Official Title: A Multi-Center, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Pridopidine in Patients with Huntington's Disease (Open PRIDE-HD)

NCT Number: NCT02494778

Document Date: 31 Mar 2016

Clinical Study Protocol

Study Number TV7820-CNS-20016

A Multi-Center, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Pridopidine in Patients with Huntington's Disease (Open PRIDE-HD)

(Open PRIdopidine Dose Evaluation in Huntington's Disease)

Phase 2

IND number: 77,419 EudraCT number: 2015-000904-24

Protocol Approval Date: 31 March 2016

Sponsor (and Monitor)
Teva Branded Pharmaceutical
Products R&D, Inc.
[redacted]

Authorized Representative
[redacted]
VP Global Head, Neurodegeneration, Clinical Development
Teva Branded Pharmaceutical Products R&D, Inc.

Sponsor's Medical Expert
[redacted]
Senior Director, Clinical Development
Leader NDD
Teva Branded Pharmaceutical
Products R&D, Inc.
[redacted]

Sponsor's Safety Representative
[redacted]
Director, PhV Safety Physician
Global Patient
Safety & Pharmacovigilance
Teva Pharmaceutical Industries, Ltd.
[redacted]

Confidentiality Statement

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the sponsor's Standard Operating Procedures (SOPs).

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AMENDMENT HISTORY

The protocol for study TV7820-CNS-20016 (original protocol dated 26 March 2015) has been amended and reissued as follows:

Global Protocol Amendment 02	31 March 2016 (94 patients enrolled to date)
Administrative Letter 02	03 February 2016
Global Protocol Amendment 01	30 June 2015 (0 patients enrolled to date)
Administrative Letter 01	05 May 2015 (0 patients enrolled to date)

[redacted]

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 02

Original protocol dated 26 March 2015

IND 77,419; EudraCT number: 2015-000904-24

A Multi-Center, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Pridopidine in Patients with Huntington's Disease (Open PRIDE-HD)

(Open PRIdopidine Dose Evaluation in Huntington's Disease)

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the drug that were furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all patient information, study drug with local and national Good Clinical Practice (GCP) regulations.

Principal Investigator	**Signature**	**Date**

Protocol Approval

Sponsor's Authorized Representative	**Signature**	**Protocol with Amendment 02 Final Date**
[redacted] Global Head, Neurodegeneration, Clinical Development	[redacted]	Mar-31-2016

CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS

Central Clinical Laboratory

[redacted]

Electronic Data Capture

[redacted]

Central Electrocardiogram Evaluation

[redacted]

Web and Phone Integrated Interactive Response Technology

[redacted]

Bioanalytical Pharmacokinetics Evaluation

[redacted]

Computer-Based Rating System

[redacted]

Digital Health Sub-Study

[redacted]

CLINICAL STUDY PERSONNEL CONTACT INFORMATION

For medical issues, contact the physician listed below:

EU Sites:

[redacted]

Australian Sites:

[redacted]

US and Canadian Sites:

[redacted]

In a study-related medical emergency situation, when assigned Medical Monitors for a study cannot be reached, an on-call Physician can be reached 24 hours per day, 7 days per week via an [redacted] [Toll (not free of charge) telephone number allowing a global reach from both landlines and mobile phones]
On the following internet page [redacted] a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help desk" index. Countries without toll-free numbers need to dial the toll (not free of charge) number as indicated above. Toll-free numbers are unfortunately not available from mobile phones.

For operational issues, contact the operational lead listed below:

[redacted]

For **serious adverse events:**

Send by e mail to the local safety officer/contract research organization (LSO/CRO). The email address will be provided in the serious adverse event (SAE) report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.

CLINICAL STUDY PROTOCOL SYNOPSIS

Study TV7820-CNS-20016

Title of Study: A Multi-Center, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Pridopidine in Patients with Huntington's Disease (Open PRIDE-HD- Open PRIdopidine Dose Evaluation in Huntington's Disease)

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

IND Number: 77,419 **EudraCT Number:** 2015-000904-24

Name of Active Ingredient: 4-[3-(Methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride (pridopidine)

Name of Investigational Product: Pridopidine capsules

Phase of Clinical Development: 2

Number of Investigational Centers Planned: Up to 54

Countries Planned: Australia, Austria, Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Russia, United Kingdom (UK), United States (US)

Planned Study Period: First Patient First Visit in Q3 2015. Enrollment will continue until the last patient from the TV7820-CNS-20002 study (PRIDE-HD) has entered the study. Treatment duration will be extended for an additional 52 weeks (ie, total of 104 weeks), until approximately Q3 2017 (last patient last visit for the extended study period).

Number of Patients Planned: Up to 300

Study Population: Male and female patients, aged ≥21 years and with body weight ≥50 kg with HD who completed the double-blind, randomized phase in PRIDE-HD study, including the follow-up period, or who participated in the open-label ACR16C015 (Open-HART) extension study.

Primary Objective: The primary objective of this study is to evaluate safety and tolerability of pridopidine in patients with HD**.**

Secondary Objectives: The secondary objectives of the study are to assess the effects of long-term, open-label dosing with pridopidine on motor symptom severity, overall patient function, physical performance, and health-related quality of life.

Study Endpoints:

Safety endpoints:

Safety measures will include the following:

- adverse events (AEs)
- vital signs assessments
- concomitant medication usage
- physical examination findings
- clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis)

- Electrocardiography (ECG) findings
- Suicidality [using the Columbia-Suicide Severity Rating Scale (C-SSRS)] and Problem Behaviors Assessment-Short form (PBA-s)_

Tolerability endpoints:

- Proportion of subjects (%) who prematurely discontinued from the study
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs

Efficacy endpoints:

Long-term efficacy evaluations are the secondary objective of this study. Efficacy endpoints include the following

- Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS)
- Modified Physical Performance Test (mPPT)
- Unified Huntington's Disease Rating Scale - Total Functional Capacity (UHDRS-TFC)
- Short Form 12 (SF-12) questionnaire (acute version)
- Problem Behaviors Assessment-Short form (PBA-s) (also part of safety assessments)
- Quantitative motor (Q-motor) assessment

General Design and Methodology:

This is an open-label, multi-center study to evaluate the safety, tolerability, and efficacy of pridopidine 45 mg twice-daily (bid) in patients with HD.

It is planned to enroll up to 300 patients from the PRIDE-HD and Open-HART studies.

The following titration scheme will be followed:

- Week 1: Patients will receive 1 capsule of 22.5 mg pridopidine bid (22.5 mg bid, total daily dose of 45 mg pridopidine).
- Week 2 to study completion: Patients will receive 1 capsule of 45 mg pridopidine bid (total daily dose of 90 mg pridopidine).

Upon meeting eligibility criteria, patients who transition from the ACR16C015 (Open-HART) study may perform the baseline visit assessments and procedures. They do not have to undergo titration as they will continue taking the same dose as in Open-HART (45 mg bid).

Patients will be treated with study drug for 104 weeks. Safety will be assessed after 4, 12, 26, 52, 78, and 104 weeks of treatment and at the follow-up End-of-study (EoS) visit (Week 106). Safety evaluation telephone calls will be performed at weeks 18 and 38. During these phone calls, inquiries about adverse events, concomitant medication (including changes in use of benzodiazepines and antidepressants), changes in use of alcohol and illicit drugs, C-SSRS, and an abbreviated PBA-s (a subset of PBA-s questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, and obsessive-compulsive behaviors) will be conducted.

Patients who discontinue study medication due to safety or tolerability reasons may continue in the study off drug and perform the scheduled visits and assessments.

Doses of up to 112.5 mg bid are currently being investigated in the ongoing PRIDE-HD study. Upon completion of PRIDE-HD and following analysis of safety, tolerability, and efficacy data the dose administered in this study may be adjusted to a maximum of 112.5mg bid after a titration period at the discretion of the sponsor.

During the study, an independent Data and Safety Monitoring Board (DSMB) will review accumulating safety data. The DSMB will meet as detailed in the charter. In case of a significant emerging safety concern the DSMB will have the authority to discontinue enrolled patients from study drug administration, and stop enrollment of new patients. Thereafter, the DSMB will decide whether there is a need for additional meetings, and, if needed, will determine when these will take place.

Digital Health Sub-study (optional participation):

Motor symptoms can be objectively assessed in Huntington's disease patients using different quantitative motor assessments.

Objective motor assessments aim at improving the limited sensitivity observed with categorical clinical rating scales, and reducing the intra- and inter-rater variability, as well as potential placebo effect observed in scales such as the UHDRS. Improved sensitivity for early-stage clinical studies of efficacy of a new drug on motor dysfunction is expected with objective assessments and may support early go/no go decisions in smaller cohorts of patients (Reilmann et al. 2001; Reilmann et al. 2011).

A feasibility sub-study including up to 60 patients with chorea will be conducted to collect accelerometry data using a wearable sensor-mobile application tool. The overall objective of the sub-study is to test the hypothesis of using wearable sensor data to estimate clinically relevant measures of HD in patients while on their medication regimen, which includes pridopidine. The aim is to develop algorithms to objectively quantify chorea by analyzing the data from the wearable sensors. The application will also include a simple diary to track medication use during the study. Patients enrolled in the sub-study will be provided with a commercial grade wearable digital sensor (Pebble watch), an android smartphone and will be granted access to the accompanying mobile application. The mobile application will collect accelerometry and medication data and transmit for storage and processing. Participating subjects will be asked to continuously wear the digital sensor for a period of 6 months. Participation in the sub-study will be optional. The accelerometry data collection will be performed on the wrist of the non-dominant limb. A training session will be done at screening for the sub-study. Assessments will be done at times specified in the Schedule of Activities section of the protocol. A separate user's manual and training on the tool will be provided to sites. This system of data collection will allow researchers and clinicians to gather detailed patient data outside of the clinical setting. The data analysis is expected to facilitate future research and clinical studies on the effectiveness of new interventions in HD.

Method of Blinding and Randomization:

This is a nonrandomized, open-label study with no blinding.

Study Drug Dose, Mode of Administration, and Administration Rate:

Pridopidine will be provided as a white hard gelatin capsule, size 2 containing 45 mg pridopidine and a white hard gelatin capsule, size 4 containing 22.5 mg pridopidine or a light pink/white hard gelatin capsule, size 2 with black color imprinting containing 45 mg pridopidine and a white hard gelatin capsule, size 4, with black imprinting containing 22.5 mg pridopidine.

The mode of administration is oral. Capsules will be swallowed whole with water. One capsule should be taken in the morning and 1 in the afternoon, 7 to 10 hours after the morning dose. Study drug can be taken irrespective of meals.

Each medication pack will contain distinct labeled bottles in accordance with the associated dose strength. The capsules will be provided in 2 configurations: Each bottle will contain 30 capsules (of 22.5 mg or 45 mg white capsules; or 22.5 mg white imprinted capsules) or 60 capsules (of 45 mg light pink/white imprinted capsules).

Bottles will be used to accomplish the dosing of possible treatment options including possible dose escalation and de-escalation. Each bottle will be labeled with a unique pack number.

All medication supplied in connection with this study must be used only for this study and no other purpose.

Duration of Patient Participation: Treatment duration is 104 weeks. Study participation will be 108 weeks, including a screening period of up to 2 weeks and an end-of-study (EoS) follow-up visit.

Criteria for Inclusion: Patients may be included in the study only if they meet all of the following criteria:

a. [Revision 1] Patient has completed the PRIDE-HD trial within the last 6 months, including the follow-up period, or transitioned from Open-HART.
For patients that have failed to complete PRIDE-HD or those who completed the PRIDE-HD study over 6 months prior to the screening visit, and meet all other inclusion criteria, eligibility should be discussed with the Open-PRIDE medical monitor and clinician on a case-by-case basis

b. [Revision 1] For patients that experienced a drug-related serious adverse event (SAE) or had a major compliance violation during PRIDE-HD or Open-HART, eligibility approval should be discussed with PRIDE-HD's or Open-HART's medical monitor and clinician. Patients that experienced an adverse event/serious adverse event of suicidal ideation/behavior will be excluded without discussion.

c. Able and willing to provide written informed consent prior to any study related procedure being performed. Patients with a legal guardian should be consented according to local requirements.

d. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception according to local regulations (hormone-based, intrauterine device, or double barrier contraception, i.e., condom and diaphragm). Abstinence is an acceptable method of contraception only when this is the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male study participants have to be compliant in using adequate birth control with their partners (as defined above) throughout the duration of the study.

e. Body weight ≥50 kg. Patients that meet this criterion at screening but fail to meet it at a subsequent visit may be discontinued based on Investigator or Sponsor discretion. It is allowed to repeat the weight measurement once, if clinically appropriate.

f. Willing and able to take oral medication and able to comply with the study specific procedures.

g. Ambulatory, being able to travel to the study center, and judged by the investigator as likely to be able to continue to travel for the duration of the study.

h. The patient is in good health as determined by medical examination, ECG, serum chemistry, hematology, and urinalysis.

i. The patient must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period, and willing to return to the clinic for evaluation as specified in this protocol.

Criteria for Exclusion: Patients will be excluded from participating in this study if they meet any of the following criteria:

a. A prolonged Fridericia-corrected QT (QTcF) interval (defined as a QTcF interval of >450 msec) at the screening visit. ECGs will be performed in triplicate during the screening visit, and the mean of the 3 QTcF measurements will be used to determine whether or not the patient is suitable for inclusion in the study.

b. Patients with clinically significant heart disease at the screening visit, defined as follows: (i) significant cardiac event (eg, myocardial infarction), angina pectoris or episode of congestive heart failure with symptoms >Grade 2 New York Heart Association classification within 12 weeks before randomization, or presence of cardiac disease that in the opinion of the investigator increased the risk of ventricular arrhythmia, (ii) history of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia) that was symptomatic or required treatment (Common Terminology Criteria for Adverse Events Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia, (iii) presence of left bundle branch block.

c. Patients with serum potassium, magnesium, and/or calcium levels outside of the central laboratory's reference range at the screening visit and considered clinically significantly abnormal by the investigator. Repeat testing is allowed (up to a maximum of 3 tests) if required to establish whether values are within normal range or clinically significantly abnormal.

d. Patients receiving medications (within the last 6 weeks prior to baseline) other than pridopidine that have been proven to prolong QT interval or who may require such medications during the course of the study such as but not limited to non-allowed anti-psychotic medications, tricyclic antidepressants, and/or Class I antiarrhythmics.

e. Patients receiving medications (within the last 6 weeks prior to baseline) other than pridopidine that are metabolized by Cytochrome P450 (CYP) 2D6 and have the potential of reducing seizure threshold.

f. Patients with a history of epilepsy or of seizures within the last 5 years.

g. Creatinine clearance <60 mL/min at screening, calculated using the Cockcroft-Gault equation: (140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/ dL). It is allowed to repeat the test once, if clinically appropriate.

h. Any clinically significant, abnormal, screening laboratory result which in the opinion of the investigator, affects the patients' suitability for the study or puts the patient at risk if he/she enters the study.

i. [Revision 1] Patients with adverse events of suicidal ideation or attempt at any time in the past or as measured by suicide ideation score of ≥3on the C-SSRS, or PBA-s or patients who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) if the attempt or acts were performed at any time in the past, or patients who, in the opinion of the investigator, present a risk of suicide.

j. Females who are pregnant or breastfeeding.

k. Treatment with any investigational product other than pridopidine within 6 weeks of screening or patients planning to participate in another clinical study assessing any investigational product during the study.

Measures and Time Points:

The following assessments will be performed at the specified time points:

- Eligibility criteria will be reviewed and confirmed at screening and baseline.
- Vital signs will be measured at each study visit. Vital signs include the following: pulse, blood pressure (supine and standing), body temperature.
- A brief (symptom-directed) physical examination will be performed at each study visit.
- Serum chemistry tests will be performed at each study visit.
- Hematology tests will be performed at each visit;
- Urinalysis will be performed at each visit;
- Human chorionic gonadotropin (HCG) serum test will be performed for all women of childbearing age at screening. HCG urine tests will be performed for all women of childbearing age at all subsequent visits, and if clinically indicated at any other time.
- ECG will be performed at every visit and will be centrally evaluated at a core lab.
- Adverse Events (AEs) will be monitored throughout the study.
- Suicidality will be monitored throughout the study through administration of the C-SSRS and PBA-s.
- Concomitant medications will be monitored throughout the study.
- Motor function evaluations (UHDRS Total Motor Score) will be performed at all visits
- Modified physical performance test (mPPT) will be performed at baseline, week 12, week 26, week 52, week 78, week 104 and week 106.
- Functional capacity evaluation (UHDRS-Total Functional Capacity) will be performed at baseline, week 26, week 52, week 78, week 104 and week106.
- SF-12 evaluation will be performed at baseline, week 26, week 52, week 78, week 104 and week 106.
- The PBA-s will be performed at all study visits.
- Q-motor assessment will be performed at baseline, week 52, week 78, week 104 and week 106.

Pharmacokinetics Measures and Time Points:

Pharmacokinetic (PK) samples will be aimed to be drawn, to the extent possible, in the event of a SAE, an AE leading to discontinuation, or for patients who withdrew prematurely because of lack of efficacy

Allowed and Disallowed Medications Before and During the Study:

Medications that are CYP2D6 substrates and have a narrow safety margin, eg, class I antiarrythmics and tricyclic antidepressants, will be administered according to the list of permitted and prohibited concomitant medications. Disallowed CYP2D6 substrates can be administered only 1 week after the discontinuation of pridopidine (i.e., 1-week washout), to allow enzyme recovery. CYP2D6 inhibitors can be administered to study patients.

The concomitant use of medications that are known to have a profound effect on QT interval should be avoided according to the list of permitted and prohibited concomitant medications. [redacted] concomitant treatment with tetrabenazine

is disallowed. Medications that are CYP2D6 substrates and have the potential to reduce the seizure threshold will not be permitted during the study.

Statistical Considerations:

Sample Size Rationale:

This is an open-label study. The sample size for this study is not based on statistical considerations; hence, only descriptive statistics will be presented. Up to 300 subjects who completed the PRIDE-HD or transitioned from the ongoing Open-HART study and met patient exclusion/inclusion criteria will be enrolled.

Analysis of Efficacy Endpoints: No formal inferential statistics will be applied to the efficacy endpoints. Efficacy analyses will be considered exploratory. Comparisons will generally be made to baseline, as appropriate. Descriptive statistics over time will be presented to detect trends via changes from baseline.

Multiple Comparisons and Multiplicity: Not applicable.

Safety and Tolerability Analyses:

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or system organ class (SOC) category for the analyses of safety. Summaries will be presented for all AEs (overall and by severity), AEs determined by the investigator to be related to study treatment (defined as related or with missing relationship) (overall and by severity), serious AEs, and AEs causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of SAEs and AEs leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with pre-specified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

Descriptive summaries of SAEs, patient withdrawals due to AEs, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Arc mRNA	activity-regulated cytoskeleton-associated protein messenger ribonucleic acid
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-HCG	beta human chorionic gonadotropin
bid	twice daily
BUN	blood urea nitrogen
CAG	cytosine-adenosine-guanine
CBC	Complete blood count
CDMS	clinical data management system
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed plasma drug concentration
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EM	extensive metabolizers
EoS	End-of-Study
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HART	Huntington’s disease ACR16 Randomized Trial (ACR16C009)

Abbreviation	Term
HD	Huntington’s disease
HDL	high-density lipoprotein
IB	Investigator’s Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOI	inter onset intervals
IPI	inter peak intervals
IRB	Institutional Review Board
IRT	interactive response technology
ITI	inter tap intervals
ITT	intent-to-treat
LAM	Lactational amenorrhea method
LCM	Local clinical management
LDH	lactic dehydrogenase
LDL	low-density lipoprotein
LSO	Local safety officer
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MermaiHD	Multinational European Multicentre ACR16 study in Huntington’s Disease (ACR16C008)
mMS	Modified Motor Score
mPPT	Modified Physical Performance Test
MTD	maximum tolerated dose
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
OTC	Over the counter
PBA-s	Problem Behaviors Assessment-Short form
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PM	poor metabolizer
Q-motor	Quantitative motor

Abbreviation	Term
qd	once daily
QTcF	Fridericia-corrected QT interval
ΔΔQTcF	placebo-corrected change from baseline in QTcF
RBC	red blood cell
RSI	Reference Safety Information
SAE	serious adverse event
SD	standard deviation
SF-12	Short Form 12
SOC	system organ class/standard of care
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	half life
TC	telephone contact
TD	tap durations
TF	tapping forces
TFC	Total Functional Capacity
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale
UK	United Kingdom
ULN	upper limit of the normal range
USA	United States of America
WBC	white blood cell
WHO	World Health Organization
WHO Drug	World Health Organization (WHO) drug dictionary

1. BACKGROUND INFORMATION

1.1. Introduction

1.1.1. Huntington's Disease

Huntington's disease (HD) is a fatal neurodegenerative disorder with an autosomal dominant mode of inheritance. The disease is associated with a triad of motor, behavioral, and cognitive symptoms. Motor disturbances are the defining feature of the disease and, with chorea the most evident motor symptom. Although useful for diagnosis, chorea is a poor marker of disease severity. Rather, disability and disease severity best correlate with negative motor features such as impairment in fine motor skills, bradykinesia, and gross motor coordination skills, including speech difficulties, gait, and postural dysfunction (Mahant et al 2003).

Dopamine is widely regarded as an important neurotransmitter modulating several aspects of brain functions including motor function (Nieoullon and Coquerel, 2003). A disrupted dopaminergic signaling has been implicated in a number of neurological and psychiatric conditions, (Zhan et al 2011; Dunlop and Nemeroff, 2007) and there is considerable clinical and preclinical evidence suggesting that dopaminergic functions are also compromised in HD (Kung et al 2007; Huot et al 2007).

A number of medications are prescribed to ameliorate the motor and emotional problems associated with HD; however, the scientific evidence for the usefulness of various drugs in HD is poor (Mestre et al 2009a; Mestre et al 2009b). Only 1 drug, tetrabenazine, which reduces dopamine availability and transmission, is registered specifically for the treatment of patients with HD for the management of chorea. No registered drugs are available for the management of the multifaceted motor symptoms. As such, there is a significant unmet medical need to develop medications to ameliorate symptoms of HD.

1.1.2. Pridopidine

1.2. Name and Description of Investigational Product

The investigational product is pridopidine (TV-7820), and the active ingredient is 4-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride.

Pridopidine will be provided as a white hard gelatin capsule, size 2 containing 45 mg pridopidine and a white hard gelatin capsule, size 4 containing 22.5 mg pridopidine or a light pink/white hard

gelatin capsule, size 2, with black color imprinting containing 45 mg pridopidine and a white hard gelatin capsule, size 4, with black imprinting containing 22.5 mg pridopidine.

A more detailed description of the product is given in Section 5.1.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

1.3.2. Clinical Studies

To date, 20 clinical studies have been completed or are ongoing with pridopidine, comprising 9 studies in healthy subjects (of which 1 study also included patients with schizophrenia), 1 study in patients with Parkinson's disease, 2 studies in patients with schizophrenia (including the study mentioned above), and 9 studies in patients with HD (including 3 open-label extension studies). In addition, a compassionate use program for pridopidine in patients with HD is ongoing in Europe (ACR16CU014), and an open-label, long term safety study is ongoing in the United States (US) and Canada (ACR16C015, Open-HART). A Phase 2 dose-finding, randomized, parallel-group, double-blind, placebo-controlled study, evaluating the safety and efficacy of pridopidine 45 mg, 67.5 mg, 90 mg, and 112.5 mg twice-daily (bid) for symptomatic treatment in patients with HD (TV7820-CNS-20002, PRIDE-HD) was initiated in February 2014 and is currently ongoing (Zielonka et al, 2015). Patients who complete the PRIDE-HD study may be eligible to enroll into the open-label extension study, outlined in this protocol.

As per 14 February 2016, 866 patients with HD have been enrolled in clinical studies with pridopidine, with 634 patients receiving pridopidine in doses ranging from 20 to 90 mg daily. The ongoing Phase 2 TV7820-CNS-20002 (PRIDE-HD) study is blinded; therefore, patient exposure from this study is not included in the above total.

1.3.2.1. Clinical Pharmacology Studies

[redacted]

[1] Exploratory Population Pharmacokinetic Modeling and Simulations with Pridopidine (Report CP-13-013). Pharsight Consulting Services, 10 July 2013.

[redacted]

1.3.2.2. Clinical Safety and Efficacy Studies

Three randomized, double-blind, placebo-controlled, parallel-group clinical studies investigating the efficacy and safety of pridopidine in patients with HD have been conducted.
Study ACR16C007 explored the efficacy of 44 mg pridopidine once daily (qd) in 58 patients. Subsequently, the "Huntington's disease ACR16 Randomized Trial" (HART) study (ACR16C009) was designed to explore the dose-response of pridopidine looking at 3 different daily doses (10, 22.5, and 45 mg bid) in 227 patients during 12 weeks of treatment. In parallel, the "Multinational European Multicentre ACR16 study in Huntington's Disease" (MermaiHD)

study (ACR16C008) investigated the efficacy and safety of 45 mg given qd and bid over 26 weeks of treatment in 437 patients.

[redacted]

1.4. Known and Potential Risks and Benefits to Human Patients

1.4.1. Risks of Pridopidine

The following are general risks considered to be associated with pridopidine administration:

- [redacted]
- [redacted]

- [redacted]

[redacted] and to ensure a reasonable minimum clearance in all patients through the renal pathway, patients with a creatinine clearance (calculated by the Cockcroft-Gault formula) <60 mL/min will be excluded from the study.

[redacted]; therefore, patients with body weight below 50 kg will be excluded from the study.

1.4.1.1. Drug Interactions

[redacted]. Patients on stable treatment with CYP2D6 inhibitors may be included in the study, since drug-induced inhibition of CYP2D6 metabolism is considered as functionally similar to genetic poor CYP2D6 metabolism.

[redacted], medications that are CYP2D6 substrates and have a narrow safety margin, eg, class I antiarrythmics and tricyclic antidepressants, will be administered according to the list of permitted and prohibited concomitant medications. Disallowed CYP2D6 substrates can be administered only 1 week after the discontinuation of pridopidine (i.e., 1-week washout), to allow enzyme recovery.

The concomitant use of medications that are known to have a profound effect on QT interval should be avoided according to the list of permitted and prohibited concomitant medications.

[redacted] concomitant treatment with tetrabenazine is disallowed.

Permitted and prohibited concomitant medications are detailed in Section 5.3.

1.4.1.2. Carcinogenesis, Mutagenesis, Impairment of Fertility

[redacted]

1.4.1.3. Pregnancy

[redacted] care should be taken to not expose pregnant women or women of childbearing potential to pridopidine.

[redacted]. Pridopidine use should therefore be restricted in nursing mothers.

1.4.1.4. Pharmacological Class Events

[redacted]

1.4.2. Benefits of Pridopidine

Results of 2 large previous clinical studies in HD patients, ACR16C009 (HART) and ACR16C008 (MermaiHD), suggested that pridopidine may have an effect on motor function.

[redacted]

1.4.3. Overall Risk and Benefit Assessment for This Study

The objective of the PRIDE-HD study is to investigate the safety and tolerability of pridopidine doses of 45-112.5 mg bid. Previously, doses up to 90 mg bid have been investigated in healthy volunteers (see Protocol Section 1.3.2.2 and IB sections 5.4.1, 5.4.2.5).

Although the results of the efficacy, safety and tolerability analyses of the PRIDE-HD study are not yet available, several measures have been implemented in this open-label extension study to ensure patient safety and to improve tolerability:

1. The present study design includes a 1-week titration period (see section 5.1 of the protocol) following the PRIDE-HD 2-week washout period, prior to administration of the 45 mg bid dose.

A robust set of relevant inclusion/exclusion criteria have been implemented, similar to those in PRIDE-HD:

- Patients with a clinically significant heart disease will be excluded;
- Patients with a QTcF interval of >450 msec at screening will be excluded;
- Patients with a known history of Long QT Syndrome will be excluded;
- Patients with serum potassium, magnesium and/or calcium levels outside of the central laboratory's reference range at the screening will be excluded;
- Patients receiving medications that have been proven to prolong QT interval will be excluded;
- Patients with a history of epilepsy or of seizures will be excluded;
- Patients receiving medications (that are metabolized by CYP2D6 (and hence are influenced by pridopidine treatment) and have the potential of reducing seizure threshold will be excluded;
- Patients are followed closely and monitored for suicidality and AE recording;
- In addition, a number of precautions are taken to exclude patients who might experience high exposures to pridopidine, i.e. patients with a body weight below 50 kg, and patients with renal impairment;
- Finally, the investigator will terminate the patient's participation in the study, should a QTc prolongation or a seizure occur, as defined in Section 3.6.1 of the protocol.

2. A monitoring plan has been implemented. Concomitant medication will be monitored throughout the study; ECG will be performed at every visit and will be centrally evaluated at a core lab.
3. During the study, an independent Drug Safety Monitoring Board (DSMB) will be responsible for reviewing accumulating unblinded safety data. The DSMB will meet on a regular basis (at least every 3 months) to ensure the continuing safety of the study patients and study conduct issues (see Section 3.6.1).

[redacted]

Therefore, all treatment arms in the study will be continued with updated informed consent and an amended protocol with additional increased precautionary safety measures (eg Section 3.1), including updated individual patient stopping rules (see Section 3.10.1) while the sponsor closely monitors psychiatric AEs in all pridopidine studies for emergence of any potential safety signal identified.

No new significant information or safety signal has been identified or obtained for the previously identified risks associated with use of pridopidine.

Taken collectively, the sponsor believes that the study is well equipped, as described above, to adequately investigate the long term safety and tolerability profile of pridopidine, while caring for the individual patient's safety.

Additional information regarding risks and benefits to human patients may be found in the current IB.

1.5. Selection of Drugs and Dosages

A detailed description of study drug administration is presented in Section 5.1.

1.5.1. Justification for Dosage of Active Drug

The dosages to be administered in this open-label extension study [i.e., 22.5 mg for 1 week and 45 mg bid from Week 2 onwards] were selected on the basis of previous doses investigated in clinical studies with pridopidine.

Studies MermaiHD (ACR16C008) and HART (ACR16C009) have shown that a pridopidine 45 mg bid dose is associated with improvement in UHDRS-TMS (of approximately 3 points relative to placebo) and motor subscores, with no aggravation in other domains of the disease (cognition, behavior).

Pridopidine has been shown to have a benign safety profile, similar to placebo, in 45 mg bid doses so far tested in patients with HD. Hence it was perceived as relevant to investigate higher doses, with the potential to increase the beneficial effects of pridopidine. Consequently, doses of 67.5, 90, and 112.5 mg bid are being explored in the ongoing PRIDE-HD study. Upon completion of PRIDE-HD and following analysis of safety, tolerability, and efficacy data the dose administered in this study may be adjusted to a maximum of 112.5mg bid after a titration period at the discretion of the sponsor.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations

[21CFR] Parts 11, 50, 54, 56, 312, and 314, European Union [EU] Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor and other forms as required by national authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the applicable study staff must be familiar with the background to, and requirements of, the study and with the properties of the study drug(s) as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the study at that center and for contacts with study management, with the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and with local authorities.

1.7. Population To Be Studied and Justification

The study population will consist of male or female patients aged ≥21 years and with body weight ≥50 kg, with diagnosis of HD, who completed the double-blind, randomized phase of the TV7820-CNS-20002 (PRIDE-HD) study, including the 2-week follow-up period, or patients who transitioned from the ACR16C015 (Open-HART) study. Eligible patients will be allowed to enter this open-label extension study to continue to receive treatment with pridopidine. Patients should be in good general health, ambulatory and have the capacity to travel to the clinic visits.

1.8. Location and Timing of Study

This study is planned to be conducted in Australia, Austria, Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Russia, UK, and the USA at up to 54 centers. It is expected to start in Q3 2015. Enrollment will continue until the last patient from the TV7820-CNS-20002 study (PRIDE-HD) has entered the study. Treatment duration will be extended for an additional 52 weeks (ie total of 104 weeks), until approximately Q3 2017 (last patient last visit for the extended study period).

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

The present clinical study is planned as an open-label extension of the TV7820-CNS-20002 (PRIDE-HD) study, in order to collect and assess long term data on the safety, tolerability, and efficacy of pridopidine in patients with Huntington's disease (HD).

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to evaluate safety and tolerability of pridopidine in patients with HD**.**

2.2.2. Secondary Objectives

The secondary objectives of the study are to assess the effects of long-term, open-label dosing with pridopidine on motor symptom severity, overall patient function, physical performance, and health-related quality of life in patients with HD.

2.3. Study Endpoints

2.3.1. Safety and Tolerability Endpoints

2.3.1.1. Safety Endpoints:

The safety endpoints for this study are as follows:

- adverse events (AEs) throughout the study
- vital signs assessments
- concomitant medication usage throughout the study
- physical examination findings
- clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis)
- ECG findings
- Suicidality [using the Columbia-Suicide Severity Rating Scale (C-SSRS)] and Problem Behaviors Assessment-Short form (PBA-s)

2.3.1.2. Tolerability Endpoints:

The tolerability endpoints for this study are as follows:

- Proportion of subjects (%) who prematurely discontinued from the study
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs

2.3.2. Efficacy Endpoints

Long-term efficacy evaluations are the secondary objective of this study. Efficacy endpoints include the following:

- Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS)
- Modified Physical Performance Test (mPPT)
- Unified Huntington's Disease Rating Scale - Total Functional Capacity (UHDRS-TFC)
- Short Form 12 (SF-12) questionnaire (acute version)
- Problem Behaviors Assessment-Short form (PBA-s) (also part of safety assessments)
- Quantitative motor (Q-motor) assessments

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a multicenter, open-label study to evaluate the safety, tolerability, and efficacy of pridopidine treatment at a dosage of 45 mg bid in adults with HD. The study will consist of a screening period up to 2 weeks, followed by an open-label treatment period.

The assessments and procedures performed during each study visit are detailed in Table 1 and Section 3.12.

Up to 300 patients from the PRIDE-HD and the Open-HART studies are planned to be enrolled to receive a total daily dose of 90 mg pridopidine (45 mg bid) for the duration of the study.

If medically necessary (e.g. following discussion with the medical monitor), the patient may be allowed to de-escalate to a dose of 22.5 mg bid. The start date and reason for de-escalation will be entered into the electronic case report form (eCRF).

Upon meeting eligibility criteria, patients who transition from the ACR16C015 (Open-HART) study may perform the baseline visit assessments and procedures. They do not have to undergo titration as they will continue taking the same dose as in Open-HART (45 mg bid).

Upon completion of the PRIDE-HD study and analysis of the efficacy, safety, and tolerability data, the dose of study drug administered to the patients in this long-term study may be adjusted.

After the 1 week titration period, patients will be seen at Weeks 4, 12, 26, 52, 78, and 104. An EoS follow-up visit will take place at Week 106. Safety evaluation telephone calls will be performed at weeks 18 and 38. During these phone calls, inquiries about adverse events, concomitant medication (including changes in use of benzodiazepines and antidepressants), changes in use of alcohol and illicit drugs, C-SSRS, and an abbreviated PBA-s (a subset of PBA-s questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, and obsessive-compulsive behaviors) will be conducted.

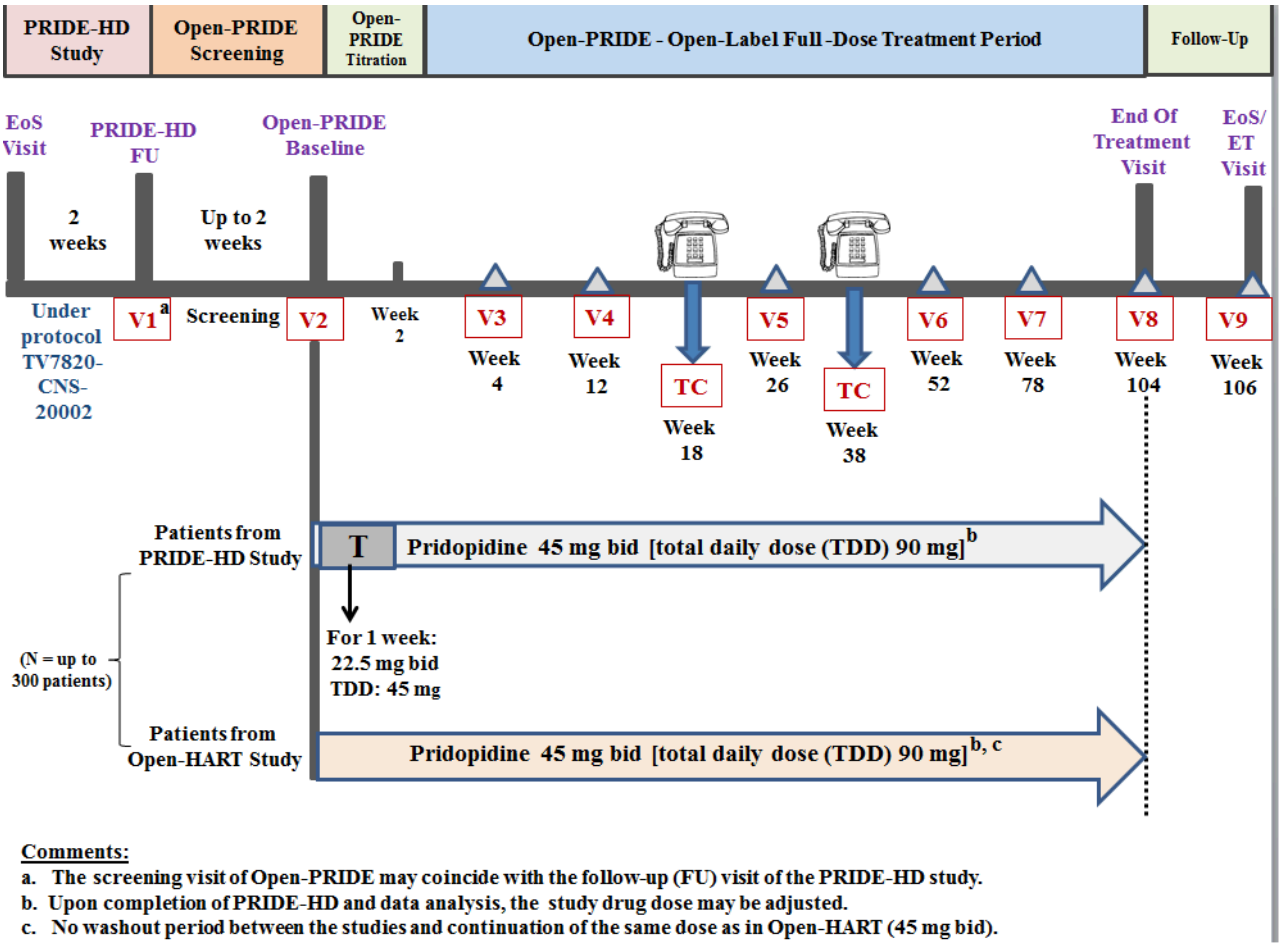
Patients who discontinue study medication due to safety or tolerability reasons may continue in the study off drug and perform the scheduled visits and assessments.

Patients who withdraw from the study will have the early termination procedures and assessments performed at their final visit.

An independent DSMB will oversee the study (see Section 3.6.1).

The study schema is presented in Figure 1.

Figure 1: Overall Study Schema



Comments:
a. The screening visit of Open-PRIDE may coincide with the follow-up (FU) visit of the PRIDE-HD study.
b. Upon completion of PRIDE-HD and data analysis, the study drug dose may be adjusted.
c. No washout period between the studies and continuation of the same dose as in Open-HART (45 mg bid).

Abbreviations: EoS=end of study; ET=early termination; FU=follow up; PRIDE-HD=PRIdopidine Dose Evaluation in Huntington's Disease (Study TV7820-CNS-20002); T=titration period; TDD=total daily dose; V=visit.

Digital Health Sub-study (optional participation):

Motor symptoms can be objectively assessed in Huntington's disease patients using different quantitative motor assessments.

Objective motor assessments aim at improving the limited sensitivity observed with categorical clinical rating scales, and reducing the intra- and inter-rater variability, as well as potential placebo effect observed in scales such as the UHDRS. Improved sensitivity for early-stage clinical studies of efficacy of a new drug on motor dysfunction is expected with objective assessments and may support early go/no go decisions in smaller cohorts of patients (Reilmann et al. 2001; Reilmann et al. 2011).

A feasibility sub-study including up to 60 patients with chorea will be conducted to collect accelerometry data using a wearable sensor-mobile application tool. The overall objective of the sub-study is to test the hypothesis of using wearable sensor data to estimate clinically relevant measures of HD in patients while on their medication regimen, which includes pridopidine. The aim is to develop algorithms to objectively quantify chorea by analyzing the data from the wearable sensors. The application will also include a simple diary to track medication use during

the study. Patients enrolled in the sub-study will be provided with a commercial grade wearable digital sensor (Pebble watch), an android smartphone and will be granted access to the accompanying mobile application. The mobile application will collect accelerometry and medication data and transmit for storage and processing. Participating subjects will be asked to continuously wear the digital sensor for a period of 6 months. Participation in the sub-study will be optional. The accelerometry data collection will be performed on the wrist of the non-dominant limb. A training session will be done at screening for the sub-study. Assessments will be done at times specified in the Schedule of Activities section of the protocol. A separate user's manual and training on the tool will be provided to sites. This system of data collection will allow researchers and clinicians to gather detailed patient data outside of the clinical setting. The data analysis is expected to facilitate future research and clinical studies on the effectiveness of new interventions in HD.

3.2. Justification for Study Design

The open label study design is considered standard practice to gain additional experience in the clinical setting, to increase exposure, and to enhance understanding of the safety, tolerability, and efficacy profile of the drug.

3.3. Efficacy Measures and Time Points

Efficacy analyses will be considered exploratory. Comparisons will generally be made to baseline, as appropriate. Efficacy endpoints include the following:

- UHDRS-TMS - will be performed at all visits during the Open-PRIDE study.
- mPPT - will be performed at baseline and at weeks 12, 26, 52, 78, 104 and 106.
- UHDRS-TFC - will be performed at baseline and at weeks 26, 52, 78, 104 and 106.
- SF-12 (acute version) - will be administered at baseline and at weeks 26, 52, 78, 104 and 106.
- PBA-s – will be performed at all visits during the Open-PRIDE study (also part of safety assessments).
- Q-motor – will be performed at baseline and at weeks 52, 78, 104 and 106.

3.4. Safety and Tolerability Measures and Time Points

The following safety and tolerability measures will be assessed during the study:

- AEs – will be monitored at every study visit.
- Vital signs assessments – will be monitored at every study visit.
- Concomitant medication usage - will be monitored at every study visit.
- Physical examination findings – brief physical examination will be performed at every study visit.
- Clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis) - will be performed at each study visit

- ECG findings – ECG will be performed at every study visit (in triplicate at baseline; single measurement at all subsequent visits)
- Suicidality (C-SSRS and PBA-s) will be assessed throughout the study.

Tolerability endpoints:

- Proportion of subjects (%) who prematurely discontinued from the study
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs

A description of the safety measures is provided in Section 7.

3.5. Pharmacokinetic Measures and Time Points

Pharmacokinetics is not evaluated in this open-label study. Pharmacokinetic samples will be aimed to be drawn, to the extent possible, in the event of a SAE, an AE leading to discontinuation, or for patients who withdrew prematurely because of lack of efficacy.

3.6. Randomization and Blinding

This is a non-randomized, open-label study and there is no blinding.

3.6.1. Data and Safety Monitoring Board

During the conduct of this study, a DSMB will review accumulating safety data on a regular basis (as detailed in the DSMB charter) to ensure the continuing safety of the study patients and study conduct issues.

The DSMB will be comprised of the same members as that of the PRIDE-HD study. It is composed of independent physicians with expertise in the relevant therapeutic field and other relevant experts, such as a statistician. The DSMB will receive safety data periodically in an unblinded fashion. They will have the right to recommend discontinuation of the study for safety reasons.

All DSMB sessions will be open. During open sessions, representatives of the sponsor may be present and information is provided and discussed in an unblinded fashion.

The DSMB chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the study. The sponsor will work closely with the committee to provide the necessary data for review.

The conduct and specific details regarding the DSMB sessions are outlined in the DSMB charter.

3.7. Drugs Used in the Study

3.7.1. Investigational Product

A more detailed description of pridopidine administration procedures is given in Section 5.1.

This is an uncontrolled study with no other study drug.

Additional details may also be found in the current version of the IB for pridopidine.

3.8. Drug Supply and Accountability

3.8.1. Drug Storage and Security

All medication supplied in connection with this study must be used only for this study and no other purpose.

Study drug supplies will be stored securely according to the manufacturer's drug product stipulation in a temperature-controlled storage area (a locked cupboard or pharmacy with limited access). Only authorized personnel will have access to the study drug. The study site personnel at each site will be responsible for correct storage and handling of the study drug.

All study drug supplies must be stored in a dry place, at room temperature (15°C to 25°C/59°F to 77°F). Medication must not be refrigerated.

Any actual or suspected theft or diversion must be reported to the sponsor immediately.

3.8.2. Drug Accountability

Each study drug shipment will include a packing slip listing the contents of the shipment, drug return instructions, and any applicable forms. Distribution of study drugs will be performed under the sponsor's responsibility.

The investigator is responsible for ensuring that deliveries of study drug and other study materials from the sponsor are correctly received, recorded, handled and stored safely and properly in accordance with the CFR or local regulations, and used in accordance with this protocol.

If the study drug supplies appear to be damaged or missing upon arrival at the investigational site, the sponsor should be contacted immediately.

Patients will be instructed to return all used empty bottles and unused study drug at each visit.

A record of study drug accountability (i.e., study drug and other materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty, partially used, and unused bottles of study drug will be destroyed or returned to the sponsor or its designee. The Monitor is responsible for the accountability of the returned study drugs.

3.9. Duration of Patient Participation and Justification

This study will consist of an up to 2-week screening period, an open-label treatment period of 104 weeks and an end-of-study visit (at week 106). Patients are expected to participate in this study for its entire duration. See Section 12.4 for the definition of the end of the study.

3.10. Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study.

During the conduct of the study, SAEs will be reviewed (see Section 7.1.5) as they are reported from the investigational center to identify safety concerns. The study may be terminated by the sponsor at any time.

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, and adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol violation or deviation as defined in Section 11.1.2, noncompliance, or adverse event).

3.10.1. Discontinuation of Individual Patients

If hypokalemia is observed, dosing will be interrupted and should not be started again until normal electrolyte values are confirmed and maintained for 7 days. Patients needing more than 14 days to reach stable potassium levels, without study drug, should be withdrawn from the study drug. The patient will be asked to continue in the study and follow the visit schedule as outlined in the protocol.

At any visit, if a QTcF of >500 msec is recorded in a single measurement, 2 additional measurements will be performed and the mean value will be calculated. If the mean value is above >500 msec, the patient should be withdrawn from the study.

If the local ECG reading results at the site match the above criterion, the patient 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 patient should restart study medication.

Patients should also be discontinued if:

- they experience a seizure or convulsions (regardless of the relationship to treatment);
- their body weight decreases to <50 kg (may be discontinued based on Investigator or Sponsor discretion);
- and/or if creatinine clearance decreases to <60 mL/min (calculated using the Cockcroft-Gault equation). It is allowed to repeat the test once, if clinically appropriate.
- they experience adverse event/serious adverse event of suicide ideation or attempt; or
- they have a C-SSRS suicidal ideation score >2 (ie, 3, 4 and 5); or
- they have a C-SSRS report of suicidal act; or
- they have a PBA-s suicidal ideation item score >2 (ie, 3, 4, 5) .

Patients who discontinue study medication due to safety or tolerability reasons may continue in the study off drug and perform the scheduled visits and assessments.

In case the 45 mg bid treatment arm in PRIDE-HD is discontinued for safety reasons, the Open-PRIDE-HD study (utilizing the same 45 mg bid dose) will be stopped.

3.11. Source Data Recorded on the Case Report Form

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed onto the case report form (CRF). Data may not be recorded directly onto the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly onto the CRF.

If data are processed from other institutions (eg, clinical laboratory, central image center, electronic diary data), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database (see Section 13.1). All data from other institutions will be available to the investigator.

The CRFs are filed in the sponsor's central file.

3.12. Study Procedures

Study procedures and assessments with their timing are summarized in Table 1.

Detailed by-visit information is provided in the sections following the table. Detailed descriptions of each assessment are provided in Section 6 (efficacy assessments), Section 7 (safety assessments), and Section 8 (pharmacokinetic and other assessments).

Table 1: Study Procedures and Assessments

Study period		**Open label treatment period**									**Follow Up**
Visit number	**V1**	**V2**	**V3**	**V4**	**TC**	**V5**	**TC**	**V6**	**V7**	**V8 End-Of-Treatment Visit**	**V9 End–Of – Study / ET Visit**
Procedures and assessments	**Screening** [a b]	**Baseline**[c]	**Week 4**[d]	**Week 12**[d]	**Week 18**	**Week 26** [d]	**Week 38**	**Week 52** [d]	**Week 78**	**Week 104**	**Week 106** [d]
Allowed time windows	**Up to 2 weeks**		**±3 days**	**±4 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**
On-site visit	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	**X**
Telephone call					**X**		**X**				
Informed consent	X										
Medical and psychiatric history[e]	X										
Prior medication history[e]	X										
Inclusion and exclusion criteria	X	X									
Clinical laboratory tests (Clinical chemistry, hematology and urinalysis)	X	X	X	X		X		X	X	X	X
Brief physical examination [f g]	X	X	X	X		X		X	X	X	X
Electrocardiography	X[h]	X	X	X		X		X	X	X	X
Vital signs measurement[i]	X	X	X	X		X		X	X	X	X
Serum/urine β-HCG test for women of childbearing potential	X[j]	X[k]	X	X		X		X	X	X	X
C-SSRS	X[l]	X	X[m]	X[m]	X	X[m]	X	X[m]	X	X	X[m]
UHDRS-TMS	X	X	X	X		X		X	X	X	X
UHDRS-TFC		X				X		X	X	X	X
mPPT		X		X		X		X	X	X	X
SF-12		X				X		X	X	X	X
PBA-s	X	X	X	X		X		X	X	X	X

Study period		**Open label treatment period**									**Follow Up**
Visit number	**V1**	**V2**	**V3**	**V4**	**TC**	**V5**	**TC**	**V6**	**V7**	**V8 End-Of-Treatment Visit**	**V9 End–Of – Study / ET Visit**
Procedures and assessments	**Screening** [a b]	**Baseline**[c]	**Week 4**[d]	**Week 12**[d]	**Week 18**	**Week 26** [d]	**Week 38**	**Week 52** [d]	**Week 78**	**Week 104**	**Week 106** [d]
Allowed time windows	**Up to 2 weeks**		**±3 days**	**±4 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**
On-site visit	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	**X**
Telephone call					**X**		**X**				
Abbreviated PBA-s					X[n]		X[n]				
Q-motor[o]		X						X	X	X	X
Adverse event inquiry	X	X	X	X	X	X	X	X	X	X	X
PK sampling[p]											
Dispense/collect study drug		X	X	X		X		X	X	X[q]	
Dosage review and adjustment (titration)		X[r]									
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X	X
Benzodiazepines and antidepressants inquiry[s]	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
Inform patients of study restrictions and compliance requirements	X	X									
Review of study compliance and adherence			X	X	X[t]	X	X[t]	X	X	X	X

[a] The screening visit of the Open-PRIDE study may coincide with the follow-up visit of PRIDE-HD. If found operationally convenient and effective for a site, the screening visit may take place over the course of more than 1 day; however, the allowed 2-week screening period may not be exceeded.

[b] If a certain procedure or assessment was completed for the PRIDE-HD study, which took place on the same day as the Open-PRIDE screening visit, this procedure or assessment does not need to be repeated for Open-PRIDE.

[c] All baseline (Visit 2) assessments must take place on the same day.

[d] If found operationally convenient and effective for a site, the procedure and assessment visits (V3 through End of Study/ ET) may be performed over several days, as long as they are completed within the defined visit window.

[e] A gap of up to 3 months is allowed between the patient's completion of the PRIDE-HD study and the Open-PRIDE screening visit. If less than 3 months have passed, and there are no changes to psychiatric, medical, or medication history since completion of the PRIDE-HD study, these data do not have to be re-captured in the eCRF. If the gap is between 3-6 months, the information has to be re-captured.

[f] Weight will be measured at the screening visit and at baseline (for study eligibility) and at week 26, 52 78, 104 and 106.

[g] Brief physical exam will be focused on general appearance, the cardiovascular, pulmonary, abdominal exams, as well as directed towards any patient-reported symptoms. The brief neurological exam includes observation for cerebellar (intention) tremor and for non-cerebellar tremors (eg, resting or positional), finger-nose, heel-shin, Romberg, tandem walking, positional, and gaze-evoked nystagmus.

[h] ECGs will be performed in triplicate at screening.

[i] Vital signs include pulse, blood pressure (supine and standing), body temperature.

[j] Serum B-HCG test will be performed for all women of childbearing potential at screening.

[k] Urine HCG tests will be performed for all women of childbearing potential at all subsequent visits.

[l] If less than 3 months have passed since the patient's completion of the PRIDE-HD protocol and the Open-PRIDE screening visit, the "since last visit" version of the scale can be used. If 3-6 months have passed, the screening/baseline version of the scale should be administered.

[m] The "Since Last Visit" version will be administered at all subsequent visits.

[n] The safety telephone calls will include an abbreviated PBA-s (a subset of PBA-s questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, and obsessive-compulsive behaviors).

[o] Including digitomotography (speeded index finger tapping), dysdiadochomotography (pronation/supination hand tapping), manumotography and choreomotography (grip force and chorea analysis) and pedomotography (speeded foot tapping).

[p] PK samples will be aimed to be drawn, to the extent possible, in the event of a SAE, an AE leading to discontinuation, or for patients who withdrew prematurely because of lack of efficacy.

[q] At the end-of-treatment (EoT) visit (Visit 8), study drug will only be collected.

[r] Patients will undergo a 1-week titration in which a pridopidine dose of 22.5 mg bid (total daily dose 45 mg) will be taken. From week 2 onwards, patients will receive a pridopidine dose of 45 mg bid (total daily dose 90 mg). Doses up to 112.5 mg bid are currently being investigated in the ongoing PRIDE-HD study. Following availability of PRIDE-HD results, the dose administered in this study may be adjusted.

[s] This information will be collected as part of concomitant medication inquiry.

[t] Study adherence will be reviewed during the safety telephone calls.

Abbreviations: bid=twice daily; β-HCG=beta human chorionic gonadotropin ; C-SSRS=Columbia-Suicide Severity Rating Scale; ET=Early Termination; mPPT=Modified Physical Performance Test; PBA-s=Problem Behaviors Assessment-Short form; PK=pharmacokinetic(s); Q26=every 26 weeks after the Month 12 visit; TC=telephone contact; TFC=Total Functional Capacity; TMS=Total Motor Score; SAE=serious adverse event; SF-12=Short Form 12; Q-motor=Quantitative motor; UHDRS=Unified Huntington’s Disease Rating Scale; V=Visit

3.12.1. Procedures for Screening and Enrollment (Visit 1)

A signed and dated informed consent form will be obtained before screening procedures commence (see Section 12.1). Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations. In addition, disease-specific assessments performed within a specified time frame before informed consent may be used for the study. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, patients will be enrolled into the Open-PRIDE study and will continue with their assigned subject identification number from the PRIDE-HD study.

The screening visit of the Open-PRIDE study may coincide with the follow-up visit of the PRIDE-HD study. If the Open-PRIDE screening visit occurs on the same day as the last visit of the PRIDE-HD study, procedures or assessments completed for the PRIDE-HD study do not need to be repeated for Open-PRIDE.

A patient who is screened but not enrolled, eg, because entry criteria were not met or enrollment did not occur within the specified time, or other logistical or operational issues occurred, may be considered for screening again if, eg, there is a change in the patient's medical background or a modification of study entry criteria.

The screening visit (Visit 1) will take place not more than 2 weeks before the baseline visit. If found operationally convenient and effective for a site, the screening visit may take place over the course of more than 1 day; however, the allowed 2-week screening period may not be exceeded.

The following procedures will be performed at Visit 1:

- obtain written informed consent before any other study-related procedures are performed
- review inclusion/exclusion criteria
- review medical, medication and psychiatric history
    - If less than 3 months have passed between the patient's completion of the PRIDE-HD study and the Open-PRIDE screening visit, and there are no changes to medical, medication, or psychiatric history since completion of the PRIDE-HD study, these data do not have to be re-captured in the eCRF.
    - If the gap is between 3-6 months, the information has to be re-captured.
- perform clinical laboratory tests
- perform vital signs measurements
- perform ECG (in triplicate)
- perform brief physical examination (including weight)
- serum β-HCG test for women of childbearing potential

- C-SSRS
    - If less than 3 months have passed between the patient's completion of the PRIDE-HD study and the Open-PRIDE screening visit, the "Since Last Visit" version of the scale may be administered.
    - If the gap is between 3-6 months, the screening/baseline version of the scale will be administered.
- UHDRS-TMS
- PBA-s
- inquire about AEs
- concomitant medication inquiry (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- inform patients of study restrictions and compliance requirements

3.12.2. Procedures Before Study Drug Treatment (Baseline [Visit 2])

Patients who meet the inclusion/exclusion criteria at Visit 1 will continue to Visit 2, when baseline evaluations will be conducted. All baseline (Visit 2) assessments must take place on the same day.

The following procedures will be performed at Visit 2:

- review inclusion/exclusion criteria
- perform clinical laboratory tests
- perform brief physical examination
- perform ECG
- perform vital signs measurements
- urine β-HCG test for women of childbearing potential
- C-SSRS ("Since Last Visit" version)
- UHDRS-TMS
- mPPT
- UHDRS-TFC
- SF-12 questionnaire
- PBA-s
- Q-motor
- inquire about AEs

- concomitant medication inquiry (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- dispense study drug
- inform patients of study restrictions and compliance requirements

A patient who is not enrolled in the study on the basis of results of baseline assessments (eg, because entry criteria were not met or enrollment did not occur within the specified time) may be considered for screening again if there is a change in the patient's medical background, a modification of study entry criteria, or other relevant change.

Patients who continue to meet the inclusion/exclusion criteria may be enrolled into the study, and study drug will be dispensed.

3.12.3. Procedures During Study Drug Treatment – Open Label Treatment Period

If found operationally convenient and effective for a site, the procedure and assessment visits (V3 through End of Study/ ET) may be performed over several days, as long as they are completed within the defined visit window.

3.12.3.1. Weeks 4 and 12 [Visits 3 and 4]

The following procedures/assessments will be performed at weeks 4 and 12 (visits 3 and 4):

- perform clinical laboratory tests
- perform brief physical examination
- perform ECG
- perform vital signs measurements
- urine β-HCG test for women of childbearing potential
- C-SSRS ("Since Last Visit" version)
- UHDRS-TMS
- mPPT - **at Week 12 only**
- PBA-s
- inquire about AEs
- concomitant medication inquiry (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- dispense/collect study drug
- review study compliance

3.12.3.2. Telephone Contact at Week 18 and Week 38

Patients will be contacted by telephone at week 18 and week 38 to evaluate safety and tolerability to the study drug through the following:

- assessment of adverse events
- use of concomitant medications (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- C-SSRS ("Since Last Visit" version)
- abbreviated PBA-s (a subset of PBA-s questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, and obsessive-compulsive behaviors)
- review of study adherence

3.12.3.3. Week 26 (Visit 5), Week 52 (Visit 6), Week 78 (Visit 7) and Week 104 (End Of Treatment, Visit 8)

The following procedures/assessments will be performed at Weeks 26, 52, 78, and 104 (s Visits 5-8):

- perform clinical laboratory tests
- perform brief physical examination
- perform ECG
- perform vital signs measurements
- urine β-HCG test for women of childbearing potential
- C-SSRS ("Since Last Visit" version)
- UHDRS-TMS
- mPPT
- UHDRS-TFC
- SF-12 questionnaire
- PBA-s
- Q-motor assessments – **at Visits 6, 7, and 8 only**
- inquire about AEs
- concomitant medication inquiry (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- dispense study drug – **only at Visits 5, 6, and 7**
- collect study drug **– at Visits 5, 6, 7, and 8**

- review study compliance

3.12.3.4. Week 106 (Visit 9) - End of Study / Early Termination Visit

The following procedures/assessments will be performed at the end-of-study visit:

- perform clinical laboratory tests
- perform brief physical examination
- perform ECG
- perform vital signs measurements
- urine β-HCG test for women of childbearing potential
- C-SSRS ("Since Last Visit" version)
- UHDRS-TMS
- mPPT
- UHDRS-TFC
- SF-12 questionnaire
- PBA-s
- Q-motor
- inquire about AEs
- concomitant medication inquiry (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- PK sampling
    - PK samples will be aimed to be drawn, to the extent possible, in the event of an AE leading to discontinuation, or for patients who withdrew prematurely because of lack of efficacy.
- collect study drug
- review study compliance

3.12.4. Procedures After Study Drug Treatment

For patients who complete the study or withdraw prematurely, final evaluations will be performed at an end-of treatment visit or on the last day the patient receives the study drug, or as soon as possible thereafter. Procedures for patients who withdraw prematurely from the study are described in Section 4.4. As appropriate, patients should be treated with standard of care (SOC) following termination of the study.

Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2.

Patients who discontinue study medication due to safety or tolerability reasons may continue in the study off drug and perform the scheduled visits and assessments.

3.12.5. Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures performed during unscheduled visits include the following:

- concomitant medication review (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- vital signs measurements
- AE inquiry
- review of study drug accountability
- collect study drug
- study compliance review
- C-SSRS ("Since Last Visit" version) and PBA-s (if visit scheduled to assess psychiatric adverse events)

Other procedures may be performed at the discretion of the investigator.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study eligibility criteria to allow patients to enter a study are not granted by Teva (see Section 11.1.2).

4.1. Patient Inclusion Criteria

Patients may be included in this study only if they meet all of the following criteria:

a. [Revision 1] Patient has completed the PRIDE-HD trial within the last 6 months, including the follow-up period, or transitioned from Open-HART.

   For patients that have failed to complete PRIDE-HD or those who completed the PRIDE-HD study over 6 months prior to the screening visit, and meet all other inclusion criteria, eligibility should be discussed with the Open-PRIDE medical monitor and clinician on a case-by-case basis.

b. [Revision 1] For patients that experienced a drug-related SAE or had a major compliance violation during PRIDE-HD or Open-HART, eligibility approval should be discussed with PRIDE-HD's or Open-HART's medical monitor and clinician. Patients that experienced an adverse event/serious adverse event of suicidal ideation/behavior will be excluded without discussion.

c. Able and willing to provide written informed consent prior to any study related procedure being performed. Patients with a legal guardian should be consented according to local requirements.

d. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception according to local regulations (hormone-based, intrauterine device, or double barrier contraception, i.e., condom and diaphragm). Abstinence is an acceptable method of contraception only when this is the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male study participants have to be compliant in using adequate birth control with their partners (as defined above) throughout the duration of the study.

e. Body weight ≥50 kg. Patients that meet this criterion at screening but fail to meet it at a subsequent visit may be discontinued based on Investigator or Sponsor discretion. It is allowed to repeat the weight measurement once, if clinically appropriate.

f. Willing and able to take oral medication and able to comply with the study specific procedures.

g. Ambulatory, being able to travel to the study center, and judged by the investigator as likely to be able to continue to travel for the duration of the study.

h. The patient is in good health as determined by medical examination, ECG, serum chemistry, hematology, and urinalysis.

i. The patient must be willing and able to comply with study restrictions and to remain at the clinic for the required duration during the study period, and willing to return to the clinic for evaluation as specified in this protocol.

4.2. Patient Exclusion Criteria

Patients will be excluded from participating in this study if they meet any of the following criteria:

a. A prolonged QTcF interval (defined as a QTcF interval of >450 msec) at the screening visit. ECGs will be performed in triplicate during the screening visit, and the mean of the 3 QTcF measurements will be used to determine whether or not the patient is suitable for inclusion in the study.

b. Patients with clinically significant heart disease at the screening visit, defined as follows: (i) significant cardiac event (eg, myocardial infarction), angina pectoris or episode of congestive heart failure with symptoms >Grade 2 New York Heart Association classification within 12 weeks before randomization, or presence of cardiac disease that in the opinion of the investigator increased the risk of ventricular arrhythmia, (ii) history of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia) that was symptomatic or required treatment (Common Terminology Criteria for Adverse Events Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia, (iii) presence of left bundle branch block.

c. Patients with serum potassium, magnesium, and/or calcium levels outside of the central laboratory's reference range at the screening visit and considered clinically significantly abnormal by the investigator. Repeat testing is allowed (up to a maximum of 3 tests) if required to establish whether values are within normal range or clinically significantly abnormal.

d. Patients receiving medications (within the last 6 weeks prior to baseline) other than pridopidine that have been proven to prolong QT interval or who may require such medications during the course of the study such as but not limited to non-allowed anti-psychotic medications, tricyclic antidepressants, and/or Class I antiarrhythmics.

e. Patients receiving medications (within the last 6 weeks prior to baseline) other than pridopidine that are metabolized by CYP2D6 and have the potential of reducing seizure threshold.

f. Patients with a history of epilepsy or of seizures within the last 5 years.

g. Creatinine clearance <60 mL/min at screening, calculated using the Cockcroft-Gault equation: (140 - age) × mass (kg) × [0.85 if female] / 72 × serum creatinine (mg/ dL). It is allowed to repeat the test once, if clinically appropriate.

h. Any clinically significant, abnormal, screening laboratory result which in the opinion of the investigator, affects the patients' suitability for the study or puts the patient at risk if he/she enters the study.

i. [Revision 1] Patients with adverse events of suicidal ideation or attempt at any time in the past or as measured by suicide ideation score of ≥3on the C-SSRS, or PBA-s or patients who answer "Yes" on any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) if the attempt or acts were performed at any time in the past, or patients who, in the opinion of the investigator, present a risk of suicide.

j. Females who are pregnant or breastfeeding.

k. Treatment with any investigational product other than pridopidine within 6 weeks of screening or patients planning to participate in another clinical study assessing any investigational product during the study.

4.3. Justification for Key Inclusion and Exclusion Criteria

The key inclusion criteria are:

- PRIDE-HD completion, (Note: The follow up period in the PRIDE-HD trial is 2 weeks (± 1 week). As long as the protocol visit windows are adhered to, a patient may perform baseline activities upon meeting all inclusion criteria) or transition from the ACR16C015 (Open-HART) study;
- Weight ≥50 kg at screening;
- Women of child-bearing potential or male participants: Adequate contraception and birth control;
- Good general health;

The key exclusion criteria include:

- Similar baseline criteria for ECG, vital signs, cardiovascular system, and renal function to PRIDE-HD;
- Similar concomitant medication restrictions to PRIDE-HD.

The justification for the key inclusion and exclusion criteria are to maintain the stringent safety-related characteristics from the PRIDE-HD study, which may influence patient safety during participation in this open-label study, and allow transition of patients from the Open-HART study.

4.4. Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study at any time. The investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, pregnancy (see Section 7.2), or other reasons concerning the health or well-being of the patient, or in the event of lack of cooperation. In addition, a patient may be withdrawn from the study as described in Sections 3.10, 3.12.4, 5.4, and 7.1.7.

Should a patient decide to withdraw after administration of study drug(s), or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the

patient's withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed onto the CRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a potentially clinically significant abnormal laboratory test result, monitoring will be continued at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event or test result must be recorded on the source documentation and transcribed onto the CRF.

In addition, a blood sample will be obtained for the measurement of study drug concentrations. The sample date and time will be recorded on the source documentation and transcribed onto the CRF.

All evaluations should be performed according to the protocol on the last day the patient takes study drug, or as soon as possible thereafter.

If the final visit is conducted more than 7 days after the final dose of study drug, all safety evaluations will be performed, but efficacy evaluations will not be made (see Section 3.12.4).

5. TREATMENT OF PATIENTS

5.1. Drugs Administered During the Study

Following the baseline visit, patients will be assigned to receive pridopidine 22.5 mg bid (45 mg). Capsules will be swallowed whole with water. One capsule should be administered orally once each day in the morning, and 1 in the afternoon, 7 to 10 hours after the morning dose. Study drug can be taken irrespective of meals. Study drug will be titrated for 1 week up to the dosage of 90 mg/day (45 mg bid). Following titration, patients will remain at their dosage (45 mg bid) for the duration of the study.

If medically necessary (e.g. following discussion with the medical monitor), the patient may be allowed to de-escalate to a dose of 22.5 mg bid. The start date and reason for de-escalation will be entered into the eCRF.

Pridopidine will be provided as a white hard gelatin capsule, size 2 containing 45 mg pridopidine and a white hard gelatin capsule, size 4 containing 22.5 mg pridopidine or a light pink/white hard gelatin capsule, size 2, with black color imprinting containing 45 mg pridopidine and a white hard gelatin capsule, size 4, with black imprinting containing 22.5 mg pridopidine.

An Interactive Response Technology (IRT) system will be used to manage the Pridopidine supply at the depots and sites.

Each medication pack will contain distinct labeled bottles in accordance with the associated dose strength. The capsules will be provided in 2 configurations: Each bottle will contain 30 capsules (of 22.5 mg or 45 mg white capsules; or 22.5 mg white imprinted capsules) or 60 capsules (of 45 mg light pink/white imprinted capsules). Bottles will be used to accomplish the dosing of possible treatment options including possible dose escalation and de-escalation. Each bottle will be labeled with a unique pack number.

All medication supplied in connection with this study must be used only for this study and no other purpose.

Study drug will be packaged in bottles and provided for patients to take at home (see Section 3.7). Study drug exposure will be measured and compliance to study drug administration will be monitored.

5.2. Restrictions

Medications prohibited before and/or during the study are described in Section 5.3.

Restrictions in regard to sexual activity and required laboratory values are provided in the inclusion and exclusion criteria.

There are no additional restrictions in this study.

5.3. Prior and Concomitant Therapy or Medication

Any prior or concomitant therapy, medication, or procedure a patient has had within 2 weeks prior to screening and up to the end of the study period will be recorded on the CRF. Generic or

trade name, indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHO Drug).

Medications that are not prohibited during the study (see Section 5.3.1) are allowed at the discretion of the investigator and will be documented in the CRF. To the extent possible, patients should continue on medications already prescribed at enrollment; dose modifications and introduction of new medications should be avoided unless deemed necessary for optimal patient care by the investigator.

Disallowed CYP2D6 substrates can be administered only 1 week after the discontinuation of pridopidine (i.e., 1-week washout), to allow enzyme recovery. CYP2D6 inhibitors can be administered to study patients. The concomitant use of medications that are known to have a profound effect on QT interval should be avoided according to the list of permitted and prohibited concomitant medications. [redacted] concomitant treatment with tetrabenazine is disallowed. Medications that are CYP2D6 substrates and have the potential to reduce the seizure threshold will not be permitted during the study.

Any changes to an existing concomitant medication or any new medication started during the study should be recorded in the CRF. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented on the AE Form of the CRF.

If a patient receives a prohibited treatment during the randomized phase of the study, he/she will be encouraged to continue in the study and complete the study visits in accordance with the study visit schedule; however, the patient may need to be withdrawn from study treatment (see Section 4.4). If the patient refuses to be seen for further visits, the assessments for End-of-Study (EoS)/Early Termination should be performed, as far as possible (at least attempts to capture information on AEs and concomitant medication).

At each clinic visit after the screening visit, the investigator will ask patients whether they have taken any medications (other than study drug), including over-the-counter (OTC) medications, vitamins, or herbal or nutritional supplements, since the previous visit. Indication, dosage, and start and end dates should be entered on the CRF.

5.3.1. Permitted Medication

For patients taking allowed antipsychotic, antidepressant, antiarrhythmic, or other medication, the dosing of medication must have been kept constant for at least 6 weeks before baseline and must be kept constant during the study.

If the dose was adjusted during the PRIDE-HD study, but less than 6 weeks prior to the Open-PRIDE screening visit, the patient's eligibility to participate in the study will be assessed on a case-by case basis.

Allowed antipsychotic medications are olanzapine, quetiapine, thiothixene, acetophenazine, trifluprom azine, loxapine, tiapride, chlorprothixene, and bromperidol. Aripiprazole, risperidone, and perphenazine are permitted, at no more than usual recommended doses in the approved labeling. If, according to investigator judgment, a change of usage or dosage of antipsychotic medication is required during the study, this should be recorded in the CRF and discussed with the medical monitor.

Allowed antidepressant medications are venlafaxine, paroxetine, duloxetine, sertraline, omipramol (opipramol), moclobemide, tranylcypromine, buspiron, bupropion, reboxetine, and dibenzepin. Fluvoxamine is permitted, at no more than usual recommended doses in the approved labeling.

Bupropion is an antidepressant drug potentially administered to study patients. Although no PK interactions are expected between bupropion and pridopidine, bupropion is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as 4-fold (Wellbutrin label, 2014). Retrospective analysis of clinical experience gained with bupropion suggests that the risk of seizure may be minimized if the total daily dose of bupropion does not exceed 450 mg, the daily dose is administered 3 times daily (with each single dose not to exceed 150 mg, and the rate of incrementation of dose is very gradual (Wellbutrin label, 2014).

Mexiletine and tocainide are allowed antiarrhythmic medications, at no more than usual recommended doses in the approved labeling.

Allowed medications with lowering seizure thresholds but for which no PK interactions are expected are baclofen, bupropion, ciprofloxacin, cyclosporine, isoniazid, lindane, methylphenidate, metronidazole, penicillins, theophylline, amantadine, morphine, buprenorphine, diphenoxylate, alfentanil, fentanyl, remifentanil, meptazinol, and pethidine.

5.3.2. Prohibited Medication

5.3.2.1. Antipsychotic Medication

Ziprasidone, clozapine, haloperidol, mesoridazine, thioridazine, pimozide, zuclopenthixol, chlorpromazine, paliperidone, iloperidone, fluphenazine, prochlorperazine, trifluoperazine/trifluroperazine, flupentixol, benperidol, amisulpride, and sulpiride are not allowed within 6 weeks of baseline (Visit 1) and during the study.

5.3.2.2. Antidepressant Medication

Lithium, the tricyclic/tetracyclic antidepressants trazodone, amitriptyline, nortriptyline, imipramine, desipramine, maprotiline, doxepin, clomipramine, protriptyline, and amoxapine, and the serotonin–norepinephrine reuptake inhibitors citalopram, escitalopram, and fluoxetine are not allowed within 6 weeks of baseline (Visit 1) and during the study.

5.3.2.3. Antiarrhythmic Medication

Disopyramide, procainamide, quinidine, flecainide, propafenone, amiodarone, dofetilide, ibutilide, and sotalol are not allowed within 6 weeks of baseline (Visit 1) and during the study.

5.3.2.4. Medications Lowering Seizure Thresholds

Maprotiline, dipipanone, dihydrocodeine, methadone, oxycodone, papaveretum, pentazocine, and tramadol are not allowed within 6 weeks of baseline (Visit 1) and during the study

5.3.2.4.1. Other Prohibited Medications

Due to either QT prolongation effects or metabolism by CYP2D6 into active metabolites, the following medications are not allowed within 6 weeks of baseline (Visit 1) and during the study: astemizole, terfenadine, azithromycin, erythromycin, moxifloxacin, pentamidine, sparfloxacin, clarithromycin, chloroquine, halofantrine, bepridil, cisapride, domperidone, droperidol, levomethadyl, methadone, codeine, tramadol, sevoflurane, and tamoxifene.

5.4. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. A check of study drug compliance will be performed during each visit after the initial dispensation of study drug, and study drug accountability records will be completed. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn. The IEC/IRB should be notified.

5.5. Temporary Study Drug Discontinuation

Temporary discontinuation is defined as missing more than 5 consecutive days of the study drug.

The patient will report any temporary discontinuation to the investigator and will be instructed by the investigator regarding continuation of treatment. The reasons for temporary study drug discontinuation should be recorded in the appropriate section of the study drug dispensing and compliance log in the eCRF and the local clinical management (LCM) should be notified.

Patients who discontinue study drug for less than 5 days may resume taking the study drug at the same dose they were taking prior to the drug discontinuation. No titration will be required for these patients.

Patients who discontinue study drug for 5 days or more will be required to titrate again. Sites should discuss the patient status with the Medical Monitor prior to dispensing a titration kit.

If a patient discontinues study drug for more than 30 days, a case-by-case review will be performed by the sponsor to determine whether the patient may re-start study drug treatment.

5.6. Total Blood Volume

The total volume of blood to be collected for each patient in this study, calculated for the minimum study period of 52-weeks (Visits 1-8), is approximately 103.5 mL, as detailed in Table 2.

The total blood volume collected at the end-of-study visit (Visit 9) will be 12.5 mL.

PK samples (4 mL each) will be collected as applicable.

Table 2: Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume
Clinical laboratory	10.5 mL[a]	8	84 mL
Hematology (CBC)	2 mL	8	16 mL
Serum HCG	3.5 mL	1[b]	3.5 mL
Pharmacokinetic sample	4 mL	As applicable[c]	As applicable
Total		**17**	**103.5 mL**

[a] The clinical laboratory tests are comprised as follows: Chemistry 3.5 mL; Creatine phosphokinase MB isoenzyme (CK-MB) 3.5 mL; Prolactin 3.5 mL.
[b] A serum HCG sample is collected at screening only for women of child-bearing potential. Urine HCG tests are performed during the subsequent visits.
[c] PK samples will be aimed to be drawn, to the extent possible, in the event of a SAE, an AE leading to discontinuation, or for patients who withdrew prematurely because of lack of efficacy.
Abbreviations: CBC=complete blood count; HCG=human chorionic gonadotropin.

6. ASSESSMENT OF EFFICACY

6.1. Efficacy Measures and Justification

The UHDRS-TMS and its subscales have been used in clinical studies for pridopidine and other compounds investigated in HD.

Statistically significant findings on the UHDRS-TMS were found in both HART (ACR16C009) and MermaiHD (ACR16C008) studies. [redacted]

- The pivotal study of tetrabenazine (103,004/TETRA-HD), the only US Food and Drug Administration (FDA)-approved treatment for HD-associated symptoms (specifically chorea), showed a borderline significant improvement of 3.3 points on the UHDRS-TMS (p=0.075; 45 to 47 points at baseline). The improvement induced by treatment with
- tetrabenazine was entirely attributable to improvement of chorea and no significant effect was observed on other motor components. The study was powered to detect a 2.7-point improvement in total chorea score (which constitutes the chorea items on the UHDRS-TMS) and a neutral effect on other UHDRS-TMS items (Huntington Study Group, 2006).
- The RID-HD study of riluzole was powered to the same effect size (2.8 points on the total chorea score) (Huntington Study Group, 2003).
- The TREND-HD study of ethyl-eicosapentaenoic acid used as its primary endpoint a modified version of the UHDRS-TMS (TMS-4, encompassing chorea, dystonia, and ocular pursuit). The study was powered to detect an effect size of 2.7 to 3.2 (depending on cytosine-adenosine-guanine [CAG] repeat length) (Huntington Study Group, 2008).

The primary efficacy variable and endpoint of the PRIDE-HD study was the change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week 26. The secondary efficacy variable and endpoint was the change from baseline in the mPPT at Week 26.

In the Open-PRIDE study, long-term efficacy evaluations are the secondary objective. Efficacy endpoints include the following:

- UHDRS-TMS
- mPPT
- UHDRS-TFC

- SF-12 (acute version)
- PBA-s (also part of safety assessment)
- Q-motor assessment

Efficacy analyses will be considered exploratory.

Except for baseline, efficacy assessments can take place before or after the afternoon dose, with the time of the evaluation recorded.

UHDRS-TMS and mPPT should always be assessed in priority over other exploratory efficacy endpoints.

6.1.1. UHDRS-TMS

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

The TMS component of UHDRS comprises 31 assessments from the 15 items of the UHDRS, with each assessment rated on a 5-point scale from 0 (normal) to 4 (maximally abnormal).

6.1.2. Modified Physical Performance Test

The mPPT quantifies the patient's performance in physical tasks (Brown et al 2000). It is a standardized 9-item test that measures the patient's performance on functional tasks. Assistive devices are permitted for the tasks that require a standing position (items 6 to 9). Both the speed and accuracy at which the patients complete the items are taken into account during scoring. The maximum score of the test is 36, with higher scores indicating better performance.

6.1.3. UHDRS Total Functional Capacity

The TFC scale of the UHDRS assesses 5 functional domains associated with disability (occupation, finances, domestic chores, activities of daily living, and care level).

6.1.4. Short Form 12 (SF-12) Health Survey

The SF-12® is a multipurpose short-form generic measure of health status. It was developed to be a much shorter, yet valid, alternative to the SF-36® for use in large surveys of general and specific populations as well as large longitudinal studies of health outcomes. The 12 items in the SF-12® are a subset of those in the SF-36®; SF-12® includes 1 or 2 items from each of the 8 health concepts. Thus, the SF-12® measures 8 concepts commonly represented in widely used surveys: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well-being). Both standard (4-week) and acute (1-week) recall versions are available (Ware et al, 1996; Ware et al, 2000).

The acute form of the SF-12 was created by changing the recall period for 6 SF-12 scales (Role Physical, Bodily Pain, Vitality, Social Functioning, Role Emotional, and Mental Health) from "the past four weeks" to "the past week". Two SF-12 scales (Physical Functioning and General Health) do not have a recall period, so are identical across acute and standard forms.

The rationale behind the use of the 1-week recall period for the SF-12 was that shorter recall periods would be more sensitive than longer recall periods to recent changes in health status.

6.1.5. Problem Behaviors Assessment-Short Form

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

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

Only the abbreviated PBA-s (i.e. items of the PBA-s relevant to suicidality [depressed mood, suicidal ideation, anxiety, irritability, loss of motivation, obsessive-compulsive behaviors]) will be collected during the additional safety TC. If the patient has a positive score 1 and 2 on the suicidal ideation item or depressed mood item of the PBA-s, the patient will be monitored more closely and treated according to the investigator's medical judgment. Patients with C-SSRS or PBA-s suicidality scores 1 and 2 may be handled by study investigator/neurologist with a consultancy with psychiatrists where necessary per investigator’s medical judgement.

A referral for psychiatric evaluation is required for AE/SAE of suicidal ideation/suicidal attempt or significant increase in the suicidality scale from baseline (e.g., 2 point increase or higher) or C-SSRS or PBA-s suicidality score 3 and above. All patients with PBA-s suicidal ideation item score >2 (ie, 3, 4, 5) will be discontinued from treatment with study drug. Patients who are discontinued from treatment may continue their participation in the study and perform the scheduled visits and assessments, while off study drug. They will continue to be closely monitored by the investigator and will be referred for psychiatric evaluation per the investigator's medical judgment.Where possible, the same person should act as a patient’s caregiver/informant throughout the study. If this is not possible, a patient should have no more than 2 caregivers/informants throughout the study. All possible attempts should be made to assure that the caregiver/informant will attend the clinical visits in person together with the patient. If the caregiver/informant is not available to attend the clinic visit, the interview can be done over the phone.

6.1.6. Quantitative Motor (Q-Motor) Assessment

Q-Motor assessments will be performed only in those sites that have access to the devices needed to perform the assessments and, where this is the case, only in those patients who are capable of performing the assessments.

Motor deficits can be objectively assessed using different Q-Motor assessments. All Q-Motor assessments are based on the application of pre-calibrated and temperature-6.1.6controlled force transducers and 3-dimensional position sensors with very high sensitivity and test-retest reliability across sessions and sites in a multicenter clinical study. Q-Motor measures thus aim to reduce the limited sensitivity of categorical clinical rating scales, the intra- and inter-rater variability, and placebo effects observed in scales such as UHDRS-TMS. In addition, Q-Motor assessments allow for the objective monitoring of unintended motor side effects in clinical studies.

Tasks detailed in the sections below have been selected for use in the current study. Data transfer will be performed using a secure web-based platform, allowing continuous centralized data monitoring and quality control.

6.1.6.1. Digitomotography (Speeded Index Finger Tapping)

The patient will place their hand on a hand rest with their index finger positioned above a force-transducer. Recordings will start after practice runs. The patient will be instructed to finger tap as fast as possible between 2 auditory cues. The beginning of a tap is defined as a rise of the force by 0.05 N above maximal baseline level. The tap ends when it drops to 0.05 N before the maximal baseline level is reached again. The duration and variability of tap durations (TD), inter onset intervals (IOI), inter peak intervals (IPI), and inter tap intervals (ITI) are the exploratory outcome measures for speeded tapping. In addition, variability of peak tapping forces (TF) will be calculated as coefficient of variation, and the tapping frequency (Freq), ie, the number of taps between the onsets of the first and the last tap divided by the time in between, will be determined. Five trials of 10 seconds duration are performed with each hand.

6.1.6.2. Dysdiadochomotography (Pronation/Supination Hand Tapping)

This task assesses the regularity of hand taps performed when alternating between the palm and dorsal surface of the hand performing a repetitive pronation/supination movement. The force and duration of the hand taps are recorded similarly to the speeded tapping task. A tone cues the start and end of an assessment. Five trials of 10 seconds duration are performed with each hand.

6.1.6.3. Manumotography and Choreomotography (Grip Force and Chorea Analysis)

This task assesses the coordination of isometric grip forces in the precision grip between the thumb and index finger. Grip forces are assessed during grip initiation, object transport, and in a static holding phase. Patients are instructed to grasp and lift a device equipped with a force transducer and 3-dimensional position sensor in the precision grip between thumb and index finger and hold it stable adjacent to a marker 10-cm high. Grip forces and 3-dimensional position and orientation of the object are recorded. Mean isometric grip forces and grip force variability in the static phase (expressed as coefficient of variation = standard deviation [SD]/mean × 100) (GFV-C) are calculated during a 15-second period starting 8 seconds after the first cueing tone. Five trials of 20 seconds duration are performed with each hand. Chorea is assessed calculating a

"position-index" and "orientation-index." Start and end of assessment are signaled by a cueing tone.

6.1.6.4. Pedomotography (Speeded Foot Tapping)

The patient will place a foot on the foot device such that the ball of the foot is positioned above a force-transducer. Recordings will start after practice runs. The patient will be instructed to tap with the foot as fast as possible between 2 auditory cues. The beginning of a tap is defined as a rise of the force by 0.05 N above maximal baseline level. The tap ends when it dropped to 0.05 N before the maximal baseline level is reached again. The duration and variability of TD, IOI, IPI, and ITI are the exploratory outcome measures for speeded tapping. In addition, variability of peak TF will be calculated as coefficient of variation, and the tapping Freq, ie, the number of taps between the onsets of the first and the last tap divided by the time in between, will be determined. Five trials of 10 seconds duration are performed with each foot.

6.2. Methods and Timing of Assessing, Recording, and Analyzing Efficacy Data

Methods and timing of assessing efficacy data are discussed in Section 3.12. Procedures for recording efficacy data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.5.2.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight measurements), suicidality, and concomitant medication usage.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent form should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

New symptoms of HD or deterioration of previously existing symptoms should be recorded as an AE only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

In any event of suspected suicidality or clinical findings suggesting that the patient is dangerous to him or herself at the moment of evaluation or during the duration of the clinical study, the patient should be discontinued from treatment with study drug, referred for **immediate** psychiatric evaluation and an AE/SAE should be reported. Patients with an AE/SAE of suicide ideation or attempt will be discontinued from treatment with study drug. Patients who are discontinued from treatment may continue their participation in the study and perform the scheduled visits and assessments, while off study drug.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and that occurs during this study should be recorded as an adverse event.)
- drug interactions

- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a SAE, or require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)
- all events of possible drug-induced liver injury with hyperbilirubinemia (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3 times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN or International Normalized Ratio >1.5) or Hy's Law events require immediate study treatment cessation and reporting as an SAE. Hy's Law events are defined as follows:
  - The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.
  - Among patients showing such aminotransferase elevations, often with aminotransferases much greater than 3 × ULN, some patients also show elevation of serum total bilirubin to >2 × ULN, without initial findings of cholestasis (serum alkaline phosphatase activity >2 × ULN).
  - No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

7.1.2. Recording and Reporting Adverse Events

For adverse event recording, the study period is defined for each patient as that time period from signature of the informed consent form through the end of the study.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug. For SAEs, the SAE Form must also be completed and the SAE must be reported immediately (see Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a SAE, on the SAE Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the patient is referred for continued care to a another health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.1.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the study drug. • It could readily have been produced by the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the study drug. • It does not reappear or worsen when the study drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the study drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the study drug, yet a drug relationship clearly exists. • It follows a known pattern of response to the study drug.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A SAE is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (i.e., the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled prior to study entry will not be considered SAEs, unless

there was worsening of the preexisting condition during the patient's participation in this study.

- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.1.5.2. Expectedness

A SAE that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is the IB.

A SAE that is not included in the Listing of Adverse Reactions in the IB by its specificity, severity, outcome, or frequency is considered an unexpected adverse event.

The sponsor's Pharmacovigilance Department will determine the expectedness for all SAEs.

For the purpose of suspected unexpected serious adverse reaction (SUSAR)/IND safety reporting, the version of the reference safety information (RSI) at the moment of occurrence of the SUSAR/IND safety report applies.

7.1.5.3. Reporting a Serious Adverse Event

7.1.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all SAEs (as described in Section 7.1.5.1) that occur during the study period (including the protocol-defined follow-up period, described in Section 7.1.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the SAE form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The SAE form should be sent to the LSO or other designated personnel (a contract research organization [CRO] in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO or other designated personnel will forward the report to the sponsor's Global Patient Safety & Pharmacovigilance Department.

The following information should be provided to record the event accurately and completely:

- Study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

Each report of a SAE will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the investigational center within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety & Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO/CRO for local submission to the regulatory authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IRB/EC is also informed of the event, in accordance with local regulations.

Note: Although pregnancy is not a SAE, the process for reporting a pregnancy is the same as that for reporting a SAE, but using the pregnancy form (see Section 7.2).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of pridopidine and the appropriate regulatory authorities (and IEC/IRB, if appropriate).

In addition to notifying the investigators and regulatory authorities (and IEC/IRB, if appropriate), other measures may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing current study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to pridopidine

7.1.6. Protocol-Defined Adverse Events for Expedited Reporting

Adverse events of suicidal ideations or attempt should be reported to the sponsor within 24 hours of learning of the event. The corresponding dedicated CRF should be completed, but the events should not be marked as serious unless deemed serious by the investigator. The words "protocol defined adverse event" should be added after the adverse event term. Once the adverse event of suicidal ideation or attempt is received, the patient should be discontinued from the study and from study medication, and referred to a psychiatrist for evaluation and monitoring (see Section 7.1.7).

7.1.7. Withdrawal Due to an Adverse Event

Any patient who experiences an adverse event may be withdrawn from the study or from study treatment at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an adverse event, both the adverse events page and termination page of the CRF will be completed at that time.

In addition, a blood sample will be aimed to obtained, to the extent possible, for the measurement of study drug concentrations. The patient will be monitored at the discretion of the investigator (eg, until the event has resolved or stabilized, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The investigator must inform the Medical Monitor as soon as possible of all patients who are being considered for withdrawal due to adverse events. Additional reports must be provided when requested.

If a patient is withdrawn from the study for multiple reasons that include adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a

prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

All patients for whom an adverse event of suicidal behavior/ideation was reported at any time during the study should be discontinued from study medication and the need for an evaluation by a psychiatrist should be assessed. Discontinued patients should attend an early termination visit to return study medication, perform drug accountability, and will be asked to complete all protocol required study procedures. Adverse events of suicidal behavior/ideation should be followed until resolution of the suicidal behavior/ideation.

All patients who are discontinued from the study medication due to active suicidal behavior/ideation should be referred to a psychiatrist and followed by the investigator until resolution of the suicidal behavior/ideation.

Patients who discontinue study medication due to safety or tolerability reasons may continue in the study off drug and perform the scheduled visits and assessments.

7.1.8. Overdose of Study Drug

Any dose of pridopidine, whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, departures from the protocol may be allowed on a case-by-case basis. After stabilization and/or treatment has been administered to ensure patient safety, the investigator or other physician in attendance must contact the individual identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.2. Pregnancy

All pregnancies of women participating in the study and partners of men participating in the study that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the LSO/CRO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a SAE (see Section 7.1.5.3).

Any female patient becoming pregnant during the study will discontinue treatment. All patients (or partners) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after termination from the study will be reported as an adverse event or SAE, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a SAE.
- For an elective abortion due to developmental anomalies, report as a SAE.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.3. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be interpreted by the investigator as belonging to one of the following categories:

- abnormal but not a potentially clinically significant worsening from baseline
- abnormal and a potentially clinically significant worsening from baseline

A laboratory test result that has significantly worsened (according to medical judgment) from the baseline result will be recorded on the source documentation, transcribed onto the CRF as an adverse event, and monitored as described in Section 7.1.2. An adverse event includes a laboratory or diagnostic test abnormality (once confirmed by repeat testing) that results in the withdrawal of the patient from the study, the temporary or permanent cessation of treatment with study drug, or medical treatment or further diagnostic work-up.

In addition, potentially clinically significant values will be predefined by the sponsor for selected laboratory parameters (see Section 9.7.2) and will be detailed in the statistical analysis plan.

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are listed below.

7.3.1. Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphorus
- sodium
- magnesium
- potassium
- chloride
- bicarbonate or carbon dioxide
- glucose
- blood urea nitrogen (BUN)
- creatinine
- cholesterol (low-density lipoprotein (LDL)/high-density lipoprotein (HDL)/total)
- uric acid

- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- lactic dehydrogenase (LDH)
- gamma-glutamyl transpeptidase (GGT)
- alkaline phosphatase (ALP)
- creatine phosphokinase (CPK) -in case of elevated creatine phosphokinase, the MB fraction should be measured
- total protein
- albumin
- total bilirubin
- direct bilirubin
- indirect bilirubin
- prolactin

7.3.2. Hematology

The following hematology tests will be performed:

- hemoglobin
- hematocrit
- red blood cell (RBC) count
- platelet count
- white blood cell (WBC) count and differential count
    - absolute neutrophil count
    - absolute lymphocyte count
    - absolute eosinophil count
    - absolute monocytes count
    - absolute basophil count
    - absolute atypical lymphocyte count

7.3.3. Urinalysis

Urinalysis will include testing for the following:

- protein
- glucose
- ketones

- blood (hemoglobin)
- pH
- specific gravity
- microscopic
  - bacteria
  - RBCs
  - WBCs
  - casts
  - crystals

7.3.4. Other Clinical Laboratory Tests

7.3.4.1. Human Chorionic Gonadotropin Tests

Serum human chorionic gonadotropin (HCG) tests will be performed for all women at screening (visit 1). Urine HCG tests will be performed for all women of childbearing potential at all subsequent visits, and if clinically indicated thereafter. Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.4. Vital Signs

Vital signs [pulse, blood pressure (supine and standing), and body temperature] will be measured at the time points detailed in Table 1.

Before pulse and blood pressure are measured, the patient must be in a supine or sitting position and resting for at least 5 minutes. (The same position and arm should be used each time vital signs are measured for a given patient.) For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a potentially clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.5. Electrocardiography

A 12-lead ECG will be conducted at every visit, at the time points detailed in Table 1. ECGs will be performed in triplicate at screening, and a single measurement performed at all subsequent visits.

A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. Any ECG finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.6. Physical Examinations

Physical examinations and weight will be performed at the time points detailed in Table 1.

The brief (symptom-directed) physical exam will be focused on general appearance, the cardiovascular, pulmonary, abdominal exams, as well as directed towards any patient-reported symptoms. The brief neurological exam includes observation for cerebellar (intention) tremor and for non-cerebellar tremors (eg, resting or positional), finger-nose, heel-shin, Romberg, tandem walking, positional, and gaze-evoked nystagmus.

Any physical examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2.

7.7. Concomitant Therapy or Medication

Concomitant therapy or medication usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.3. As part of the additional implemented monitoring procedures, information regarding changes in use of benzodiazepines and antidepressants will be collected in inquiries about concomitant medication. Inquiries about changes in use of alcohol and illicit drugs will also be conducted. The information collected as part of the safety monitoring, together with the C-SSRS and the PBA-s, will be verified with the patient's caregiver, spouse or other support person (where necessary)[2].

7.8. Other Safety Measures and Variables

7.8.1. Columbia Suicide Severity Rating Scale

The C-SSRS will be used to rate the patient's degree of suicidal ideation on a scale ranging from "no suicidal ideation" to "active suicidal ideation with specific plan and intent" (Posner et al 2011). The C-SSRS Baseline version will be completed at screening (Visit 0), while the C-SSRS Since Last Visit version will be completed at the time points detailed in Table 1. Patients with active suicidal ideation, as measured by a score of 4 or 5 on the C-SSRS at the screening visit, will not be eligible for the study.

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

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

Patients with C-SSRS or PBA-s suicidal ideation >2 (ie, 3, 4, 5), and all patients with C-SSRS suicidal acts, will be discontinued from treatment with study medication. A referral for psychiatric evaluation is required for AE/SAE of suicidal ideation/suicidal attempt or significant

[2] In accordance with the American Psychiatric Associations 2003 Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors.

increase in the suicidality scale from baseline (e.g., 2 point increase or higher) or C-SSRS or PBA-s suicidality score 3 and above.

Patients who are discontinued from treatment may continue their participation in the study and perform the scheduled visits and assessments, while off study drug. They will continue to be closely monitored by the investigator and will be referred for psychiatric evaluation per the investigator's medical judgment.

7.9. Methods and Timing of Assessing, Recording, and Analyzing Safety Data

All adverse events will be reviewed on a periodic basis by the clinical project physician/medical monitor according to the safety monitoring plan (eg, scheduled safety reviews for pridopidine) as interim/preliminary safety databases become available. Safety data will additionally be evaluated periodically and ad hoc (if necessary) in the Product Safety Group.

Methods and timing of assessing safety data are discussed in Section 3.12. Procedures for recording safety data are discussed in Section 13.1 and methods of analyses are discussed in Section 9.7.2.

Information about the DSMB used for this study is provided in Section 3.6.1.

8. ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS BIOMARKERS/ PHARMACOGENOMICS/ IMMUNOGENICITY

Pharmacokinetics is not evaluated in this open-label study. Pharmacokinetic samples will be aimed to be drawn, to the extent possible, in the event of a SAE, an AE leading to discontinuation, or for patients who withdrew prematurely because of lack of efficacy.

Pharmacodynamics, pharmacogenomics, or immunogenicity will not be assessed in this open-label study.

9. STATISTICS

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report.

9.1. Sample Size and Power Considerations

This is an open-label study. The sample size for this study is not based on statistical considerations; hence, only descriptive statistics will be presented. Up to 300 subjects who completed the PRIDE-HD or transitioned from the ongoing Open-HART study and met patient exclusion/inclusion criteria will be enrolled.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all enrolled patients, regardless of whether or not a patient took any study drug. A patient is considered enrolled according to the status reported in the database.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive at least 1 dose of study drug.

9.2.3. Full Analysis Set

The full analysis set will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 1 post-baseline efficacy assessment.

9.3. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses, i.e., there is no plan to estimate missing data.

9.4. Study Population

The ITT analysis set (see Section 9.2) will be used for all study population summaries unless otherwise noted. Summaries will be presented for all patients.

9.4.1. Patient Disposition

Data from patients in the ITT, safety, and full analysis sets will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

9.4.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including medical history, prior medications, and ECG findings will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

9.5. Efficacy Analysis

9.5.1. Efficacy Endpoint

Efficacy measures and time points are provided in Section 3.3 and in Table 1.

9.5.2. Planned Method of Analysis

The full analysis set (see Section 9.2) will be used for all efficacy analyses.

No formal inferential statistics will be applied to the efficacy endpoints. Efficacy analyses will be considered exploratory and will include descriptive statistics. Comparisons will generally be made to baseline, as appropriate. Descriptive statistics over time will be presented to detect trends via changes from baseline.

9.6. Multiple Comparisons and Multiplicity

Not applicable.

9.7. Safety Endpoints and Analysis

Safety analyses will be performed on the safety analysis set (see Section 9.2).

9.7.1. Safety Endpoints

Safety measures and time points are provided in Section 3.4 and in Table 1.

9.7.2. Safety Analysis

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each patient will be counted only once in each preferred term or SOC category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study treatment (i.e., reasonable possibility; see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), SAEs, and adverse events causing withdrawal from the study. Summaries will be presented by treatment group and for all patients. Patient listings of SAEs and adverse events leading to withdrawal will be presented.

Changes in laboratory and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with study drug.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of SAEs, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

If any patient dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the patient narrative included in the clinical study report.

9.8. Tolerability Variables and Analysis

9.8.1. Tolerability Variables

The tolerability variables assessed in this study are:

- Proportion of subjects (%) who prematurely discontinued from the study
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs

9.8.2. Tolerability Analysis

Number and percent of patients who prematurely discontinued from the study and patients who prematurely discontinued from the study due to AEs will be presented.

9.9. Planned Interim Analysis

No interim analysis is planned for this study.

9.10. Reporting Deviations from the Statistical Plan

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the clinical study report, or any combination of these, as appropriate, and in accordance with applicable local and regional requirements and regulations.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The medical experts, study monitors, auditors, IEC/IRB, and health authority inspectors (or their agents) will be given direct access to source data and documentation (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with local requirements.

The investigator must maintain the original records (i.e., source documents) of each patient's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol-required worksheets, and CRFs that are used as the source (see Section 3.11).

The investigator will maintain a confidential patient identification list that allows the unambiguous identification of each patient. All study-related documents must be kept until notification by the sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol Amendments and Protocol Deviations and Violations

11.1.1. Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and local competent authorities as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. Each investigator and the sponsor will sign the protocol amendment.

11.1.2. Protocol Violations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol.

Important protocol deviations, referred to as protocol violations, are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Protocol violations include enrolling patients in violation of key eligibility criteria designed to ensure a specific subject population; failing to collect data necessary to interpret primary endpoints; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients or compromise the scientific value of the trial.

Protocol violations will be identified and recorded by investigational center personnel on the CRF. All protocol violations will be reported to the responsible IEC/IRB, as required.

When a protocol violation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical representative. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

Deviations from the inclusion/exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol eligibility criteria was entered into a study, they must immediately inform the sponsor of the protocol violation. If such patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded. If such patient is still participating in the study, a determination will be made by the sponsor and the investigator as to whether it is in the best interest of the patient to continue in the study.

11.2. Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the

investigational center authorization form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study Monitoring

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitor will contact the investigator and visit the investigational center at regular intervals throughout the study. The study monitor will be permitted to check and verify the various records (CRFs and other pertinent source data records, including specific electronic source documentation [see Section 3.11]) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded. If electronic CRFs are used for the study, the study monitor will indicate verification by electronically applying source document verification flags to the CRF and will ensure that all required electronic signatures are being implemented accordingly.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits and/or provided in follow-up written communication.

11.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies and/or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to the following:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc.)
- defective components

- missing or extra units (eg, primary container is received at the site with more or less than the designated number of units inside)
- incorrect packaging or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the Product Complaint Form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

11.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the Product Complaint Form cannot be completed, the investigator will obtain the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated SAE Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a complaint must not be delayed because not all the required information can be immediately obtained. Known information must be immediately reported. The sponsor will collaborate with the investigator to obtain any outstanding information.

11.4.2. Handling the Study Drug at the Investigational Center

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the

product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug.

If it is determined that the investigational center must return all of the study drug, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A SAE or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

11.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or SAE, the protocol should be followed.

11.4.4. Documenting a Product Complaint

The investigator will record a description of the product complaint in the source documentation as well as any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

11.5. Audit and Inspection

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The sponsor’s Global Clinical Quality Assurance department, independent of the Global Clinical Development department, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICS

Details of compliance with regulatory guidances and applicable laws are provided in Section 1.6.

12.1. Informed Consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and/or oral information about the study will be provided in a language as nontechnical as practical and understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documentation.

Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IEC/IRB requirements. The patient's willingness to participate in the study will be documented in a consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Adult patients with a legal guardian should provide informed consent according to local requirements.

12.2. Health Authorities and Independent Ethics Committees/Institutional Review Boards

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and health authority (where applicable) for the center give written approval or a favorable opinion.

12.3. Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification code (i.e., identification number).

Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

12.4. Declaration of the End of the Clinical Study

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

12.5. Registration of the Clinical Study

In compliance with local regulations and in accordance with Teva standard procedures, this clinical study may be registered on clinical trials registry websites.

13. DATA HANDLING, DATA QUALITY CONTROL, AND RECORD KEEPING

13.1. Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a clinical data management system (CDMS) that meets the technical requirements described in 21CFR Part 11. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the CDMS, all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF. Data will be verified using the data source by the study monitor, and reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator’s review and acceptance of the data as being complete and accurate.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, ePRO Tablet), the results will be sent to the investigational center, where they will be retained but not entered into the CRF unless otherwise specified in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database. Laboratory test results will not be entered into the CRF unless otherwise noted in the protocol. All data from other sources will be available to the investigators.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screen failure reason, demography, and adverse events from the time of informed consent will be entered into the CRF.

13.2. Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality control, will comply with international regulatory guidelines, including ICH GCP guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality control, will be described in a data management plan.

Case report forms received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS. Discrepancies found will be queried.

Data corrections in the CDMS will be made using the CDMS update function. The system requires a reason for each change and keeps a complete audit trail of the data values, dates and times of modifications, and authorized electronic approvals of the changes.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

13.3. Archiving of Case Report Forms and Source Documents

13.3.1. Sponsor Responsibilities

The sponsor will have final responsibility for the processing and quality control of the data. Data management oversight will be carried out as described in the sponsor's SOPs for clinical studies.

Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities. The original CRFs will be archived by the sponsor. Center-specific CRFs will be provided to the respective investigational centers for archiving.

13.3.2. Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports and data related to the study and any additional records required to be maintained under country, state/province, or other local laws, including, but not limited to, the following:

- full case histories
- signed informed consent forms
- patient identification lists
- case report forms for each patient on a per-visit basis
- data results from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the study drug
- copies of all correspondence with sponsor, the IRB/IEC, and any regulatory authority

The investigator will retain all records related to the study until the CRO or sponsor sends written notification that records may be destroyed. If, after 10 years from study completion, or earlier in the case of the investigative center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least sixty 60 days before any planned disposition of study records. Upon receipt of such request, the sponsor may make arrangements for appropriate archival or

disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

14. FINANCING AND INSURANCE

[redacted]

15. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements and regulations for registration and posting of results.

The sponsor is responsible for the preparation of a clinical study report, in cooperation with the principal investigators. The final report is signed by the sponsor and, if applicable, by the principal investigators.

When the sponsor generates reports from the data collected in this study for presentation to regulatory authorities, drafts may be circulated to the principal investigators for comments and suggestions. An endorsement of the final report will be sought from the principal investigators.

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor. The primary publication from this study will report the results of the study in accordance with the current "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" (www.ICMJE.org). Publication of the results will occur in a timely manner according to applicable regulations. Authorship will be based on meeting all the following 4 criteria:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

No patent applications based on the results of the study may be made by the investigators nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

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