.5.7). If a participant took a medication during a specific Treatment Period, this medication will be attributed to the treatment the subject received during this Treatment Period. As a result, one medication could be attributed to both Main Study and OLE Treatment Periods for a participant. If missing or partial dates indicate a medication may have been taken after first day of study drug treatment, it will be considered a concomitant medication.

The incidence of prior and concomitant medication use will be separately summarized using descriptive statistics by WHO (ATC) anatomical therapeutic class and PT (Standardized Name) for each treatment group and overall in the safety population. Participants are counted only once in each therapeutic class category, and only once in each PT category.

Non-pharmacological therapies and procedures will be classified by MedDRA SOC and PT, and will be reported by treatment group and overall for the safety population.

A separate summary of prior and concomitant medications taken for COVID-19 symptoms, use of tetrabenazine and deutetrabenazine or antidepressants, may be presented separately by treatment groups.

6.6. Protocol Deviations

All-important deviations related to study inclusion or exclusion criteria, conduct of the trial, participant management or participant assessment will be summarized by site and grouped into different categories, such as:

- those who entered the study even though they did not satisfy the entry criteria
- those who developed withdrawal criteria during the study but were not withdrawn

- those who received the wrong treatment or incorrect dose
- those who received an excluded concomitant treatment

Additional details of reviewing and classifying PDs as important are detailed in the Protocol Deviation Management Plan.

In the CSR Appendix 16.2.2, individual participants with important PDs will be listed.

Final categorization of PDs will be done prior to database lock and unblinding.

Since this trial is being conducted during the COVID-19 pandemic, separate summaries of PDs related to COVID-19 were planned to be tabulated by treatment groups. However since there were no important PDs due to COVID-19 no separate Table was created. Additional analyses may also be conducted to see the impact of these deviations on interpretation of key safety or efficacy analyses. Since the impact of COVID-19 related events such as AEs, medications taken, etc., will not be fully known until the trial has progressed sufficiently, these will be finalized prior to locking the database and unblinding the study.

7. EFFICACY ANALYSIS

7.1. General

Study procedures and timing are summarized in the SoA (Table 1 - Main Study and Table 2 – OLE).

Efficacy analyses will be conducted using the estimand framework described in the ICH E9 R(1) Guidance and related publications[2]. The estimands will be described in detail in the endpoint analysis sections hereafter.

7.1.1. Intercurrent Events (ICEs) and Estimand Strategy

The ICEs considered for the PROOF-HD trial include treatment discontinuation due to, for example, death, AEs, progressive disease, or meeting Stopping Rules for QT/CrCl/psychiatric reasons.

If a participant has COVID-19 symptoms, their visit can be delayed within a reasonable period (up to 4 weeks) to perform UHDRS-TFC and other efficacy and safety assessments until after their COVID-19 symptoms have resolved. There is also a low likelihood of participants stopping study drug or discontinuing from study due to COVID-19. If intermittent efficacy assessments are missing due to COVID-19 impact, it will be handled by analysis, such as MMRM, under MAR assumptions[3].

Also, since pridopidine is taken over a long term (65 to 78 weeks) in the Main Study, temporary treatment interruptions are expected to have minimal impact on key efficacy endpoints.

ICH E9 R(1) describes five strategies to address ICEs (Mallinckrodt et. al., 2020; Ratitch et. al., 2020a and 2020b) which include:

(1) **Treatment Policy** (similar to ITT principle) where the ICE is ignored;

(2) **Composite** where the ICE is taken to be a component of the endpoint as in a responder analysis where participants who die due to disease progression are considered non-responders;

(3) **Hypothetical** where hypothetical scenarios are considered in which the ICE did not occur such as excluding observations where the UHDRS was measured while the participant was exhibiting COVID-19 symptoms;

(4) **Principal Stratum,** where the effect of the treatment is considered only in the stratum of interest such as excluding participants infected by COVID-19 anytime during the trial, and excluding participants on antipsychotics;

(5) **While on Treatment**, where the response to the treatment prior to discontinuing treatment is of interest.

For the PROOF-HD trial we will use the treatment policy, composite, hypothetical strategies, and/or a combination of strategies to address the specific impact of ICEs on efficacy.

Based on the regulatory feedback, the main estimand for the primary endpoint, change from Baseline in UHDRS-TFC at Week 65, will be defined separately for the EMA and non-EMA regions.

- For the EMA region, an estimand using a composite of treatment policy and hypothetical strategies is defined for the primary analysis. The treatment policy strategy will apply to all observed values including those collected after treatment discontinuation, and the hypothetical strategy will apply to missing values using PMM with control-based pattern imputation under MNAR assumptions (as described in Section 5.8.1.2).
- For the non-EMA regions, the primary analysis will be based on an estimand using treatment policy strategy, under which all observed data will be used regardless of occurrence of ICEs.

For the EMA region, the estimand applying treatment policy strategy (i.e., the primary estimand for the non-EMA regions) will be used as a supportive estimand, while for the non-EMA regions, the estimand applying a composite of treatment policy and hypothetical strategies (i.e., the primary estimand for EMA region) will be used as a supportive estimand.

The main estimands for secondary and exploratory endpoints will be the same for both EMA and non-EMA regions. The main estimand for key secondary endpoint, change from Baseline in cUHDRS at Week 65, will be based on treatment policy strategy and mITT population. The binary secondary endpoints, for example, the proportion of participants with improvement or no worsening in UHDRS-TFC, will use combined composite and hypothetical strategies for the main estimand. In this estimand, participants who discontinue the treatment due to disease progression-related death, or meet the Stopping Rules will be considered non-responders, while the participants who discontinue the treatment for other reasons will be imputed by hypothetical values from treatment discontinuation onward as if the participants had continued receiving the study treatment (MAR assumptions). A similar combined composite and hypothetical strategy estimand may be used for sensitivity analyses with MNAR MI under hypothetical strategy.

Other secondary and exploratory efficacy endpoints for both EMA and non-EMA regions, evaluated as changes from Baseline, will follow treatment policy strategy based estimand. Binary endpoints indicated for responder analyses will follow a similar estimand strategy as described above, where appropriate.

7.1.2. Analysis Populations

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.

7.2. Primary Efficacy Variable and Analysis

The primary efficacy variable for this study is the change from Baseline to Week 65 in the UHDRS-TFC. The calculation of the UHDRS-TFC is detailed in Appendix 12.1.1.

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.

Based on regulatory feedback, the hypothesis testing will be based on the main estimand separately defined for EMA and non-EMA regions.

For non-EMA regions, the main estimand is defined as **non-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 mITT 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 and placebo from MMRM model in change of UHDRS-TFC from Baseline to Week 65
- ICEs and Strategies for Addressing ICEs:

  Treatment policy strategy will be used to handle the ICEs, where occurrence of an ICE is irrelevant. All observed values will be used regardless of occurrence of an ICE. No imputation is performed.

Analysis will be performed on in-clinic observed data using MMRM. The model will include the following effects: treatment, Baseline UHDRS-TFC, region (Europe, North America), neuroleptic use (yes, no), Baseline HD stage (HD1 and HD2), categorical week, and treatment by categorical week interaction.

The unstructured covariance matrix for repeated observations within participants will be use. If the model does not converge, then a simpler covariance structure with fewer parameters will be used, and we will examine these structures in the following order based on the first structure below that converges:

1. Toeplitz with heterogeneity (TOEPH),
2. Autoregressive with heterogeneous (1) [ARH(1)],
3. Compound symmetry with heterogeneous variances (CSH),
4. Toeplitz (TOEP),
5. Autoregressive (1) [AR(1)], and
6. Compound Symmetry (CS).

Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation. The least square mean (LSM) and standard error (SE) of the LSM for each treatment group, the 95% CI and p-value for the comparisons (change from Baseline in pridopidine 45 mg bid vs. placebo) will be presented at Week 65.

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
- ICEs and Strategies for Addressing ICEs:

  ICEs 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 MI will be applied to impute the missing data using PMM with control-based pattern imputation under MNAR assumptions (details in Section 5.8.1).

Since UHDRS-TFC is used as a continuous variable in the MI procedure, the imputed values will take continuous values instead of the discrete values ranging from 0 to 13. To avoid the influence of extreme values outside the range, the continuous values will be categorized to 0 if the imputed values <0.5, and to 13 if the imputed values ≥ 12.5. All the other values in [0.5, 12.5) will be rounded to the nearest integer between 1 and 12.

The MI method uses SAS PROC MI and MIANALYZE to generate multiple complete datasets and combine the model results from them as described in Section 5.8.1. The LSM and associated SE for each treatment group, the 95% CI and p-value for the comparisons (pridopidine 45 mg bid vs. placebo) will be presented at Week 65.

In addition, actual observed values and changes from Baseline to each visit in the UHDRS-TFC will be summarized using descriptive statistics.

For all analysis at Week 65 only data through the Week 65 visit will be included.

7.3. Sensitivity Analyses for Primary Variable

7.3.1. Sensitivity Analyses Under Various Assumptions for Missing Values

The sensitivity analyses specific for non-EMA regions include the following supportive estimand:

- EMA-Estimand using MAR and MNAR MI methods using ITT population to impute the missing values

The sensitivity analyses specific for EMA region include the following supportive estimands:

- Non-EMA-Estimand using MMRM with mITT population
- EMA-Estimand using MAR MI methods to impute the missing values using ITT population

For both non-EMA and EMA regions, an estimand similar to EMA-Estimand with population changed to mITT population will be used for sensitivity analyses, and missing values imputed by MAR and MNAR MI methods separately.

7.3.2. Subgroup Analysis

The treatment effect of the pridopidine active group vs. placebo will be evaluated for the primary endpoint in participant subgroups according to the following variables at Baseline:

- Age categorized into three groups (<55, 55 to <65, and ≥65 years)
- Sex (Male vs Female)
- Randomization strata: HD stage (HD1 vs HD2)
- Randomization strata: Baseline neuroleptic use (Y/N)
- Region (North America, Europe)
- CAG repeats categorized into 2 groups by median Baseline CAG
- The CAG-Age-Product (CAP) score calculated as: age *(CAG – 33.66), and categorized into two groups by median Baseline CAP
- Four groups based on crossing median Baseline CAP and median Baseline age
- Baseline NfL categorized into 2 groups by median Baseline NfL
- Concomitant use of medication for Chorea management

Subgroup analyses by median will use the median in the ITT population irrespective of the population analyzed.

The primary model for subgroup analyses will contain main effects and 2-factor interactions Treatment x Week and Treatment x Subgroup to determine the p-value. The structure of the covariance matrix will follow the same approach as indicated for the primary endpoint. Assessment of impact of subgroups on efficacy will be evaluated by the interaction between Treatment x Subgroup.

For each subgroup (assuming not already in the primary model), the MMRM model under MAR will be estimated for each subgroup level to determine the treatment effect and CI. When analyzing HD1 vs HD2, the randomization stratification factor of HD stage will not be included in the MMRM model. The same applies to subgroups of neuroleptic use.

The LSM and SE of the LSM change from Baseline for each treatment group, and the 95% CI for the comparisons (pridopidine 45 mg bid vs. placebo) will be presented for each subgroup along with the p-value for the interaction term.

If a subgroup has <50 participants in any Treatment a subgroup analysis may not be performed since there would be less reliable comparison between the treatment groups.

7.3.3. Other Efficacy Analysis

To explore potential impact of other confounding factors on efficacy, the primary efficacy endpoint, select secondary and exploratory endpoints analyses may be conducted if there are enough participants in these cohorts.

Following sensitivity analyses may be performed, where applicable:

- Similar to non-EMA-Estimand with population changed to Week 65 PP Population
- Non-EMA Estimand with an additional covariate, CAP score, included in the analysis model
- EMA-Estimand with an additional covariate, CAP score, included in the analysis model
- A sensitivity analysis excluding those who had received any neuroleptics during the study that could impact efficacy may be performed.
- In addition, further sensitivity analysis may be conducted excluding those who had changes in neuroleptic use after randomization.

7.4. Multiplicity-Adjusted Secondary Efficacy Variable and Analysis

7.4.1. Key Secondary Efficacy Variable and Analysis

The key secondary efficacy variable is change from Baseline to Week 65 in cUHDRS. The null hypothesis is that pridopidine is no different than placebo in improvement of cUHDRS score at Week 65. The hypothesis testing will be based on the main cUHDRS estimand similarly defined as non-EMA-Estimand for primary endpoint (Section 7.2). Change from Baseline to Week 65 in cUHDRS will be analyzed using MMRM in the mITT population, under treatment policy strategy for handling missing data. The LSM and associated SE for change from Baseline in each treatment group, the 95% CI and p-value for the pridopidine treatment effect will be presented at Week 65.

The following sensitivity analyses will be performed for change from Baseline to Week 65 in cUHDRS:

- Analysis based on supportive estimand similar to EMA-Estimand for primary endpoint (Section 7.2) using MNAR imputation for missing values in the ITT population
- Analysis based on supportive estimand similar to EMA-Estimand for primary endpoint (Section 7.2) using MAR imputation for missing values in the ITT population
- Analysis based on supportive estimand similar to non-EMA-Estimand with population changed to W65PP population

7.4.2. UHDRS-TFC Response as a Binary Endpoint

The binary UHDRS-TFC response (yes or no) is defined as achieving improvement or no worsening in UHDRS-TFC score, i.e., change from Baseline to Week 65 in UHDRS-TFC ≥ 0

points. The responder analysis will be performed for the proportion of participants with change from baseline to Week 65 in UHDRS-TFC ≥0.

The hypothesis testing to compare the percentage of responders between the two treatment groups will be based upon the mITT population. Logistic regression will be used to analyze and compare the probability of whether a participant is a UHDRS-TFC responder or not. The model will adjust for Baseline UHDRS-TFC, region, Baseline randomization stratification factors of neuroleptic use (Yes/No) and HD stage (HD1 and HD2).

The hypothesis testing of the UHDRS-TFC responder analysis 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 points) 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 points) 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 7.2. 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 odds ratio (OR) of treatment effect (pridopidine 45 mg bid vs placebo) along with a 2-sided 95% CI and p-value will be presented. An estimate of OR >1 will indicate a beneficial treatment effect. Descriptive statistics and 95% CI using Clopper-Pearson will be provided for the observed proportions at each visit, along with the difference between treatment groups in the proportions and 95% normally approximated CI for the difference.

Following supportive estimands will be used to support the analysis of this secondary endpoint:

Supportive Estimand 1: similarly defined as the main estimand for UHDRS-TFC responder analysis, but with population changed to ITT population, and MNAR instead of MAR MI will be used under the hypothetical strategy.

Supportive Estimand 2: similarly defined as the main estimand for UHDRS-TFC responder analysis, but with population changed to ITT population.

Supportive Estimand 3: similarly defined as the main estimand for UHDRS-TFC responder analysis, but with ICE handling strategy changed to treatment policy strategy (using observed data without imputation).

Supportive Estimand 4: similarly defined as Supportive Estimand 3 for UHDRS-TFC responder analysis, but with population changed to W65PP population.

7.4.3. Other Multiplicity Adjusted Secondary Efficacy Variable and Analysis

For continuous endpoints such as change from Baseline using observed data only, the main estimand will be similar to the non-EMA-Estimand for the primary endpoint, analyzed using the mITT population with treatment policy strategy to handle ICEs. An MMRM model as described in Section 7.2 for the primary endpoint will be used with Baseline value of the analyzed variable replacing Baseline UHDRS-TFC as a covariate. For the specified visits, the LSMs, SE of the estimates, p-values, and 2-sided 95% CIs will be provided for the within treatment group changes from Baseline and for the comparison of change from Baseline between pridopidine and placebo.

Supportive estimands for continuous endpoints will be similar to the EMA-Estimand for the primary endpoint, with population as the ITT population and missing values imputed using copy reference method under MNAR assumption. Additional missing value imputation approach under MAR assumption may be used as a sensitivity analysis.

For analysis of change from Baseline in UHDRS-TFC at Week 78, main analysis will include observed values at scheduled visits up to 78 weeks. A sensitivity analysis for Week 78 endpoints will be performed with assessments between Week 65 and 78 mapped to Week 78.

For positive response defined using values of continuous variables:

- Unless otherwise specified, where a decrease reflects disease progression, a responder will be defined as those with no change or improvement (change from Baseline ≥ 0)
- Unless otherwise specified, where an increase in score reflects disease progression, a responder will be defined as those with change from Baseline ≤ 0

Main estimands for binary endpoints will be similar to the main estimand for the binary UHDRS-TFC response, analyzed in the mITT population and with ICEs handled by a combined composite and hypothetical strategy. Supportive estimand for the binary endpoints will be similar to Supportive Estimand 1 for the binary UHDRS-TFC response. All responder analyses or analyses of binary variables will be performed using logistic regression as indicated for the binary secondary variable above in Section 7.4.1.

The p-values from the main estimand will be used in the hierarchical testing for multiplicity adjusted secondary endpoints following the order described in Section 3.2.2.

Subgroup analyses as described in Section 7.3.2 for the primary efficacy endpoint will also be performed for the multiplicity adjusted secondary endpoints and log2-transformed NfL.

7.5. Non-Multiplicity Adjusted Secondary Efficacy Variable and Analysis

Other non-multiplicity adjusted secondary efficacy variables are listed and defined in Sections 2 and 3.2.3.

For all Q-Motor analyses [redacted] Analysis of Q-Motor [redacted]

For continuous variables, an MMRM model as described in Section 7.2 for the primary endpoint in mITT population will be used, with Baseline value of the analyzed variable replacing Baseline UHDRS-TFC as a covariate. For the specified visits, the LSMs, SE of the estimates, p-values, and 2-sided 95% CIs will be provided for the within treatment group changes from Baseline and for the comparison of change from Baseline between pridopidine and placebo. This will be repeated in W65PP or W78PP population depending on whether change to Week 65 or 78 is analyzed.

In addition, actual values and changes from Baseline to each visit will be summarized using descriptive statistics for each endpoint. The sub-scale scores of each endpoint will also be summarized where applicable.

The proportion of responders will be analyzed in a similar way to how the binary UHDRS-TFC response is analyzed for the main estimand and Supportive Estimand 1. Different thresholds than specified above may be explored. Descriptive statistics and 95% CI using normal approximation will be provided for the proportions at each visit. In order to minimize impact of outliers that may represent unrealistic changes in key endpoints, analyses using robust regression or other methods may be performed.

7.6. Other Exploratory Efficacy Variable and Analyses

Other exploratory efficacy variables include:

- Change from Baseline to Weeks 26, 52, 65 and 78 in PBA-s domains subscale scores and total scores
- Change from Baseline to Weeks 26, 52, 65 and 78 in HDQoL

These will be analyzed similar as described in Section 7.5 for non-multiplicity adjusted secondary efficacy variables in their main estimand.

Responder analyses for select efficacy endpoints, such as UHDRS-TFC and cUHDRS, using clinically meaningful thresholds may be performed.

In addition, the observed virtual UHDRS-TFC assessments at virtual Baseline, Weeks 13, 32, and 58 and change from virtual Baseline (Day -7 Visit) at each post-baseline virtual visit will be summarized.

The impact of PIN_{HD}, defined as prognostic index normed for HD, on treatment effects for select efficacy variables may be explored using categorized PIN_{HD} score, where $PIN_{HD} = (PI_{HD} - 883) / 1044$, and $PI_{HD} = 51 \times TMS + (-34) \times SDMT + 7 \times Age \times (CAG - 34)$, defined as prognostic index for HD (10).

Treatment effect on change from Baseline in weight over visits may also be explored adjusting for sex and age.

7.7. OLE Efficacy 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.

The OLE analysis will be presented using the following labels for treatment group, in the order displayed:

- Placebo bid (Main Study) to Pridopidine 45 mg bid (OLE)
- Pridopidine 45 mg bid (Main Study) to Pridopidine 45 mg bid (OLE)
- Total of above two groups (where applicable)

Proportion of participants with change of UHDRS-TFC from Main Study Baseline ≥-1 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 in Section 7.4.1. This analysis will be repeated using a threshold of 0 for proportion of participants with change of UHDRS-TFC from Main Study 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 as described below:

- Change from Main Study Baseline and the observed values of UHDRS-TFC, cUHDRS, UHDRS-TMS, and Q-Motor measurements at each OLE visit
- Change from OLE Baseline and the observed values of UHDRS-TFC, cUHDRS, UHDRS-TMS, and Q-Motor measurements at each OLE visit

In addition, the durability of treatment response to pridopidine in the OLE period will be assessed by the proportion of participants who continue to respond to pridopidine in OLE among the responders in double-blind treatment period. Responders defined using following endpoints will be assessed for the durability:

- Change from Main Study Baseline to Week 65 in UHDRS-TFC ≥0, and change from Main Study Baseline to each OLE visit in UHDRS-TFC ≥-1
- Change from Main Study Baseline to Week 65 in UHDRS-TFC ≥0, and change from Main Study Baseline to each OLE visit in UHDRS-TFC or ≥0
- Change from Main Study Baseline to Week 65 in cUHDRS ≥-1, and change from Main Study Baseline to each OLE visit in cUHDRS ≥-1.5

- Change from Main Study Baseline ≤0 in UHDRS-TMS at Week 65, and change from Main Study Baseline ≤0 in UHDRS-TMS at each OLE visit
- Change from Main Study Baseline ≤0 in Q-Motor [redacted] and change from Main Study Baseline ≤0 msec in Q-Motor [redacted] at each OLE visit

The Kaplan-Meier curve will be used to display by treatment group the distribution of time to first UHDRS-TFC worsening, defined as change from Main Study Baseline <-1, and no further UHDRS-TFC response (i.e. change from Main Study Baseline ≥-1) at subsequent visits after first UHDRS-TFC worsening. Time to first UHDRS-TFC worsening will be censored at the last available assessment in the OLE period if UHDRS-TFC worsening is not observed. Cox proportional hazards model will also be used to quantify the treatment difference in time to first UHDRS-TFC worsening with treatment group, region, and randomization stratification factors (HD stage and neuroleptic drug use) as the fixed effects. Hazard ratio of pridopidine vs placebo group will be displayed with 95% CI and p-value.

Other responder analyses for select efficacy endpoints in OLE period using clinically meaningful thresholds may be performed.

For pridopidine-to-pridopidine group in OLE mITT population, summary statistics will be presented for the observed values and change from Main Study Baseline in UHDRS-TFC, UHDRS-TMS, Q-Motor [redacted], and Q-Motor [redacted] in both double-blind and OLE periods. An MMRM model as described in Section 7.2 excluding treatment and treatment-by-visit effects will be used to fit the change from Main Study Baseline in these efficacy endpoints throughout Main Study and OLE Treatment Period. The LSM and 95% CI at each visit will be presented.

For placebo-to-pridopidine group in OLE mITT population, an MMRM model for Change from Main Study Baseline in UHDRS-TFC at each visit post Main Study Day 1 through Main Study and OLE periods will be used to estimate the gained treatment effect after switching to pridopidine treatment. The model will include fixed effects of treatment at each period (Main Study and OLE Treatment Period), randomization stratification factors (HD stage and neuroleptic drug use), categorical effects of study visit within each period (e.g., 26 weeks and 52 weeks within each period), interaction of treatment and visit within the period, and Main Study Baseline of UHDRS-TFC. The covariance structure for the MMRM model will be used similarly as described in Section 7.2. Mean difference in treatment effect at every 26 weeks receiving pridopidine 45 mg bid vs placebo will be presented along with 95% CIs and p-values.

For the exploratory endpoints in OLE, including CGI-C, PBA-s, HDQoL, SDMT, and SWR, the summary tables of observed values and change from Baseline over time will be provided by treatment group and OLE visit.

No imputation will be performed for the OLE analyses. Analyses using external controls may be performed to contextualize the long-term effect of pridopidine on treating HD in OLE period. These analyses, if required, will be detailed in a separate SAP.

8. SAFETY ANALYSIS

8.1. General

The SP will be used for all safety analyses based on the actual treatment received. AEs and SAEs will be collected from the Screening visit through end of the study period. Safety analyses will be presented separately for the Main Study and OLE according to the set of data associated with the two portions of the study.

Safety assessments will be summarized and listed for all data collected at in-clinic or VV (planned or converted).

8.2. Duration of Exposure

Duration of exposure to study drug (days treated) is the number of days on treatment based on the first and last days of treatment with the study drug (last day of study drug – first day of study drug + 1). In addition to summarizing overall treatment exposure in weeks, the weeks of exposure using the categories <13 weeks, ≥13 to <26 weeks, ≥26 to <39 weeks, ≥39 to <52 weeks, ≥52 to <65 weeks, ≥65 to <78 weeks and ≥78 weeks will be summarized using the number and percentage of participants exposed to study drug by treatment groups. In addition to the above intervals the number and percentage of participants exposed for ≥13 weeks, ≥26 weeks, ≥52 weeks, ≥65 weeks, ≥78 weeks will also be summarized.

Duration of treatment (days) will also be summarized by treatment group using descriptive statistics for continuous parameters as described in Section 5.4.

8.3. Study Treatment Compliance

Treatment compliance will be calculated using the following formula:

Compliance (%) = [Total number of doses taken Total number of scheduled doses] × 100

The total number of scheduled doses will be calculated based on the number of capsules planned for the days of exposure of each participant. The total number of doses taken will be calculated as the difference between capsules dispensed and capsules returned recorded for all bottles dispensed. For bottles that are lost and missing the counts of capsules returned, 50% compliance is assumed for each lost bottle (i.e., 30 capsules are taken). If a patient has completed or withdrawn from the study without returning any bottles at last visit in Main Study, 50% compliance is assumed during the period the capsules in these bottles are expected to be taken, i.e., from the bottle dispense date until the earliest of the day prior to next bottle dispensing visit, treatment completion date, or early withdrawal date. The compliance (expressed as %) will be summarized with descriptive statistics for continuous parameters by treatment group and overall.

The initial dose, titrations and Investigator-initiated dose changes that occur throughout the study as captured on the Dose Management Log and Missed Dose / Incorrect Dosing eCRF pages will be displayed in Listings.

The number and percentage of participants with compliance <80%, 80 to 100%, >100% will also be summarized by treatment group and overall.

8.4. Adverse Events

All AEs will be coded using MedDRA Version 23.0 (or a later version if updated during the study).

For statistical analysis, a TEAE is defined as an AE that occurs for the first time or worsens (as captured on the eCRF) on or after initiation of treatment in the corresponding analysis period (Main Study or OLE Treatment Period) EoS. Due to the short half-life of Pridopidine (10-12 hrs) AEs that started more than 14 days after end of treatment are not considered TEAEs.

The terms AEs and TEAEs are used interchangeably in this SAP and unless otherwise specified refer to TEAEs.

An overall summary will be presented by treatment groups that includes the number and percentage of participants who experienced at least one TEAE for the following categories: All TEAEs, serious TEAEs, TEAEs leading to study discontinuation, TEAEs leading to death, TEAEs based on maximal Severity, TEAEs leading to study drug withdrawal anytime during the study, TEAEs leading to study drug withdrawal during titration. When appropriate, a total column may appear as the last column.

Summaries will be presented for all TEAEs by SOC and PT for the following categories of TEAEs:

- TEAEs, severe TEAEs, Treatment-related TEAEs, Serious TEAEs (see below for more details), TEAEs potentially related to QT prolongation, (e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death), TEAEs related to abuse potential (See Appendix 12.2 for the AE terms), TEAEs causing discontinuation from the study.

The above summaries will include the number of events as well as number and percentage of participants experiencing at least one TEAE in each SOC and PT. To count the number of participants with any TEAEs, a participant who experiences multiple TEAEs within the same SOC will be counted only once for that SOC (if the TEAEs are coded to the same PT). A participant who experiences multiple TEAEs coded to the same PT within the same SOC will be counted only once for that PT. The number and percentage of participants experiencing any TEAE will also be provided. All percentages will use the number of participants in the SP within that treatment group as the denominator. In the summaries SOCs will be sorted in descending order based on number of participants in Total column; PT within SOC will be sorted by descending number of participants in Total column.

TEAEs will also be summarized by maximal severity. Summary table will include the number and percentage of participants experiencing at least one TEAE in each SOC, PT, and severity.

The relation of TEAEs to study drug will be summarized by their relatedness (related or not related).

Listings for deaths, serious TEAEs, and TEAEs leading to discontinuation will be presented.

8.5. Deaths

If any participant dies during the study all relevant information will be discussed in the participant's narrative included in CSR.

8.6. Clinical Laboratory Tests

All analysis of clinical laboratory tests will be performed using data from the central laboratory.

Summary statistics for chemistry, hematology, and urinalysis laboratory tests will be presented at Screening, Baseline, Weeks 4, 26, 39, 52, 65, and 78. All test results and associated normal ranges will be reported in the standard International System of Units (SI unit).

Continuous values will be summarized using descriptive statistics by treatment group. Laboratory parameters which have an upper and/or lower reference range: Number and percentage of participants with 6 categories (missing, clinically significant low, not clinically significant low, normal, not clinically significant high, clinically significant high) values at each visit for each parameter will be summarized by treatment group. If a participant has both low and high abnormalities, they will be displayed in both low and high categories based on worst low and worst high values.

Change from Baseline for continuous values will be summarized using both continuous summary statistics as well as shift tables based on normal ranges at each post-baseline visit.

Shift from Baseline (i.e., the distribution of the 5 response categories, category missing will be excluded for readability) tables will include shift from Baseline to each post-baseline visit and the worst post-baseline value across all visits.

The incidence of clinically significant (CS) abnormal values (defined in Table 4) will be summarized for laboratory data.

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 summarized.

Table 4: Criteria for Clinically Significant Laboratory Values

Laboratory Parameters	SI Units	Definition of Clinically Significant Values	
Serum Chemistry		**Low**	**High**
Liver Function			
Alanine aminotransferase (ALT)			>3 x ULN
Aspartate aminotransferase (AST)			>3 x ULN
Alkaline phosphatase (ALP)			>3 x ULN
Gamma-glutamyl transpeptidase (GGT)			>3 x ULN
Albumin	g/L	<31	
Lactate dehydrogenase (LDH)			>3 x ULN
Total bilirubin			>3 x ULN
Renal Function			
Bicarbonate	mmol/L	<18	
Blood urea nitrogen (BUN)	mmol/L		>14
Creatinine	µmol/L		>3 x Baseline
Creatinine clearance	mL/sec	<0.5 (<30 mL/min)	

General Chemistry			
Calcium	mmol/L	<2.0	>2.74
Chloride	mmol/L	<88	>112
Potassium	mmol/L	<3.4	>6.0
Hematology		**Low**	**High**
Hemoglobin (Males)	mmol/L	<7.76 (<12.5 g/dL)	>11.92 (>19.2 g/dL)
Hemoglobin (Females)	mmol/L	<6.83 (<11.0 g/dL)	>10.98 (>17.7 g/dL)
White blood cell counts (WBC)	10^9/L	<3	>20
Lymphocytes	10^9/L	<0.75	>10
Neutrophils	10^9/L	<1	
Eosinophils	10^9/L		>1.5
Platelet	10^9/L	<75	>700

Box plots will be presented for laboratory parameters listed in Table 4 by visit. Evaluation of drug-induced liver injury will be performed and displayed in eDISH figure which is a log/log scatter plot of peak total bilirubin vs ALT or AST, both in multiples of ULN, with horizontal and vertical lines indicating Hy's law thresholds (i.e., ALT=3 x ULN, AST=3 x ULN, and total bilirubin=2 x ULN).

8.7. Vital Signs

Summary statistics for vital signs will be presented at Screening, Baseline, Weeks 4, 26, 39, 52, 65, and 78.

The original protocol required triplicate measurements for blood pressure and HR. It was determined as a non-safety concern therefore this requirement was removed as part of a protocol amendment 6.0 dated 13 May 2021 to reduce burden on participants. Since up to triplicate measurements may have been collected, for descriptive statistics of actual values and changes from Baseline to each visit and assessment, multiple values around the same timepoint will be averaged.

Actual values and changes from Baseline to each visit and assessment will be summarized using descriptive statistics. The incidence of clinically significant abnormal values will be summarized for select vital signs using descriptive statistics.

Descriptive statistics for each orthostatic vital sign parameter (supine minus standing systolic blood pressure [SBP], and supine minus standing diastolic blood pressure [DBP]) at Baseline and over time will be presented by treatment group.

The incidence of orthostatic clinically significant abnormal values (defined in Table 5) will be summarized using descriptive statistics. Clinically relevant abnormalities will be summarized using two methods (a) the observed values and (b) both observed value and the change relative to Baseline.

A listing for clinically significant abnormal vital signs will be presented.

Table 5: Criteria to Determine Clinically Relevant Abnormalities in Vital Signs

Vital Sign	Observed Value	Change Relative to Baseline
Temperature	>38 °C	Increase of >1 °C
	<36 °C	
Heart rate	>100 beats per minute	Increase of >15 beats per minute
	<60 beats per minute	Decrease of >10 beats per minute
SBP	>160 mm Hg	
	>140 mm Hg	Increase of >15 mm Hg
	<90 mm Hg	Decrease of >15 mm Hg
DBP	>100 mm Hg	
	>90 mm Hg	Increase of >15 mm Hg
	<50 mm Hg	Decrease of >15 mm Hg
Body Weight		Increase of ≥7%
		Decrease of ≥7%
SBP Supine minus Standing	>20 mm Hg	
DBP Supine minus Standing	>10 mm Hg	

8.8. Electrocardiography (ECG)

8.8.1. ECG Measures Handling and Time Points

A single resting 12-lead ECG is conducted after at least 5 minutes of supine rest at Screening (Visit 0). If there is evidence of a prolonged QTcF interval at Screening (defined as a QTcF interval of >450 msec for men and >470 msec for women) then the ECG is repeated twice, and the mean of the 3 measurements will be used for the summary.

Planned timepoint ECG assessments are specified in the SoAs (Table 1 and Table 2).

If the local ECG reading results at the site match any of the below Stopping Rules, the participant should stop taking study medication until the central ECG reader's report is received. If the central reader does not report a QTcF interval that would lead to discontinuation according to the above, then the participant should restart study medication.

Participants should be discontinued from study drug if any of the following QTcF Stopping Rules are met at any visit:

- QTcF >500 msec (based on any ECG administration)
- QTcF >480 msec with concurrent increase in QTcF >60 msec (ΔQTcF, based on the mean value from ECG administrations) from Baseline (Day 1)

If the local ECG reading results at the site meet the Monitoring Rule (QTcF >480 msec or ΔQTcF >60 msec), the participant can continue the study drug per protocol until the central ECG reader's report is received. If central reader confirms meeting a Monitoring Rule, the participant will stay on study drug (per protocol) and will return for a follow-up ECG after 3-14 days. If at the follow-up ECG, QTcF change is confirmed (meets Monitoring Rule) then the participant will be discontinued from study drug.

8.8.2. ECG Parameters Data Presentations

Change from Baseline values will be calculated for each participant and visit as the value at the visit (averaged if measurements are taken in triplicate as described above) subtracted by the average Baseline value.

ECG data summaries and listings will include the following:

- The numbers and percentages of participants with the following clinically potential significant values will be presented at Baseline and each post-baseline visit:
  - Absolute QTcF values >450 msec; >480 msec; >500 msec
  - Change from Baseline in QTcF >30 msec; >60 msec

    For HR, PR and QRS use below:
  - HR: decrease of HR from baseline >10 bpm resulting in HR <60 bpm
    Increase of HR from baseline >15 bpm resulting in HR >100 bpm
  - PR: increase of PR from baseline >25% resulting in PR >200 ms
  - QRS: increase of QRS from baseline >25% resulting in QRS >100 ms

Data listing of these values together with Baseline value and change from Baseline will also be provided:

- The number of participants and percentages of ECG interpretation (Normal/Abnormal Not Clinically Significant, Abnormal Clinically Significant) as determined by the ECG Central Lab at each scheduled visit and time point as well as the shift table from Baseline to each post-baseline visit will be presented by treatment groups
- The number and % of participants with ECG alerts as determined by the ECG Central Lab will be presented by treatment groups
- Descriptive statistics and boxplots of quantitative 12-Lead ECG parameters (HR [bpm], QTcF [msec], QTcB [msec], QT [msec], PR [msec], QRS [msec] and RR [msec]) and changes from Baseline will be presented by scheduled visits, time point and treatment group
- Central ECG Review of abnormalities will be summarized.

8.9. Columbia-Suicide Severity Rating Scale (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". The C-SSRS Baseline version will be completed at Screening (Visit 0), while the C-SSRS Since Last Visit version will be completed as specified in the SoA (Table 1 and Table 2).

Summary statistics for the C-SSRS at each visit will be presented by treatment group using observed data. The Baseline value will be based on the closest non-missing recency score prior to first dose of study drug.

The number of participants evaluated and the number and percentage of participants with any positive report of Suicidal Behavior, Suicidal Ideation, and Suicidal Behavior or Ideation at Baseline and post-baseline visits will be presented by treatment group. A positive report of Suicidal Behavior or Ideation is defined as a "yes" response on any ideation item (positive Suicidal Ideation), or a "yes" response to any behavior item (positive Suicidal Behavior). The shift from Baseline will be summarized by (a) worst post-baseline value (b) Last observed non-missing post-Baseline value and then (c) at each post baseline visit. .

C-SSRS assessment results for each participant at each visit will be listed by treatment group using observed data. Both lifetime and recency scores at Screening Visit will be listed.

8.10. Pregnancy Test

Serum/urine pregnancy test results will be listed for women of child-bearing potential only.

8.11. Physical and Neurological Examination

The physical (full and brief) and neurological examination results, graded as normal or abnormal (or for some neurological examinations other categories are used such as hypoactive, hyperactive, etc.), will be summarized using counts and percentages at visits described in Table 1 and Table 2. Denominator for the percentages will be the number of participants in the treatment group.

9. PHARMACOKINETIC (PK), BIOMARKER (NFL) AND PHARMACOGENOMIC ANALYSIS

9.1. Blood Sampling and Handling

Blood samples for plasma concentration of study drug and its main metabolite (TV-45065) will be collected 1-2 hours after the dosing and after the ECG is administered as specified in Table 1 (SoA-Main Study). Samples for PK analysis will be analyzed for the concentration of pridopidine and its main metabolite TV-45065 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 study personnel until the study has been unblinded.

Samples for biomarker analysis of biomarker (NfL) will be collected as detailed in Table 1 (SoA–Main Study).

Sampling analyses for DNA extraction will be performed only once during the study, for future genetic analysis related to pridopidine response or HD.

Blood samples will always be collected after the ECG is administered (not before).

9.1.1. PK Analysis

PK assessments include plasma concentration of pridopidine and its main metabolite (TV-45065) at Weeks 26, 52, 65, and 78 and at last participants' visit.

All pridopidine and TV-45065 concentration data will be listed for participant at each visit and timepoint, including date and time of sample collection and elapsed time from last dose.

Descriptive statistics of plasma concentrations of pridopidine and TV-45065 as continuous variables additionally with geometric mean and coefficient of variation (CV) will be presented by treatment groups, scheduled visit and timepoint. For these summaries, values which are below lower limit of quantification (LLOQ) will be treated as zero; if the mean of the numbers is <LLOQ, the value would be reported as "BLQ" (below limit of quantification).

Additional PK samples collected in case of an SAE will be listed but not included in the summaries.

An exposure-response correlation between pridopidine plasma concentrations vs efficacy and safety measures (including QTcF), as well as exploratory analysis and additional covariate analysis may be performed and reported separately as applicable.

Additional PK analyses may be specified in a SAP addendum, or separate SAPs.

9.1.2. Biomarker (NfL) Analysis

Biomarker assessments include:

- 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 select efficacy endpoints for pridopidine 45 mg bid vs. placebo

- Proportion of participants with stabilization or improvement in change from Baseline to Weeks 26, 52, 65 and 78 in plasma NfL protein

Objectives of the NfL analysis

(1) To investigate the effect of pridopidine 45 mg bid vs. placebo on changes in log-transformed plasma NfL from Baseline to Weeks 26, 52, 65 and 78 (as pg/mL, with $\log_2$ transformation), accounting for the effects of Baseline NfL and other possible factors as listed below.

The main analysis is based on change from Baseline in $\log_2$(NfL) over time, and similar analysis will be repeated for actual values of $\log_2$-transformed plasma NfL levels. Analysis will be performed on observed data using MMRM separately for actual values and change from Baseline over time. The model will include the following fixed effects: *treatment*, *categorical weeks, Baseline* $\log_2$*(NfL), Age and BMI at Baseline*, randomization stratification factors (*HD stage and neuroleptic use at Baseline*), interaction effect of *treatment*categorical weeks*. The spatial power covariance matrix for repeated observations within participants will be used. The denominator degrees of freedom for the tests of fixed effects will be approximated by Kenward-Roger method.

Each fixed effect will be tested at a type I error level $\leq$0.05, two-sided and the 95% two-sided confidence intervals (CI) of the parameters will be computed. The LSMs of actual values and change from Baseline in $\log_2$(NfL) and associated SE for each treatment group, as well as the LSM, 95% CI, and p-value for the treatment difference (pridopidine 45 mg bid vs. placebo) will be presented at all visits in analysis. The LSM of change from Baseline in $\log_2$(NfL) at each visit will be back transformed to the percent change in NfL as $2^{LSM} \times 100 - 100$. The 95% CI of the LSM will also be back transformed.

In addition, actual values, change from Baseline to each visit of $\log_2$(NfL) and actual value, and % change from Baseline in raw NfL value will be summarized using descriptive statistics and graphics where applicable.

To investigate the additional covariates that may have an effect on change in NfL over time, more covariates will also be added one at a time or altogether to the above model: CAG repeats, age, sex, CAP score, BMI, region, Baseline UHDRS-TFC, Baseline cUHDRS, Baseline Q-Motor [redacted] Baseline UHDRS-TMS, Baseline SDMT, and Baseline SWR. When all covariates are added to the model together, a stepwise model selection approach (specifically, a variable needs to be significant at the level of 0.25 to enter the model during the first forward step and to be significant at the level of 0.10 to remain in during the second backward step) will be adopted in order to see the most influential covariates on the change in NfL over time. Each covariate will be tested at a type I error level $\leq$0.05, two-sided and the 95% two-sided CIs of the effect estimates will be computed.

(2) To investigate how Baseline NfL, as a covariate, impacts change from Baseline to Weeks 26, 52, 65 and 78 in efficacy endpoints including UHDRS-TFC, cUHDRS, Q-Motor [redacted], UHDRS-TMS, SDMT, and SWR accounting for the effect of pridopidine 45 mg bid vs placebo.

The main analysis is based on the change from Baseline in UHDRS-TFC, cUHDRS, Q-Motor [redacted] UHDRS-TMS, SDMT and SWR over time. Each dependent

variable will be fit by one model. Similar analyses will be repeated for actual values of the endpoints.

Analysis will be performed on observed data using MMRM separately for actual values and change from Baseline. The model will include the following effects: *treatment*, *categorical weeks*, *Baseline value of efficacy endpoint to be analyzed*, *Baseline log2(NfL)*, randomization stratification factors (*HD stage and neuroleptic use at Baseline*), interaction effects of *treatment*categorical weeks*, and *treatment*Baseline log2(NfL)*. The spatial power covariance matrix for repeated observations within participants will be used. The denominator degrees of freedom for the tests of fixed effects will be approximated by Kenward-Roger method.

Baseline log2(NfL) and its interaction with other factors will be tested at a type I error level ≤0.05, two-sided and the 95% two-sided CI of the parameters will be computed.

The LSM and the associated SE of the Baseline NfL-adjusted efficacy endpoint at some specified Baseline NfL values (such as median, first quartile [low level], and third quartile [high level]) for each treatment group, and the LSM, 95% CI and p-value for the treatment difference (pridopidine 45 mg bid vs. placebo) will be presented for all visits.

To investigate the additional covariates that may have an effect on the efficacy endpoints, more covariates will also be added one at a time or altogether to above model: CAG repeats, age, sex, CAP score, BMI, region. When all covariates are added to the model together, a stepwise model selection approach, as described in Objective (1), will be adopted to see the most influential covariates on the change in NfL over time. Each covariate will be tested at a type I error level ≤0.05, two-sided and the 95% two-sided CIs of the parameters will be computed.

(3) To investigate the relationship between change in NfL over time and change in clinical efficacy endpoints including UHDRS-TFC, cUHDRS, Q-Motor [redacted], UHDRS-TMS, SDMT and SWR accounting for the effect of pridopidine 45 mg bid vs placebo.

The dependent variables investigated are clinical outcomes such as UHDRS-TFC, cUHDRS, Q-Motor [redacted] UHDRS-TMS, SDMT and SWR over time, with one dependent variable fit at a time.

The main analysis is based on change from baseline in both efficacy endpoints and $\log_2$(NfL), and similar analyses will be repeated for actual values of efficacy endpoints and $\log_2$(NfL). Analysis will be performed on observed data using MMRM separately for actual values and change from Baseline over time. The model for change from Baseline in a specific efficacy endpoint over time will include the following effects: *treatment*, *categorical weeks*, *Baseline value of efficacy endpoint to be analyzed*, randomization stratification factors (*HD stage and neuroleptic use at Baseline*), *change from Baseline in log2(NfL)*, interaction effects of *treatment*categorical weeks*, *treatment*change from Baseline in log2(NfL)*. The spatial power covariance matrix for repeated observations within participants will be used. The denominator degrees of freedom for the tests of fixed effects will be approximated by Kenward-Roger method.

The effect of *change from Baseline in log2(NfL)* by treatment group will be tested at a type I error level ≤0.05, two-sided and the 95% two-sided CI of the parameter will be computed.

Another simpler approach to perform a simple linear model on the change from Baseline of these clinical outcomes at the specified timepoint may be performed. For Week 65 analysis, the model will include the following effects: *treatment*, Baseline *log_2(NfL), log_2(NfL) at Weeks 26, 52 and 65*, and interaction effects of *treatment*log_2(NfL) at Baseline and Weeks 26, 52 and 65*. Each covariate related to *log_2(NfL)* will be tested at a type I error level ≤0.05, two-sided and the 95% two-sided CI of the parameters will be computed.

To investigate the additional possible covariates that can have an effect on change in efficacy endpoints over time, more covariates will also be added one at a time or altogether to the above model: CAG repeats, age, CAP score, BMI, region. When all covariates are added to the model together, a stepwise model selection approach, as described in Objective (1), will be adopted to see the most influential covariates on the change in NfL over time. Each covariate will be tested at a type I error level ≤0.05, two-sided and the 95% two-sided CI of the parameters will be computed.

(4) To investigate the proportion of participants with no increase from Baseline to Weeks 26, 52, 65 and 78 in plasma NfL levels. Other thresholds may also be explored.

The dependent variable is a binary variable which is defined as follows:

$$Dependent\ variable = \begin{cases} 1 & \text{if Change from Baseline in log2(NfL)} \leq 0 \\ 0 & \text{otherwise} \end{cases}.$$

This binary variable dichotomizes changes from Baseline in log2(NfL) over time to show whether or not there is a beneficial decrease in log2(NfL) from Baseline. Analysis will be performed on the binary data at each visit using logistic regression model. In this model, the log odds of the dependent variable are modelled.

The model will include the following fixed effects: *treatment*, *Baseline log_2(NfL)*, randomization stratification factors (*HD stage and neuroleptic use at Baseline*), interaction effect of *treatment*Baseline log_2(NfL)*.

Each fixed effect will be tested at a type I error level ≤0.05, two-sided, and the 95% two-sided confidence intervals (CI) of the parameters will be computed. Odds Ratios of treatment effect with their 95% CI at each visit will be presented in analysis.

Subgroup analysis which divides the participants by median Baseline NfL level will be performed for above objectives where applicable.

9.1.3. Pharmacogenomic Analysis

Details of pharmacogenomic data collection and analysis will be included in a SAP addendum, appendix or separate SAPs.

10. STATISTICAL SOFTWARE

All derived datasets, data listings, summaries, and statistical programming/analyses will be performed using SAS® 9.4 or higher.

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12. APPENDIX

12.1. Efficacy Variables Calculation Methods

12.1.1. Unified Huntington's 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. 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 undertake domestic chores (0=Unable to 2=Normal), activities of daily living (0=Total Care to 3=Normal), take care of finances (0=Unable to 3=Normal), maintain care level (0=Full time skilled nursing to 2=Home), and maintain their occupation (0=Unable to 3=Normal). UHDRS-TFC questionnaires are collected as specified in the SoA (Table 1 and Table 2) to assess change from Baseline.

A UHDRS-TFC evaluation will only be considered valid if all 5 assessments of Domestic Chores, Activities of Daily Living, Finances, Care Level, and Occupation are completed. If any of these is not completed, the UHDRS-TFC assessment will be considered invalid and treated as missing value.

Participants with improvement or no worsening in UHDRS-TFC at a particular post-baseline visit during Main Study are defined as those with change from Baseline ≥ 0 at that visit.

TFC responders at a scheduled visit during OLE are defined as participants with change from Main Study Baseline in UHDRS-TFC ≥ -1.

12.1.2. Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS)

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. The worst possible score is 124. UHDRS-TMS questionnaires are collected to assess change from Baseline.

The subscales of UHDRS-TMS include:

- Gait and balance score, defined as the sum of UHDRS Items 13, 14 and 15 (gait, tandem walking, and retropulsion pull test)
- Eye movement score, defined as the sum of UHDRS Items 1a Horizontal, 1b Vertical, 2a Horizontal, 2b Vertical, 3a Horizontal, 3b Vertical (ocular pursuit, saccade initiation, and saccade velocity)
- Dystonia score, defined as the sum of Items 11a – 11e
- Chorea score, defined as the sum of Items 12a – 12g

Participants with improvement or no worsening in UHDRS-TMS at a particular post-baseline visit during Main Study are defined as those with change from Baseline ≤ 0 at that visit.

12.1.3. Unified Huntington's Disease Rating Scale – Composite Score (cUHDRS)

The cUHDRS (Schobel et. al., 2017) is a composite measure of motor, cognitive, and global functional decline computed as follows:

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

A cUHDRS responder is defined as one with change from Baseline in cUHDRS ≥1.

12.1.4. Quantitative Motor (Q-Motor)

[redacted]

[redacted]

12.1.5. Clinical Global Impression

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

The CGI-S (modified) scale was initially designed to assess treatment response in participants with mental disorders but is now used widely in a range of illnesses. Illness severity is rated by qualified site personnel on a 7-point scale (1 = normal, not at all ill to 7 = among the most extremely ill participants) as shown in the table below. The assessment is based on qualified site personnel judgment, supported by a comprehensive, semi structured, participant/caregiver interview.

CGI-S (modified) will be collected at Baseline.

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

12.1.5.2. Clinical Global Impression – Change (CGI-C)

The CGI-C scale measures the change in the participant's clinical status from a specific point in time, using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change.

Responder analyses will be performed at Week 65 as a secondary efficacy endpoint with analysis at all other post-baseline visits as additional efficacy analyses. Responder analyses comparing participants randomized to pridopidine vs placebo will be performed using CGI-C for those:

(a) who have no change or improve (Scores of 1,2,3 or 4)

(b) who Minimally or more improved (Scores of 1,2, or 3)

(c) who Are Much or Very Much improved (Scores of 1 or 2)

(d) who are Very Much improved (Score of 1)

Description	Score
Not assessed	0
Very Much Improved	1
Much Improved	2
Minimally improved	3
No change	**4**
Minimally worse	5
Much worse	6
Very much worse	7

12.1.6. Exploratory Assessments

12.1.6.1. Stroop Word Reading (SWR)

The SWR is a neuropsychological test commonly used to measure the participant's attention and mental flexibility. The participant's accuracy and speed at the SWR will 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.

SWR is collected to assess the proportion of responders and change from Baseline for efficacy endpoints.

12.1.6.2. 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. Scoring involves summing the correct substitution within the 90 second interval (max=110).

SDMT is collected to assess responder analysis and change from Baseline for exploratory efficacy endpoints.

12.1.6.3. Problem Behaviors Assessment-Short Form (PBA-s)

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 every day); and 4 = all day, every day.

Severity and frequency scores are multiplied (after setting all values outside the range of 0-4 to missing) to produce an overall 'PBA score' for each symptom.

The total PBA score is calculated by the sum of all PBA scores across symptoms/domains. The PBA-s sub-scores include depression score (sum of low mood, suicidal ideation, and anxiety), irritability/aggregation score (sum of irritability and anger/aggressive behavior), executive function (sum of perseverative thinking or behavior and obsessive-compulsive behaviors), apathy (loss of motivation), and psychosis (sum of paranoid thinking, hallucinations, and behavior suggestive of disorientation).

The PBA assessments are collected to assess change from Baseline for exploratory efficacy endpoints.

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

The HDQoL questionnaire includes 40 items (ranged 0='Never' to 6='All the Time'). The HDQoL total score is defined as the sum of the 40 items. The HDQoL total score range is from 0 to 240.

HDQoL is collected to assess responder analyses and change from Baseline for exploratory efficacy endpoints.

12.2. Abuse Potential

Drug abuse potential will be identified using PT of AEs in accordance with the standardized search strategy [redacted]:

- Abuse, dependence, withdrawal or diversion (using the following PT: drug abuser, drug dependence, dependence, drug tolerance, drug tolerance increased, drug withdrawal syndrome)
- Euphoria/mood-elevation (using the following PT: dizziness, elevated mood, euphoric mood, feeling abnormal, feeling drunk, feeling of relaxation, and inappropriate affect)
- Depressant/sedative effects (using the following PT: asthenia, fatigue, lethargy, sedation, sluggishness, somnolence, and stupor to identify AEs with central nervous system depressant effects)
- Stimulant effects (using the following PT: agitation, anxiety, energy increased, feeling jittery, hypervigilance, nervousness, psychomotor hyperactivity, and restlessness to identify AEs indicating stimulation and anxiety symptoms)
- Perceptual disturbances, dissociative and psychotomimetic effects (using the following PT: abnormal dreams, acute psychosis, aggression, anger, communication disorder, confusional state, delirium, delusion, depersonalisation, derealisation, disorientation, dissociation, dissociative disorder, dysarthria, flashback, hallucination,

hallucination auditory, hallucination mixed, hallucination olfactory, hallucination synaesthetic, hallucination tactile, hallucination visual, hostility, hypoesthesia, illusion, indifference, muscle rigidity, nightmare, paraesthesia, paranoia, psychotic disorder, sensory disturbance, somatic delusion, somatic hallucination, thinking abnormal, thought blocking, transient psychosis)

- Mood disorders and disturbances (using the following PT: abnormal behaviour, affective disorder, affect lability, depressed mood, depression, emotional disorder, emotional distress, impatience, mood altered, mood swings, and personality change)
- Mental and cognitive impairment (using the following PT: amnesia, cognitive disorder, disturbance in attention, memory impairment, mental impairment and psychomotor skills impaired)
- Possible discontinuation-emergent stimulant effects (using the following PT: affect lability, agitation, anger, anhedonia, anorexia, anxiety, apathy, appetite suppression, bradycardia, decreased appetite, decreased interest, depressed mood, disturbance in attention, drug dependence, fatigue, feeling abnormal, food craving, hangover, hyperphagia, hypersomnia, increased appetite, insomnia, irritability, lethargy, listless, malaise, mood altered, mood swings, oral intake reduced, paranoia, restlessness, somnolence, suicidal behaviour, suicidal ideation, tension)