CLINICAL STUDY PROTOCOL WITH AMENDMENT 05

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 versus Placebo for Symptomatic Treatment in Patients with Huntington's Disease

Phase 2

Study TV7820-CNS-20002

(PRIDE-HD – Pridopidine Dose Evaluation in Huntington's Disease)

US IND Number: 77,419

EudraCT Number: 2013-001888-23

Protocol Amendment Approval Date: 31 March 2016

Sponsor and Monitor
Teva Branded Pharmaceutical Products R&D, Inc
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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).

PROTOCOL AMENDMENTS

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 versus Placebo for Symptomatic Treatment in Patients with Huntington's Disease

Study TV7820-CNS-20002

The original protocol for study TV7820-CNS-20002 (dated 20 May 2013) has been amended and reissued as follows:

Amendment 05	31 March 2016 (408 patients enrolled to date)
Administrative Letter 09	04 February 2016
Administrative Letter 08	03 August 2015
Amendment 04	12 January 2015 (133 patients enrolled to date)
Amendment 03	16 September 2014 (24 patients enrolled to date)
Administrative Letter 07 (retracted)	4 June 2014
Administrative Letter 06	3 May 2014
Administrative Letter 05	5 March 2014
Administrative Letter 04	27 February 2014
Amendment 02	3 February 2014
Administrative Letter 03	12 December 2013
Administrative Letter 02	25 October 2013
Administrative Letter 01	8 October 2013
Amendment 01	24 September 2013
Protocol Approval Date	20 May 2013

INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 05

Original Protocol Dated 20 May 2013

IND Number: 77,419; EudraCT Number: 2013-001888-23

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 versus Placebo for Symptomatic Treatment in Patients with Huntington's Disease

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

_____

Tel: _____

I have read the protocol with Amendment 05 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 national or 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 shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

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

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	**Signature**	**Date**
Spyros Papapetropoulos, MD, PhD Vice President, Global Head Clinical Development, Neurodegenerative Diseases		Mar-31-2016

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 05

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 versus Placebo for Symptomatic Treatment in Patients with Huntington's Disease

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I have read the protocol with Amendment 05 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 national and 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 shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

Global Coordinating Investigator Prof. Dr. G. Bernhard Landwehrmeyer, MD, FRCP	**Signature**	**Date** 04/01/16

Coordinating Investigator, North America Dr. Karl Kieburtz, MD, MPH	**Signature**	**Date** 31 Mar 2016

Coordinating Investigator, Europe Dr. Ralf Reilmann, MD, PhD	**Signature**	**Date** 31 March 2016

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Middlesex TW5 9QA
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Tan Tock Seng Hospital Dept of Laboratory
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Podium Block Tan Tock Seng Hospital
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SINGAPORE

Central Electrocardiogram Evaluation

eResearchTechnology, Inc.
1818 Market Street 10th floor
Philadelphia, Pa 19103
USA

Web and Phone Integrated Interactive Response Technology

Parexel International
Suite 3 Kelvin House
Kelvin Way
Crawley
West Sussex
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Computer-Based Rating System

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Bioanalytical Pharmacokinetics Evaluation

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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 ICON Call-Center: Telephone: +1 919 674 5468 [Toll (not free of charge) telephone number allowing a global reach from both landlines and mobile phones]
On the following internet page (https://icophone.iconplc.com), 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:

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(Located in the US)
Clinical Project Manager, Global Clinical Operations Project Management
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For serious adverse events:

Contact details for notifications of SAEs are as follows:

Austria	signal@ratiopharm.at
Australia	Fax number: +65-6565-7939 e-mail: STUDY-MA-DL-075-070-Blinded@iconplc.com 24-hour hotline: +65-6896-0378
Canada	phv@tevacanada.com
Denmark	Safety.Denmark@tevapharm.dk
France	safety.france@tevafrance.com
Germany	Safety.Germany@teva.de
Italy	safety_PhVItaly@tevaitalia.It
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CLINICAL STUDY PROTOCOL SYNOPSIS

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc

Title of Study: 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 versus Placebo for Symptomatic Treatment in Patients with Huntington's Disease

Study Number: TV7820-CNS-20002

IND Number: 77,419

EudraCT Number: 2013-001888-23

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

Name of Investigational Product: Pridopidine (TV-7820)

Phase of Clinical Development: 2

Number of Investigational Centers Planned: approximately 50

Number of Patients Planned: 400 (80 patients per treatment arm)

Study Population: Male or female patients aged ≥21 years and with body weight ≥50 kg with Huntington's disease (HD)

Planned Study Period: Q1 2014 (first patient enrolled) to Q1 2016 (last patient last visit for the first 26-week study period) and Q3 2016 (last patient last visit for the second study period)

Primary Objective: The primary objective of this study is to assess the efficacy of pridopidine 67.5 to 112.5 mg twice daily (bid) on motor impairment in patients with HD after 26 weeks of treatment using the Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score (TMS).

Secondary Objectives: The secondary efficacy objective of the study is to assess the effect of 26 weeks of treatment with pridopidine 67.5 to 112.5 mg bid on the modified Physical Performance Test (mPPT).

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of a range of pridopidine doses in patients with HD during the entire 52-week study period
- To explore the pharmacokinetics (PK) of pridopidine in the study population
- To investigate the relationship between exposure to pridopidine and outcome measures (eg, clinical efficacy and toxicity parameters)

Other efficacy endpoints will also be analyzed (see below).

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

a. Diagnosis of HD based on clinical features and the presence of ≥36 cytosine-adenosine-guanine (CAG) repeats in the huntingtin gene.
b. Male or female age ≥21 years, with an onset of HD after 18 years' old.
c. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study, including the follow-up period. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, or double barrier contraception, ie, 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.

d. Body weight ≥50 kg.
e. A sum of ≥25 points on the UHDRS-TMS at the screening visit.
f. UHDRS Independence Score (IS) equal to or less than 90% at the screening visit.
g. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. Patients with a legal guardian should be consented according to local requirements.
h. Willing to provide a blood sample for genetic analyses (including CAG analysis, cytochrome P450 [CYP] 2D6 status, genetic long QT syndrome in patients who had QT prolongation following study drug administration or any other genetic analyses related to pridopidine response or HD) at the screening visit.
i. Willing and able to take oral medication and able to comply with the study specific procedures.
j. Ambulatory, being able to travel to the study centre, and judged by the investigator as likely to be able to continue to travel for the duration of the study.
k. Availability and willingness of a caregiver, informant or family member to accompany the patient to the clinic at study visits assessing CIBIC-Plus, HD Quality of life (QoL), and Clinical Global Impression of Severity (CGI-S)/Clinical Global Impression of Change (CGI-C). For the purposes of this study, a caregiver is recommended to be someone who attends to the patient at least 2 to 3 times per week for at least 3 hours per occasion, and the suitability of the caregiver should be judged by the investigator.
l. For patients taking allowed antipsychotic, antidepressant or other psychotropic 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.

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. If there is evidence of a prolonged QTcF interval at screening from the initial (single) measurement, then the electrocardiogram (ECG) will be repeated twice, and the mean of the 3 screening 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 a known history of Long QT Syndrome or a first degree relative with this condition.
d. Patients with a history of epilepsy or of seizures within the last 5 years.
e. Have other serious medical illnesses (including but not limited to uncontrolled hypertension, respiratory disease including severe form of asthma, hepatic disease, renal disease, AIDS, unstable psychiatric or other neurologic disorder) which in the opinion of the investigator may put the patient at risk when participating in the study or may influence the results of the study or affect the patient's ability to take part in the study.
f. 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.
g. Patients receiving medications (within the last 6 weeks prior to baseline) 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.

h. Patients receiving medications (within the last 6 weeks prior to baseline) that are metabolized by CYP2D6 and have the potential of reducing seizure threshold.
i. [Revision 1] 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.
j. 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.
k. Alcohol and/or drug abuse within the 6 months prior to screening, as defined by Diagnostic and Statistical Manual – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse.
l. Patients with active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Columbia-Suicide Severity Rating Scale (C-SSRS), 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 within 1 year of screening, or patients who, in the opinion of the investigator, present a serious risk of suicide.
m. Patients with known intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage.
n. [Revision 1] Females who are pregnant or breastfeeding.
o. Known allergy to any ingredients of the study medication or placebo (pridopidine, silicified microcrystalline cellulose, magnesium stearate).
p. Previous exposure with pridopidine.
q. Treatment with tetrabenazine within 6 weeks of study baseline.
r. Treatment with any investigational product within 6 weeks of screening or patients planning to participate in another clinical study assessing any investigational product during the study.

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

The dose levels of pridopidine are 45, 67.5, 90, and 112.5 mg bid. Every patient will receive 3 capsules bid, ie, 3 capsules in the morning and 3 capsules in the afternoon, during the whole study period. There will not be an afternoon dose at the final visit (Visit 11, Week 52).

Investigational Product: Pridopidine oral capsules 22.5 mg and 45mg

Weeks 1 to 4 (up to Day 27): Titration Period

Patients randomized to the pridopidine 45 mg bid treatment arm: Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine)

Patients randomized to the pridopidine 67.5 mg bid treatment arm: Weeks 1 and 2: Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine). Weeks 3 and 4: Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg placebo bid (45 mg bid, total daily dose of 90 mg pridopidine)

Patients randomized to the pridopidine 90 mg bid treatment arm: Week 1: Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine). Week 2: Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg placebo bid (45 mg bid, total daily dose of 90 mg pridopidine). Weeks 3 and 4: Patients will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg pridopidine and 1 capsule of 22.5 mg placebo bid (67.5 mg bid, total daily dose of 135 mg pridopidine)

Patients randomized to the pridopidine 112.5 mg bid treatment arm: Week 1: Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine). Week 2: Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg

placebo bid (45 mg bid, total daily dose of 90 mg pridopidine).Week 3: Patients will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg pridopidine and 1 capsule of 22.5 mg placebo bid (67.5 mg bid, total daily dose of 135 mg pridopidine). Week 4: Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg pridopidine (90 mg bid, total daily dose of 180 mg pridopidine)

Week 4 (Day 28 Only) to Week 52: Full Dose Period

Patients randomized to the pridopidine 45 mg bid treatment arm will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (total daily dose of 90 mg).

Patients randomized to the pridopidine 67.5 mg bid treatment arm will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg pridopidine and 1 capsule of 45 mg placebo bid (total daily dose of 135 mg).

Patients randomized to the pridopidine 90 mg bid treatment arm will receive 2 capsules of 45 mg pridopidine and 1 capsule of 22.5 mg placebo bid (total daily dose of 180 mg).

Patients randomized to the pridopidine 112.5 mg bid treatment arm will receive 2 capsules of 45 mg pridopidine and 1 capsule of 22.5 mg pridopidine bid (total daily dose of 225 mg).

Placebo: Matching placebo capsules 22.5 mg and 45 mg

Weeks 1 to 4 (up to Day 27): Titration Period

Patients randomized to placebo arm will receive 2 capsules of 22.5 mg placebo and 1 capsule of 45 mg placebo bid.

Week 4 (Day 28 Only) to Week 52: Full Dose Period

Patients randomized to placebo arm will receive 2 capsules of 45 mg placebo and 1 capsule of 22.5 mg placebo bid.

Method of Blinding and Randomization: Randomization will be performed by interactive response technology (IRT) using dynamic randomization to balance the treatment arms within centers and neuroleptics use or no use. Patients will be equally assigned to the 5 treatment arms of the study (4 active treatment arms and placebo, allocation ratio of 1:1:1:1:1).

Should the Drug Safety Monitoring Board (DSMB) not approve the administration of 1 or more doses of pridopidine, the dynamic randomization algorithm will be adjusted to apply an equal allocation ratio to all approved remaining treatment arms.

Duration of Participation: For each patient, the duration of participation is planned to be up to 66 weeks, consisting of a screening period of up to 12 weeks, a 52-week randomized double-blind treatment period (comprised of a 4-week titration and 48-week full dose period), and a 2-week safety follow-up period following the last dose of study medication.

General Design and Methodology: This is a multicenter, multinational, randomized, parallel-group, double-blind, placebo-controlled study to compare the efficacy and safety of pridopidine 45, 67.5, 90, and 112.5 mg bid versus placebo in the treatment of motor impairment in HD. The 45 mg dose level will not be formally included in the efficacy analyses. It is planned to enroll a total of 400 patients (80 patients within each treatment arm).

Patients will be equally randomized (1:1:1:1:1) to receive pridopidine 45, 67.5, 90, or 112.5 mg or placebo bid for 52 weeks, including a 4-week progressive titration period. During the study, an independent DSMB will review accumulating unblinded safety data. The DSMB will meet monthly until 20 patients from each treatment arm (i.e. a total of 100 patients) have completed two weeks of treatment on full dose (6 weeks in the study). In case of a significant emerging safety concern in 1 or more treatment arm(s), the DSMB will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatments arm(s) with safety concerns. Thereafter, the DSMB will decide whether there is a need for additional meetings, and, if needed, will determine when these will take place.

After having signed an informed consent, including consent to provide a blood sample for genetic analyses, patients will be screened for a period of up to 12 weeks in order to determine whether they are eligible to participate into the study. The investigator should aim to perform the baseline visit as soon as possible after the screening visit. Patients with a legal guardian should be consented according to local requirements. The screening period will include a comprehensive medical and psychiatric history, rating of the C-SSRS, a record of previous medications, a full physical and neurological examination, measurements of vital signs, typical clinical laboratory tests (hematology, biochemistry, urinalysis), serum pregnancy tests (if female of childbearing potential), and a single 12-lead ECG. The diagnosis of HD will be established based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene. UHDRS-TMS and UHDRS-IS will be assessed. In addition, in order to pre-expose participants to tests prior to measuring baseline performance (and by this way reduce the practice effects), the Quantitative motor (Q-Motor) and cognitive assessment battery (CAB) tests (Symbol Digit Modalities Test [SDMT], Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised [HVLT-R], Paced Tapping at 3 Hz, One Touch Stockings of Cambridge [OTS, abbreviated 10-trial version]) will be administered at screening. In case the devices needed for the CAB and the Q-Motor assessments are not available at all the sites, those evaluations will be done only in sites where devices are available. Eligible patients will be randomized to receive active drug or placebo and will be titrated during the first 4 weeks from pridopidine 22.5 mg bid to the final dose of 45, 67.5, 90, or 112.5 mg bid according to the treatment arm they are randomized to.

The investigator should aim to perform the baseline visit as soon as possible after the screening visit.

During titration (Days 0 to 27), there will be 2 on site visits: at Visit 1 (baseline) and at Visit 2 (Week 2). There will be additional phone calls on Week 1 and Week 3.

At the baseline visit, before the first dose of study drug, the Clinician's Interview Based Impression of Severity (CIBIS) will be rated by an independent rater, while another qualified site personnel will assess the mPPT, the CGI-S, the Timed Up and Go (TUG) Test, the Physical Disability Scale (PDS), the UHDRS-TMS, the UHDRS-FA, the UHDRS-IS, the UHDRS Total Functional Capacity (TFC), the CAB, and the Problem Behaviors Assessment-Short form (PBA-s). A full physical and neurological examination, including weight, will be performed. The patient will fill the Walk 12- and the HD-QoL, EQ5D, and Q-Motor assessments will be performed.

Triplicate 12-lead ECG recordings and PK sampling for determination of the levels of pridopidine (TV-7820) and its main metabolite (TV-45065) will be performed before and 1 to 2 hours after first dose administration. PK samples will be collected after ECG measurements.

Phone calls on Weeks 1 and 3 will be performed to inquire about adverse events (AEs) and concomitant medications, and to allow the weekly dose increase on the following day. During the on-site visit atWeek 2, before the afternoon dose of the study drug, a blood sample will be taken for electrolyte monitoring; if hypokalemia is observed, dosing will be interrupted 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. Vital signs will be assessed in addition to the inquiry about AEs and concomitant medications. Twelve-lead ECGs will be performed in triplicate 1 to 2 hours after the afternoon dose of study drug on Week 2, followed by collection of a PK sample.

During the full treatment dose period (Weeks 4-52), there will be a total of 9 on-site visits at Weeks 4, 6, 8, 12, 16, 20, 26, 39 and 52 (or at early termination) and a phone call on Weeks 5, 32, between Weeks 40-44, on Week 45 and between Weeks 46-51 . Visits and procedures during the full dose period will be scheduled around the afternoon dose, with the exception of Week 52 where only the morning dose is administered. During the phone call at Weeks 5 and 32 inquiries about AEs and concomitant medication will be conducted. During the phone calls between Weeks 40-44, on Week 45 and between Weeks 46-51, 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.

At each of the on-site visits, safety variables will be assessed, including triplicate ECG evaluation before and 1 to 2 hours after dose administration at the site (ECG is optional on Week 8), and clinical laboratory evaluations. PK sampling for determination of the levels of pridopidine and TV-45065 will be done on Weeks 4, 6 and 16(before and 1 to 2 hours after the afternoon dose), on Weeks 12 and 20 (1 to 2 hours after the afternoon dose), and on Weeks 26 (before the afternoon dose) and 52 (before the morning dose). When concomitant to ECG, PK samples will be collected after the ECG recording.

At Weeks 4, 8, 12, 16, 20, 26 and 52, in addition to safety assessments, the UHDRS-TMS and the mPPT will be assessed by qualified site personnel.

At Weeks 4, 12, 26 and 52, in addition to safety assessments and the UHDRS-TMS and mPPT, the CIBIC-Plus will be rated by an independent rater, while another qualified site personnel will assess the PDS, the CGI-C, the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, and the PBA-s. The PBA-s will also be assessed at Week 39. UHDRS-TMS and mPPT should be evaluated prior to the other scales. The patient will fill the Walk-12 and Q-Motor assessments will be performed. The UHDRS-FA, the UHDRS-TFC, and the UHDRS-IS will also be performed on Week 20.

The CAB will be performed on Weeks 12, 26 and 52 only.

The HD-QoL and EQ5D will be completed on Weeks 26 and 52only.

Patients who complete all scheduled visits will have final procedures and assessments performed at the final visit (Week 52). Patients who withdraw from the study before completing the evaluation period will have the Week 52 procedures and assessments performed at their final visit.

There will be a follow-up visit 2 weeks after last dose of study drug for safety evaluation, including a triplicate ECG evaluation (optional) and PK sample. At this visit, UHDRS-TMS and Q-Motor will also be assessed.

The procedures and assessments for visits V0 and V4-12 may be performed over several days, as long as they are completed within the defined visit window.

In case of a serious adverse event (SAE), the aim will be to collect an additional PK sample at the closest time possible to the SAE.

Patients, who for safety or tolerability reasons have to stop study drug medication, will be asked to continue in the study and follow the visit schedule as outlined in the protocol, without taking study drug.

Patients who complete this study may have the opportunity to enter an open-label extension study.

Primary Efficacy Variable and Endpoint: The 45 mg dose level will not be formally included in the efficacy analyses. The primary efficacy variable and endpoint for this study is:

- Change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week 26

Secondary Efficacy Variable and Endpoint: The secondary efficacy variable and endpoint for this study is:

- Change from baseline in the mPPT at Week 26

Other Efficacy Variables and Endpoints:

Other efficacy variables and endpoints for this study are as follows:

Global Function Scales

- Change from baseline in the mPPT at Week 52
- CIBIC-Plus global score at Week 26 and 52 as compared to baseline (rated by an independent investigator)

- Change from baseline in the PDS score at Week 26 and 52
- Change from baseline in UHDRS-FA at Week 26 and 52
- CGI-C at Week 26 and 52 as compared to baseline (rated by qualified site personnel)
- Change from baseline in UHDRS-TFC at Week 26 and 52
- Change from baseline in UHDRS-IS at Week 26 and 52

Patient Reported Outcomes

- Change from baseline in HD-QoL at Week 26 and 52
- Change from baseline in EQ5D-5L at Week 26 and 52
- Change from baseline in Walk-12 at Week 26 and 52

UHDRS-TMS and Subscales

- Change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week 52
- Change from baseline in hand movement score (defined as the sum of UHDRS domains finger taps, pronate-supinate hands and luria [fist-hand-palm test]) at Week 26 and 52
- Change from baseline in Gait and balance score (defined as the sum of UHDRS domains gait, tandem walking and retropulsion pull test) at Week 26 and 52
- Change from baseline in UHDRS Modified Motor Score (mMS; defined as the sum of UHDRS domains dysarthria, tongue protrusion, finger taps, pronate-supinate hands, luria, rigidity, bradykinesia, gait, tandem walking, retropulsion pull test) at Week 26 and 52
- Change from baseline in UHDRS-Chorea at Week 26 and 52
- Change from baseline in UHDRS-Dystonia at Week 26 and 52
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea items
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Dystonia items
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea and Dystonia items
- Responders, defined as patients with UHDRS-TMS change from baseline ≤0 at Week 26/early termination visit prior to week 26

Other Motor Assessments

- Change from baseline in Q-Motor measurements at Week 26 and 52 including digitomotography (speeded index finger tapping), dysdiadochomotography (pronation/supination hand tapping), manumotography and choreomotography (grip force and chorea analysis) and pedomotography (speeded foot tapping)
- Change from baseline in the TUG Test at Week 26 and 52

Cognitive/Psychiatric Assessments

- Change from baseline in CAB at Week 26 and 52: SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS
- Change from baseline in PBA-s at Week 26 and 52

The primary and secondary efficacy endpoints will be evaluated at week 26.

Other efficacy endpoints will be evaluated at week 26 and week 52 and will be performed for exploratory purposes.

Safety Variables and Endpoints:

Safety variables and endpoints will include the following:

- AEs throughout the study
- Changes from baseline in QTcF and other ECG parameters throughout the study
- Clinical safety laboratory (clinical chemistry, hematology, and urinalysis) throughout the study
- Changes from baseline C-SSRS and PBA-s throughout the study
- Vital signs throughout the study

Tolerability Variables and Endpoints:

Tolerability variables and endpoints will include the following:

- the number (%) of patients who failed to complete the study
- the number (%) of patients who failed to complete the study due to AEs

Pharmacokinetic Variables and Endpoints:

The primary PK measure will be determination of plasma concentration of pridopidine. Concentrations will also be incorporated into a pridopidine population PK model and individual exposure for the study patients (maximum concentration [C_{max}] and area under concentration-time curve [AUC]) will be calculated.

Statistical Considerations:

Sample Size

It is estimated that approximately 80 patients per arm will enable a power of 84% to detect a beneficial effect of 4.0 points or more in the change from baseline in UHDRS-TMS at week 26, of an active pridopidine arm compared to placebo, assuming SD of 8.5 (as estimated from the MermaiHD [ACR16C008] study) and type I error of 5%.

Eighty patients per arm will enable a power of 71% to detect a beneficial effect of 2.0 points or more in the change from baseline in mPPT of an active pridopidine arm compared to placebo, assuming SD of 5.0.

Control of Type I Error Rate

The Hochberg's Step-Up method for multiple comparisons between treatment arms in combination with the hierarchical method between the primary efficacy endpoint and the secondary efficacy endpoint, will be used to maintain the experiment wise type I error of 5% level.

The pridopidine dose group of 45 mg bid comparison to placebo will serve as a bridging comparison to the legacy pridopidine studies (ACR16C008 [MermaiHD] and ACR16C009 [HART]), where the pridopidine dose of 45 mg bid was the maximal dose. This comparison to historical data will be performed descriptively. Hence, only a maximum of 3 multiple dose comparisons to placebo will be performed and controlled for type I error in this study: 67.5, 90, and 112.5mg bid. First, the Hochberg method will be applied for the comparisons of the 3 (or less) active

doses (67.5, 90, and 112.5 mg bid) to placebo. Then, using the hierarchical method, any statistically significant dose will continue to be tested for the secondary endpoint at an alpha level of 5%.

In addition, any treatment group that will be discontinued due to safety issues will not be formally tested for efficacy and hence not controlled for type I error.

Efficacy analyses will be performed on the full analysis set (FAS) that will include all patients who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment up to week 26.

After the data base is cleaned and locked for the analysis of the first 26-week study period and the treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code, the designated Clinical Supplies Chain and designated Pharmacovigilance personnel will be exposed to the individual patients' treatment assignments. The sponsor study core team that works on the study report and/or design of additional studies and upper management will not be exposed to individual patients' treatment assignments and only be exposed to data summaries by treatments. The investigators, the patient, and any other personnel involved in patients' assessment, monitoring, analysis, and data management are blinded to the patient assignment until the database is locked for analysis of the week 52 data. A detailed procedure that will be taken for maintaining the blinding of the study up to week 52, will be specified before the treatment assignment are revealed for analysis of the first 26-week period of the study. This procedure will include a list of people that are allowed to be exposed to safety data summaries by treatments.

Primary Statistical Analysis

The change from baseline in UHDRS-TMS up to week 26 will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in trial by treatment interaction, center, neuroleptic use or no use and baseline UHDRS-TMS score. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model will not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) [ARH(1)], Heterogeneous Compound Symmetry (CSH), Autoregressive(1) [AR(1)], and Compound Symmetry (CS). The estimated means at the Week 26 visit of the change from baseline in UHDRS-TMS will be compared between the active treatment arms (the arms from: 67.5, 90, or 112.5 mg bid that are not discontinued due to safety issues) and the placebo arm.

Secondary Statistical Analysis

The change from baseline in mPPT up to week 26 will be analyzed in the same way as the primary efficacy endpoint except that the baseline mPPT score will be included in the model instead of baseline UHDRS-TMS.

Other Statistical Analysis

A correlation between exposure (C_{max}/AUC) and response (efficacy and safety measures) will be done.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
AR	Autoregressive
Arc mRNA	activity-regulated cytoskeleton-associated protein messenger ribonucleic acid
ARH	Heterogeneous Autoregressive
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
bid	twice daily
CAB	cognitive assessment battery
CAG	cytosine-adenosine-guanine
CDMS	clinical data management system
CFR	Code of Federal Regulations
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CIBIC-Plus	Clinician's Interview-based Impression of Change plus Caregiver Input
CIBIS	Clinician's Interview-based Impression of Severity
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed plasma drug concentration
CNS	central nervous system
CO	Completers analysis set
CRF	case report form
CRO	contract research organization
CS	Compound Symmetry
CSH	Heterogeneous Compound Symmetry
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DSMB	Drug Safety Monitoring Board
DSM–IV TR	Diagnostic and Statistical Manual - Fourth Edition Text Revision

Abbreviation	Term
ECG	electrocardiogram
EM	extensive metabolizers
EQ5D-5L	European Quality of Life-5 Dimensions (5 levels)
EU	European Union
FA	Functional Assessment
FAS	Full analysis set
FASOD	Full Analysis Set On Study Drug
FDA	US Food and Drug Administration
Freq	tapping frequency
FUAS	Follow-Up Analysis Set
GCP	Good Clinical Practice
GFV-C	grip force variability in the static phase
GGT	gamma-glutamyl transpeptidase
HART	Huntington's disease ACR16 Randomized Trial
HCG	human chorionic gonadotropin
HD	Huntington's disease
ΔHR	change from baseline in heart rate
ΔΔHR	placebo-corrected change from baseline in heart rate
HVLT-R	Hopkins Verbal Learning Test, revised
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOI	inter onset interval
IPI	inter peak interval
IRB	Institutional Review Board
IRT	interactive response technology
IS	Independence Score
ITI	inter tap interval
ITT	intent-to-treat
K2EDTA	dipotassium ethylenediaminetetraacetic acid
LAM	lactational amenorrhea method
LOCF	last observation carried forward
LSO	local safety officer

Abbreviation	Term
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MermaiHD	Multinational European Multicentre ACR16 study in Huntington's Disease
ML	Maximum-Likelihood
mMS	Modified Motor Score
mPPT	Modified Physical Performance Test
MS	Multiple sclerosis
MTD	maximum tolerated dose
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
OTS	One Touch Stockings of Cambridge, abbreviated 10-trial version
PBA-s	Problem Behaviors Assessment-Short form
PD	pharmacodynamic(s)
PDS	Physical Disability Scale
PK	pharmacokinetic(s); pharmacokinetic population
PM	poor metabolizer
qd	once daily
Q-Motor	Quantitative motor
QoL	Quality of life
QTcF	Fridericia-corrected QT interval
ΔQTcF	change from baseline in QTcF
ΔΔQTcF	placebo-corrected change from baseline in QTcF
RBC	red blood cell
REML	Restricted Maximum-Likelihood
SAE	serious adverse event
SD	standard deviation
SDMT	symbol digit modalities test
SOC	system organ class
SOP	standard operating procedure
SP	Safety Population
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half life

Abbreviation	Term
TD	tap duration
TF	tapping force
TFC	Total Functional Capacity
TMS	Total Motor Score
TUG	Timed Up and Go
UHDRS	Unified Huntington's Disease Rating Scale
ULN	upper limit of the normal range
US	United States
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

Pridopidine (TV-7820, formerly known as ACR16) is a drug under development from a new class of pharmaceutical agents, the dopidines, which are considered to have dopaminergic stabilizing properties. Dopaminergic stabilizers are compounds that can both enhance and counteract dopamine dependent functions in the central nervous system (CNS), depending on the initial level of dopaminergic activity. Dopaminergic stabilizers suppress the hyperactive behavior induced by stimulants such as amphetamine. In contrast, at low levels of dopamine function, the dopamine stabilizers enhance behavioral activity. The primary effect of pridopidine on HD-related motor symptoms is therefore expected to occur via the dopamine transmissions modulating properties of pridopidine (Ponten et al 2010).

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.

A more detailed description of the investigational product is given in Section 3.4.1.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Nonclinical Studies

In vitro studies demonstrated that pridopidine displays competitive antagonism with fast dissociation rate from the dopamine D2 receptor (Dyhring et al 2010). The primary action of pridopidine at dopamine D2 receptors is further demonstrated by in vivo binding experiments showing that pridopidine dose-dependently displaces the dopamine D2 ligand raclopride from dopamine D2 receptors (Natesan et al 2006). Neurochemically, pridopidine increases neuronal synthesis, release, and metabolism of dopamine in subcortical areas. The effects on dopamine turnover and transmission biomarkers are a consequence of pridopidine's ability to inhibit dopamine D2 receptor dependent negative feedback (Carlsson and Lindqvist, 1963). These neurochemical effects are similar, but not identical, to well established dopamine D2 receptor antagonists (Ponten et al 2010).

In addition, pridopidine increases the release and turnover of dopamine and noradrenaline in cortical areas. These effects are likely to be followed by a strengthening of fronto-striatal N-methyl-D-aspartate (NMDA) receptor mediated synaptic glutamatergic neurotransmission as inferred from pridopidine induced increases in activity-regulated cytoskeleton-associated protein messenger ribonucleic acid (Arc mRNA) expression (Waters et al 2009). Abnormalities in synaptic glutamatergic function in the cortex, as well as the communication between the cortex and striatum, are being increasingly recognized as determinants contributing to the HD phenotype (Cepeda et al 2010).

Behaviorally, pridopidine reduces hyperactivity and the behavioral abnormalities induced in animal models of elevated dopaminergic or decreased glutamatergic neurotransmission, while the locomotor activity of intact animals is unaffected over the same dose range (Ponten et al 2010). In addition, pridopidine normalizes behavior in animals with a low baseline psychomotor activity up to normal levels. Pridopidine is unable to induce profound hypoactivity and catalepsy, indicating that it has a low likelihood of displaying the neurological side effects associated with classical dopamine receptor antagonists.

The pharmacological profile of pridopidine, combining state dependent inhibition or activation of dopamine-dependent psychomotor functions and a putative increased activity in cortical and subcortical NMDA-receptor dependent glutamate transmission, supports the hypothesis that pridopidine can balance aberrant functioning in the cortico-striatal network controlling motor functions (Alexander et al 1986).

The preclinical pharmacology data demonstrate the balancing effects of pridopidine on motor function through the dopamine system and putative strengthening of cortico-striatal synaptic glutamate-mediated signaling, suggesting pridopidine affects neuronal pathways disrupted in HD.

1.3.2. Clinical Studies

To date, 16 clinical studies have been completed with pridopidine, comprising 8 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 6 studies in patients with HD (including 1 open-label extension study). In addition, a

compassionate use program for pridopidine in patients with HD is ongoing in Europe, and an open-label, long term safety study is ongoing in the United States (US) and Canada. As per 18 November 2014, 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.

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 twice daily [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.

The HART study (ACR16C009) demonstrated dose-dependent efficacy of pridopidine in treating motor symptoms in HD, measured using the Modified Motor Score (mMS) and Total Motor Score (TMS) from the Unified Huntington's Disease Rating Scale (UHDRS). In the HART and MermaiHD (ACR16C008) studies, there was a strong trend for effect on mMS on the 45 mg bid dose, which did not reach the pre-specified significance criteria. However, statistically significant findings on the UHDRS-TMS were found in both HART and MermaiHD studies. The motor effects seen are congruent with the perceived mode of action of pridopidine.

The UHDRS-TMS and its subscales have been used in clinical studies for other compounds investigated in HD. The effect of 2.8 to 3 points on the UHDRS-TMS (from a baseline of 34 to 43 points across treatment groups in the MermaiHD [ACR16C008] and HART [ACR16C009] studies) was comparable to that observed in other major studies of medications aimed at symptomatic relief of motor symptoms associated with HD, namely the TETRA-HD, RID-HD and TREND-HD studies:

- The pivotal study of tetrabenazine (103,004/TETRA-HD), the only 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 most frequently reported adverse events (AEs) in patients with HD in the placebo-controlled studies with pridopidine (ACR16C007, MermaiHD [ACR16C008], and HART [ACR16C009]) were fall, diarrhea, nausea, nasopharyngitis and Huntington's chorea. Pridopidine was generally well tolerated, with an AE profile similar to placebo. Apart from transient increases in prolactin plasma levels, no clinically significant changes or trends were observed for vital signs and or laboratory parameters. Electrocardiogram (ECG) assessment, including assessment of cardiac repolarization, demonstrated no clinically significant effects of pridopidine on the ECG in HD patients. Overall the frequencies of AEs and serious adverse events (SAEs) were similar between the placebo group (58.6% and 5.2%) and the combined active group (61.2% and 4.9%). Discontinuation rate was also similar between the placebo group and the active group (8.2% and 9.2%). Four patients had an AE with fatal outcome; 2 patients treated with placebo, and 2 patients treated with pridopidine. The fatal events in the patients treated with pridopidine were assessed as unrelated to study medication.

The long-term safety has been examined in 2 open-label extension studies (completed ACR16C008-OLP and ongoing ACR16C015-open HART). Generally the safety profiles in the open-label extensions were similar to those seen in the previous randomized placebo-controlled studies with pridopidine. There were 6 cases with fatal outcome; none of them was considered related to the study medication.

1.3.2.1. Clinical Pharmacology Studies

Pridopidine has a relatively fast and almost complete absorption after oral administration, with individual maximum concentration (C_{max}) values occurring between 0.5 to 4 hours after dosing (median of 1.25 to 2 hours). Food intake has no impact on the extent of absorption of pridopidine.

After absorption, pridopidine is eliminated partly by urinary excretion and partly by hepatic metabolism (primarily via the cytochrome P450 [CYP] 2D6 pathway), with mean half-life ($t_{½}$) of approximately 10 hours at steady state. In extensive metabolizers (EMs), pridopidine is metabolized by CYP2D6 to 1 main metabolite (TV-45065, previously known as ACR30); the contribution from other enzymatic pathways does not seem to be significant. Conversely, poor metabolizers (PM) depend on renal excretion as their main elimination pathway.

In a dedicated PK study, the C_{max} and area under the concentration time curve (AUC) in PMs compared with EMs is approximately 1.6- and 2.8-fold higher after a single bid dosing day, respectively. At steady-state, however, this difference is reduced to 1.3-fold for both C_{max} and AUC.

A population PK model confirmed that, due to auto-inhibition of CYP2D6 in EMs, clearance in EMs and PMs approach each other at steady state, but they still differ significantly (9.22 L/h or 6.30 L/h in a typical EM or PM subject weighing 60 kg) (Report CP-13-013)[a]. Due to this auto-inhibition of CYP2D6, the fraction metabolized decreases with multiple doses, and renal elimination becomes a more important elimination pathway than the polymorphic CYP2D6

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

metabolism. Renal clearance of pridopidine at steady state ranges from 90 to 116 mL/min which corresponds well to the glomerular filtration rate.

In a multiple ascending dose (MAD) study (ACR16C018), tolerability and safety of pridopidine 45 to 90 mg bid for 9 days was investigated in 36 healthy subjects. The safety profile of pridopidine in the 45 and 67.5 mg bid dose groups was similar to that observed in the larger clinical studies. Overall, the most frequently reported AEs were within the system organ classes (SOCs) Nervous system disorders, Gastrointestinal disorders and Psychiatric disorders. Psychiatric symptoms and signs, such as nightmare, aggression, depressive mood, anxiety, and abnormal dreams were reported only at the 90 mg bid dose level and they were all considered related to treatment. Frequency of dizziness was markedly increased with pridopidine dose (50% and 35% of the subjects in the 90 and 67.5 mg bid arms respectively, versus 11% and 14% in the 45 mg bid and placebo arm, respectively). The 90 mg bid dose was considered the maximum tolerated dose (MTD). It should be noted that in this study there was no titration period, as opposed to the clinical studies in HD patients where the full dose was administered after a 1-month titration period. This absence of a titration period, together with the higher doses investigated, may partly explain the higher frequency observed for some of the AEs (in particular for dizziness).

An effect of pridopidine on the QT interval duration that may be of clinical concern has been observed in healthy subjects. Results of the ACR16C018 study revealed a dose-dependent Fridericia-corrected QT interval (QTcF) prolongation, with a mean placebo-corrected change from baseline in QTcF (ΔΔQTcF) of up to 24.8 msec in the 90 mg bid dose group on Day 9, observed 1 hour after study drug dose, corresponding to the time for C_{max}.

Following multiple dosing of 45, 67.5 and 90 mg bid in healthy subjects, dose proportionality was apparent for AUC and C_{max}. No information is available for higher doses, however linear pharmacokinetics (PK) are expected because of the low probability of oral absorption saturation (average 98% absolute bioavailability) and low probability of major elimination route at steady state (passive renal excretion of unchanged drug).

Mild renal impairment did not affect the steady state pharmacokinetics of pridopidine; however, subjects with moderate renal impairment had higher AUC and C_{max} values than matching healthy subjects at steady state. Studies in patients with hepatic impairment have not been performed, and PMs are expected to represent a worst case scenario for hepatic impairment.

Pridopidine is a CYP2D6 substrate and thus PK interactions can be expected with drugs that inhibit CYP2D6, although not more than what is expected from a PM.

Pridopidine is also a strong CYP2D6 inhibitor, and so drug-drug interactions with co-administered CYP2D6 substrates are anticipated.

1.4. Known and Potential Risks and Benefits to Human Subjects

1.4.1. Benefits

Results of 2 large previous clinical studies in HD patients suggested that pridopidine may have an effect on motor function. The magnitude of effect of pridopidine on UHDRS-TMS is similar to that of tetrabenazine (the only drug currently approved for HD based on its effect on chorea), but with the major impact on motor domains different from chorea. This effect on motor

function, without any negative effect on the other domains of the disease (ie, behavior or cognition) may have clinical relevance.

1.4.2. General Risks

QTc prolongation has been demonstrated in clinical studies of pridopidine; this is discussed in more detail in Section 1.5.

From preclinical data in mouse, rat, and dog, there appears to be a relationship between exposure and convulsions; this is discussed in more detail in Section 1.5.

Based on the MAD study (ACR16C018), dizziness could be observed frequently in patients treated with doses equal or higher than 67.5 mg bid. Psychiatric events (including nightmare, aggression, depressive mood, anxiety, and abnormal dreams) were also observed frequently in the patients receiving pridopidine 90 mg bid. It should be noted that there was no titration period in the MAD study while a 1-month progressive titration is implemented in the present study, which should decrease the risk of dizziness.

Since renal function impacts pridopidine elimination, 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.

Body weight has been shown to correlate with exposure; therefore, patients with body weight below 50 kg will be excluded from the study.

1.4.3. Drug Interactions

Pridopidine is a CYP2D6 substrate and thus PK interactions could be expected with drugs that inhibit CYP2D6, although not more than what is expected from a PM (where CYP2D6 is non-functional). It is not expected that CYP2D6 inhibitors have a stronger effect than 1.3-fold increase in exposure and therefore, provided no other interaction occurs, CYP2D6 inhibitors can be administered to study patients. 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.

Pridopidine is a strong inhibitor of CYP2D6. Thus, 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 (ie, 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.

A potential pharmacodynamic (PD) interaction between pridopidine and tetrabenazine cannot be excluded and concomitant treatment with tetrabenazine is disallowed.

Permitted and prohibited concomitant medications are detailed in Section 5.3.

1.4.4. Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been performed with pridopidine.

The genotoxicity of pridopidine has been evaluated in vitro and in vivo. No evidence of mutagenic or clastogenic activity has been found.

Pridopidine shows no abnormalities in male reproductive function tests in rats (including sperm motility) or in early embryonic development. In female rats, no differences were observed in comparisons of group means for fertility index, the number of corpora lutea, number of implantations, pre-implantation loss rate, number of live embryos, number of resorptions, or post-implantation loss rate.

1.4.5. Pregnancy

In the embryo-fetal development toxicity study in rats, a higher incident of cleft palate was seen in the high dose of 150 mg/kg (C_{max} 11,798 ng/mL and AUC 149,298 ng*hr/mL). The no observed adverse effect level (NOAEL) for fetuses of 50 mg/kg resulted in C_{max} of 4,540 ng/mL and AUC of 56,630 ng*hr/mL. Safety margins (based on AUC) calculated from the NOAEL compared to human predicted data by a population PK model were 3.4 for 90 mg bid and 2.7 for 112.5 mg bid (Report CP-13-013)[a].

Although teratogenic potential was not indicated in the embryo-fetal development study in rabbits, care should be taken to not expose pregnant women or women of childbearing potential to pridopidine.

There was a temporary retardation in the physical development of the pups from high dose group dams during lactation indicative of transfer of pridopidine into the milk. Pridopidine use should therefore be restricted in nursing mothers.

1.4.6. Pharmacological Class Events

Pridopidine belongs to a novel class of dopaminergic neurotransmission modulators and hence only limited information about class events is available. Considering the pharmacological profile of pridopidine, the most similar drug class is dopamine antagonists. Dopamine antagonists are known to cause some CNS adverse effects, which are due to their pharmacological mode of action. Some agents in this class have also demonstrated probable off target effects such as metabolic effects (diabetes, weight gain, increased prolactin, increased liver function enzymes, and agranulocytosis), cardiovascular effects (QT interval prolongation, tachycardia, hypotension, and syncope secondary to hypotension), anticholinergic effects (dry mouth, blurred vision, sexual dysfunction, temperature dysregulation, and constipation) and histaminergic effects (sedation).

1.5. Selection of Drugs and Dosages

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). However, the magnitude of pridopidine effect on motor function could not be shown to be of clinical significance to the patient, as measured by the functional/global measures assessed. Pridopidine has been shown to have a benign safety profile, similar to placebo, in doses so far tested in patients with HD. Hence it is 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 used in the present study.

Overall, pridopidine was generally safe and tolerable at the explored doses of up to 45 mg bid in HD patients. Extrapolation of the data from the HART (ACR16C009) and MermaiHD (ACR16C008) studies in HD patients as well as from the MAD study (ACR16C018) in healthy volunteers suggested that the safety profile of 67.5 mg bid pridopidine is similar to that observed with pridopidine up to 45 mg bid.

It should be noted that, in the MAD study (ACR16C018), in addition to the QT prolongation that may be of clinical concern, the dose of 90 mg bid, was associated with more frequent AEs, in particular dizziness and psychiatric events. A dose of 112.5 mg was not administered in the MAD study.

Justification for the use of a dose of 112.5 mg bid in the present study is presented in the following sections (Sections 1.5.1, 1.5.2, and 1.5.3).

1.5.1. QTc Prolongation

QTc prolongation has been demonstrated in healthy volunteers (Study ACR16C001, non-Good Clinical Practice [GCP] study) and in patients with schizophrenia (Study 2314-CL-001), in whom change from baseline in QTcF (ΔQTcF) reached 13 msec at 50 and 100 mg qd after 18 days of treatment.

Pridopidine has been studied in 3 randomized, placebo-controlled trials in patients with HD: a small exploratory proof of principle study (ACR16C007), a dose finding phase II study (HART [ACR16C009]), and a phase III study (MermaiHD [ACR16C008]). These 3 studies included 722 patients (362 females and 360 males), of which 490 patients received pridopidine in doses ranging from 20 to 90 mg daily. In 2 of the studies (HART and MermaiHD), a central assessment of all ECG readings was performed. In MermaiHD, ECGs were recorded in triplicate at screening and single recordings were made after 1, 4, 5, 12, and 26 weeks of treatment. In HART, ECGs were recorded in triplicate at screening and singly after 1, 4, 5, and 12 weeks of treatment. Patients with QTc prolongation at baseline or with clinically significant heart disease were excluded from the study, and concomitant treatment with antipsychotic drugs with clear association to QTc prolongation or proarrhythmias was disallowed. In MermaiHD, concomitant treatment with strong CYP2D6 inhibitors (eg, fluoxetine, paroxetine, ajmaline, and ritonavir) was disallowed; patients with PM status for CYP2D6 were enrolled in both studies. In total, 186 patients were studied on the highest dose, 45 mg bid. In MermaiHD, a small increase of heart rate was observed, based on mean change from baseline in heart rate (ΔHR) on treatment and on placebo, with a placebo-corrected change from baseline in heart rate (ΔΔHR) estimated to be approximately 3 bpm. A small mean ΔQTcF was noted, with ΔΔQTcF of approximately 3 and 4 msec for the 45 mg qd and bid groups, respectively. There were no patients with a QTcF value exceeding 480 msec and only 1 patient (1%) in the 45 mg qd group with a ΔQTcF >60 msec. The proportion of patients with ΔQTcF >30 msec at any time point during the study was comparable across treatment groups; 8%, 11%, and 8% of patients in the placebo, pridopidine 45 mg qd, and 45 mg bid groups, respectively. A small ΔHR was also observed in HART; approximately 2 and 2.5 bpm in the 2 highest groups. Consistent with the findings in MermaiHD, there was a small QTc effect observed, with ΔΔQTcF of approximately 4 to 4.5 msec for pridopidine 22.5 and 45 mg bid. There was 1 patient in the highest dose group with QTcF >480 msec and none in the QTcF >500 msec category. There were no patients with

ΔQTcF >60 msec and the proportion of patients with ΔQTcF >30 msec was largest in the placebo group (10%).

Notably, there were no patients on pridopidine with a QTcF value exceeding 500 msec and only 1 patient with QTcF >480 msec at any time point in these 2 studies; only 1 patient on pridopidine demonstrated ΔQTcF >60 msec and the proportion of patients with ΔQTcF >30 msec was either comparable across treatment groups (MermaiHD [ACR16C008]) or higher in the placebo group (HART [ACR16C009]). It should be noted that in the clinical studies in HD patients the ECG schedule was not optimized to capture peak QTc effects.

Overall, the incidence of cardiac AEs was low. There were no events of cardiac arrest, sudden death, or ventricular arrhythmias. None of the cardiac events can be linked to proarrhythmic events caused by QT prolongation, with the possible exception of 1 case of syncope, which has very low specificity.

However, a MAD study (ACR16C018), exploring doses of 45 to 90 mg bid for 9 days in 36 healthy subjects revealed a substantially higher dose-dependent QTcF prolongation. The largest ΔΔQTcF was observed 1 hour after dosing in the morning and in the afternoon (corresponding to C_{max}): in the 45 mg bid group, ΔΔQTcF reached 18.4 and 18.0 msec at these time points, respectively, and in the 67.5 mg bid group, ΔΔQTcF reached 17.9 and 20.5 msec, respectively. The upper bound of the 90% confidence interval (CI) reached 22 and 25 msec for 1 hour after dosing in the morning and in the afternoon, respectively. In the 90 mg bid group, ΔΔQTcF was 24.8 and 24.3 msec 1 hour after dosing in the morning and in the afternoon, respectively, with upper bound of the CI of 29.2 and 28.7 msec, respectively. The exposure response (PK/QTc) analysis on data from study ACR16C018 demonstrated a significant slope of the pridopidine concentration/ΔΔQTcF relationship of 0.0185 msec per ng/mL (90% CI: 0.0139 to 0.0231 msec per ng/mL) and thus confirmed that pridopidine prolongs the QT interval in a dose-dependent manner.

Based on those findings, patients with a prolonged QTc interval (defined as a QTc interval of >450 msec), or other clinically significant heart conditions are excluded from this study. In addition, extensive ECG and electrolyte monitoring and rules for drug discontinuation (see Section 3.6) are included in the study. Particular precautions are also warranted as regards with concomitant use of drugs known to prolong QTc interval.

1.5.2. Seizure Risk

From preclinical data in mouse, rat, and dog, there appears to be a relationship between exposure and convulsions with the threshold plasma exposure causing convulsions starting at approximately 6000 ng/mL (C_{max}) or 60,000 ng*hr/mL (AUC). It is thought likely that the convulsive episodes seen are C_{max} related rather than AUC related, as they are presumed examples of the exaggerated pharmacology of the compound. In the past, subjective safety limits related to this risk of convulsions were set up for clinical studies (3,000 ng/mL C_{max} or 30,000 ng*h/mL AUC). This was, however, at a time in the program when very little clinical data on patients were available, and the safety assessment had to rely mostly on animal data. Based on PK modeling, it is anticipated that approximately 1.9% of the patients on the higher dose of 112.5 mg bid (and 2.1% of patients overall) will display C_{max} above the historical threshold set before substantial clinical safety data were collected (CP-13-013)[a].

To date, in clinical studies only 3 patients have experienced convulsions. In the HART study (ACR16C009), 1 patient randomized to the 22.5 mg bid group experienced convulsion on 3 occasions, 1 event during the treatment and 2 events 8 and 17 days, respectively, after treatment discontinuation. Possible relatedness could not be excluded due to a temporal relationship of the first event with the initiation of study treatment. In the open-label extension of the HART study, 2 patients experienced convulsions. In one of these patients, the convulsions were considered related to concurrent encephalitis. In the other case, although there were certain confounding factors, relationship to the study medication could not be entirely excluded. Given that doses higher than 45 mg bid will be administered in the proposed study, no patient with epilepsy or a history of seizure(s) of unknown cause within the previous 5 years will be included and rules for drug discontinuation related to convulsions are implemented in the study. Medications that are CYP2D6 substrates and have the potential to reduce the seizure threshold will not be permitted during the study (see Section 5.3.2.4).

1.5.3. Tolerability and Adverse Events

In the MAD study (ACR16C018), tolerability and safety of pridopidine 45 to 90 mg bid for 9 days was investigated in 36 healthy subjects. The safety profile of pridopidine in the 45 and 67.5 mg bid dose groups was similar to that observed in the larger clinical studies. Overall, the most frequently reported AEs were within the SOCs Nervous system disorders, Gastrointestinal disorders and Psychiatric disorders. The majority of AEs were considered mild. Although the 90 mg bid dose was considered the MTD, there was no titration period in the MAD study. The present study will include a titration period (see Section 3.4.1.1), including a more progressive titration for the higher dose, as a means to reduce poor tolerability. Additionally, the Drug Safety Monitoring Board (DSMB) may decide to discontinue 1 or more treatment arms if more than 30% of the patients in the treatment arm have discontinued dosing due to intolerable AEs (see Section 3.6.2).

1.5.4. Psychiatric Adverse Events Reflecting Suicidal Behavior

The DSMB for the PRIDE-HD study held an unscheduled meeting on 29 February 2016, and follow-up meetings on 04 March 2016 and 12 March 2016, to review psychiatric adverse events. Upon initial review of safety data from PRIDE-HD and Open PRIDE-HD, the DSMB raised questions regarding certain psychiatric AEs, including depression, suicidal ideation, and suicide attempts observed in the PRIDE-HD study. In the ongoing PRIDE-HD study (n=408 patients), 4 patients had serious adverse events of suicidal attempts and 2 patients had a serious adverse event of suicidal ideation. In addition, 6 patients had adverse events of suicidal ideation: 4 cases were mild and 2 moderate in severity/intensity. In the ongoing Open-PRIDE-HD study, there has been 1 serious adverse event of suicidal ideation in a patient. These patients were discontinued from treatment with study medication but were permitted to continue in the study.

The data reviewed suggested that the overall rate of suicidality events reported in PRIDE-HD and Open PRIDE-HD were comparable to previous experience in HD trials. Nevertheless, following full review and discussion, Teva and members of the PRIDE-HD Steering Committee proposed an increase in safety monitoring for psychiatric AEs in both studies, which was approved by the DSMB (12 March 2016 meeting). An expert HD psychiatrist (Dr. Erik van Duijn) also issued a letter in support of the proposed monitoring plan.

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 and Section 3.6.2), including updated individual patient stopping rules (Section 3.6.1), 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.

1.6. Compliance Statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) 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 20/EC and 28/EC). Any episode of noncompliance will be documented.

The investigators are 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 each 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.

Each 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. Each 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 Investigator's Brochure 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

The study population will consist of male or female patients aged ≥21 years and with body weight ≥50 kg, with diagnosis of HD based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene. HD should have been diagnosed when the patient was aged >18 years. In addition, patients should have: 1) a sum of ≥25 points on UHDRS-TMS at the screening visit, and 2) a UHDRS Independence Score (IS) <90% at the screening visit. Patients should be ambulatory and have the capacity to travel to the clinic visits.

Inclusion and exclusion criteria are presented in Sections 4.1 and 4.2, respectively.

1.8. Relevant Literature and Data

Relevant literature is cited above. Further literature and data may be found in the current Investigator's Brochure.

2. PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1. Purpose of the Study

Although both previous clinical studies on pridopidine in patients with HD (MermaiHD [ACR16C008] and HART [ACR16C009]), failed to meet their primary objective, ie, to show an improvement on the mMS, a statistically significant effect of pridopidine 45 mg bid was observed on UHDRS-TMS, the primary endpoint in the present study. In addition, a monotone dose response relationship, as investigated in HART, was seen on the improvements on motor function by pridopidine treatment, when measured by both UHDRS-TMS and mMS. In both studies, pridopidine was considered safe and well tolerated, with a benign AE profile in the doses studied (up to 45 mg bid). The clinical relevance of the 3-point effect observed on the UHDRS-TMS was, however, debated by regulatory agencies, and the sponsor was encouraged to explore higher doses with the aim to identify the optimal dosing regimen with the potential to show higher magnitude of benefit. Hence, a dose finding study with increased doses of pridopidine is warranted.

The present clinical study is planned to primarily assess the effects and dose-response of pridopidine, compared with placebo, on improvement in motor function in patients with HD after 26 weeks of treatment.

2.2. Study Objectives

The primary objective of this study is to assess the efficacy of pridopidine 67.5 to 112.5 mg bid on motor impairment in patients with HD after 26 weeks of treatment using the UHDRS-TMS.

The secondary efficacy objective of the study is to assess the effect of 26 weeks of treatment with pridopidine 67.5 to 112.5 mg bid on the modified Physical Performance Test (mPPT).

The other secondary objectives are as follows:

- To evaluate the safety and tolerability of a range of pridopidine doses in patients with HD during the entire 52-week study period
- To explore the PK of pridopidine in the study population
- To investigate the relationship between exposure to pridopidine and outcome measures (eg, clinical efficacy and toxicity parameters)

Other efficacy endpoints will also be analyzed; these are detailed in Section 3.2.3.

3. STUDY DESIGN

3.1. General Design and Study Schema

This is a multicenter, multinational, randomized, parallel-group, double-blind, placebo-controlled study to compare the efficacy and safety of pridopidine 45, 67.5, 90, and 112.5 mg bid versus placebo in the treatment of motor impairment in HD. The 45 mg dose level will not be formally included in the efficacy analyses. It is planned to enroll a total of 400 patients (80 patients within each treatment arm).

Patients will be equally randomized (1:1:1:1:1) to receive pridopidine 45, 67.5, 90, or 112.5 mg or placebo bid for 52 weeks, including a 4-week progressive titration period. During the study, an independent DSMB will review accumulating unblinded safety data. The DSMB will meet monthly until 20 patients from each treatment arm (i.e. a total of 100 patients) have completed two weeks of treatment on full dose (6 weeks in the study). In case of a significant emerging safety concern in 1 or more treatment arm(s), the DSMB will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatments arm(s) with safety concerns. Thereafter, the DSMB will decide whether there is a need for additional meetings, and, if needed, will determine when these will take place.

After having signed an informed consent, including consent to provide a blood sample for genetic analyses, patients will be screened for a period of up to 12 weeks in order to determine whether they are eligible to participate in the study. The investigator should aim to perform the baseline visit as soon as possible after the screening visit. Patients with a legal guardian should be consented according to local requirements. The screening period will include a comprehensive medical and psychiatric history, rating of the Columbia-Suicide Severity Rating Scale (C-SSRS), a record of previous medications, a full physical and neurological examination, measurements of vital signs, typical clinical laboratory tests (hematology, biochemistry, urinalysis), serum pregnancy tests (if female of childbearing potential), and a single 12-lead ECG. The diagnosis of HD will be established based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene. UHDRS-TMS and UHDRS-IS will be assessed. In addition, in order to pre-expose participants to tests prior to measuring baseline performance (and by this way reduce the practice effects), the Quantitative motor (Q-Motor) and cognitive assessment battery (CAB) tests (Symbol Digit Modalities Test [SDMT], Emotion Recognition, Trail Making Test, Hopkins Verbal Learning Test, revised [HVLT-R], Paced Tapping at 3 Hz, One Touch Stockings of Cambridge [OTS, abbreviated 10-trial version]) will be administered at screening. In case the devices needed for the CAB and the Q-Motor assessments are not available at all the sites, those evaluations will be done only in sites where devices are available. Eligible patients will be randomized to receive active drug or placebo and will be titrated during the first 4 weeks from pridopidine 22.5 mg bid to the final dose of 45, 67.5, 90, or 112.5 mg bid according to the treatment arm they are randomized to as detailed in Section 3.3.

During titration (Days 0 to 27), there will be 2 on-site visits: at Visit 1 (baseline) and at Week 2. There will be additional phone calls on Weeks 1 and 3.

At the baseline visit, before the first dose of study drug, the Clinician's Interview Based Impression of Severity (CIBIS) will be rated by an independent rater, while another qualified site personnel will assess the mPPT, the Clinical Global Impression of Severity (CGI-S), the Timed Up and Go (TUG) Test, the Physical Disability Scale (PDS), the UHDRS-TMS, the UHDRS-FA, the UHDRS-IS, the UHDRS Total Functional Capacity (TFC), the CAB (as defined in Section 6.3.10), and the Problem Behaviors Assessment-Short form (PBA-s). A full physical and neurological examination, including weight, will be performed. The patient will fill the Walk-12 and the HD-Quality of life scale (HD-QoL), the EQ5D, and Q-Motor assessments will be performed. UHDRS-TMS and mPPT should be evaluated prior to the other scales.

Triplicate 12-lead ECG recordings and PK sampling for determination of the levels of pridopidine (TV-7820) and its main metabolite (TV-45065, previously called ACR30) will be performed before and 1 to 2 hours after first dose administration. PK samples will be collected after ECG measurements.

Phone calls on Weeks 1 and 3 will be performed to inquire about AEs and concomitant medications, and to allow the weekly dose increase on the following day. During the on-site visit at Week 2, before the afternoon dose of the study drug, a blood sample will be taken for electrolyte monitoring; if hypokalemia is observed, dosing will be interrupted 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. Vital signs will be assessed in addition to the inquiry about AEs and concomitant medications. Twelve-lead ECGs will be performed in triplicate 1 to 2 hours after the afternoon dose of study drug on Week 2, followed by collection of a PK sample.

During the full treatment dose period (Weeks 4-52), there will be a total of 9 on-site visits at Weeks 4, 6, 8, 12, 16, 20, 26, 39 and 52 (or at early termination) and a phone call on Weeks 5, 32, between Weeks 40-44, on Week 45 and between Weeks 46-51. Visits and procedures during the full dose period will be scheduled around the afternoon dose, with the exception of Week 52 where only the morning dose is administered. During the phone call at Weeks 5 and 32, inquiries about AEs and concomitant medication will be conducted. During the phone calls between Weeks 40-44, on Week 45 and between Weeks 46-51, 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.

At each of the on-site visits, safety variables will be assessed, including triplicate ECG evaluation before and 1 to 2 hours after dose administration at the site (ECG is optional on Week 8), and clinical laboratory evaluations. PK sampling for determination of the levels of pridopidine and TV-45065 will be done on Weeks 4, 6, and 16 (before and 1 to 2 hours after the afternoon dose), on Week 12 and 20 (1 to 2 hours after the afternoon dose), on Week 26 (before the afternoon dose) and on Week 52(before the morning dose). When concomitant to ECG, PK samples will be collected after the ECG recording.

At Weeks 4, 8, 12, 16, 20, 26, and 52 in addition to safety assessments, the UHDRS-TMS and the mPPT will be assessed by qualified site personnel.

At Weeks 4, 12, 26 and 52, in addition to safety assessments and the UHDRS-TMS and mPPT, the CIBIC-Plus will be rated by an independent rater, while another qualified site personnel will assess the PDS, the CGI-C, the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, and the PBA-s. The PBA-s will also be assessed at Week 39. UHDRS-TMS and mPPT should be evaluated prior to the other scales.

The patient will fill the Walk-12 and Q-Motor assessments will be performed. The UHDRS-FA, the UHDRS-TFC and the UHDRS-IS will also be performed on Week 20.

The CAB will be performed on Weeks 12, 26 and 52 only.

The HD-QoL and EQ5D scales will be completed on Weeks 26 and 52only.

Patients who complete all scheduled visits will have final procedures and assessments performed at the final visit (Week 52). Patients who withdraw from the study before completing the evaluation period will have the Week 52 procedures and assessments performed at their final visit.

There will be a follow-up visit 2 weeks after last dose of study drug for safety evaluation, including a triplicate ECG evaluation (optional) and PK sample. At this visit, UHDRS-TMS and Q-Motor will also be assessed.

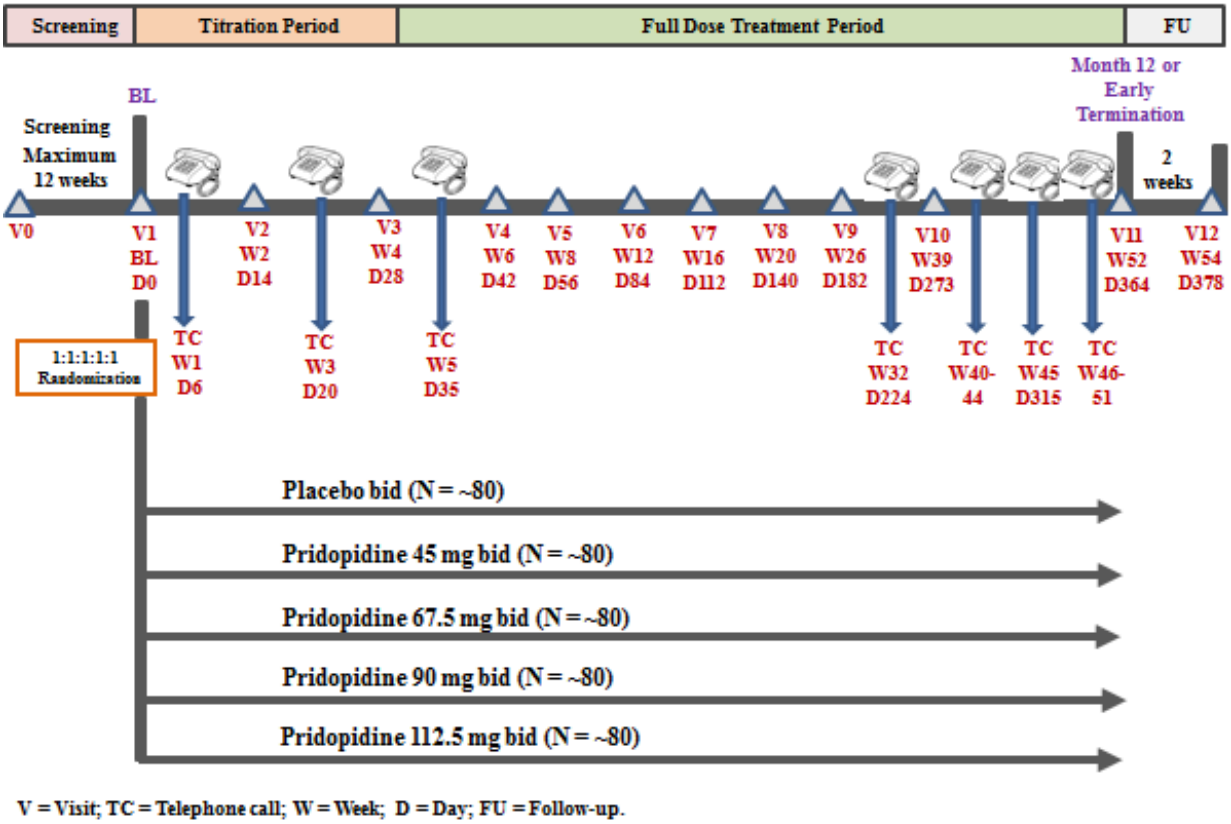
The procedures and assessments for visits V0 and V4-12 may be performed over several days, as long as they are completed within the defined visit window.

In case of an SAE, the aim will be to collect an additional PK sample at the closest time possible to the SAE.

Patients, who for safety or tolerability reasons have to stop study drug medication, will be asked to continue in the study and follow the visit schedule as outlined in the protocol, without taking study drug. Patients who complete this study may have the opportunity to enter an open-label extension study.

The study schema is presented in Figure 1.

Figure 1: Overall Study Schema



V = Visit; TC = Telephone call; W = Week; D = Day; FU = Follow-up.

3.2. Primary and Secondary Variables and Endpoints

The primary and secondary efficacy endpoints will be evaluated at week 26.

Other efficacy endpoints will be evaluated at week 26 and week 52 and will be performed for exploratory purposes.

3.2.1. Primary Efficacy Variable and Endpoint

The primary efficacy variable and endpoint for this study is:

- Change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week 26

3.2.2. Secondary Efficacy Variable and Endpoint

The secondary efficacy variable and endpoint is:

- Change from baseline in the mPPT at Week 26

3.2.3. Other Efficacy Variables and Endpoints

Global Functional Scales:

- Change from baseline in the mPPT at Week 52
- CIBIC-Plus global score at Week 26 and 52 as compared to baseline (rated by an independent investigator)
- Change from baseline in the PDS score at Week 26 and 52
- Change from baseline in UHDRS-FA at Week 26 and 52
- CGI-C at Week 26 and 52 as compared to baseline (rated by qualified site personnel)
- Change from baseline in UHDRS-TFC at Week 26 and 52
- Change from baseline in UHDRS-IS at Week 26 and 52

Patient Reported Outcomes:

- Change from baseline in HD-QoL at Week 26 and 52
- Change from baseline in EQ5D-5L at Week 26 and 52
- Change from baseline in Walk-12 at Week 26 and 52

UHDRS-TMS and Subscores:

- Change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week 52
- Change from baseline in hand movement score (defined as the sum of UHDRS domains finger taps, pronate-supinate hands and luria [fist-hand-palm test]) at Week 26 and 52
- Change from baseline in Gait and balance score (defined as the sum of UHDRS domains gait, tandem walking and retropulsion pull test) at Week 26 and 52
- Change from baseline in UHDRS-mMS (defined as the sum of UHDRS domains dysarthria, tongue protrusion, finger taps, pronate-supinate hands, luria, rigidity, bradykinesia, gait, tandem walking, retropulsion pull test) at Week 26 and 52
- Change from baseline in UHDRS-Chorea at Week 26 and 52
- Change from baseline in UHDRS-Dystonia at Week 26 and 52
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea items
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Dystonia items
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea and Dystonia items
- Responders, defined as patients with UHDRS-TMS change from baseline ≤0 at Week 26/early termination visit prior to week 26

Other Motor Assessments:

- Change from baseline in Q-Motor measurements at Week 26 and 52 including digitomotography (speeded index finger tapping), dysdiadochomotography (pronation/supination hand tapping), manumotography and choreomotography (grip force and chorea analysis) and pedomotography (speeded foot tapping)
- Change from baseline in the TUG Test at Week 26 and 52

Cognitive/Psychiatric Assessments:

- Change from baseline in CAB at Week 26 and 52: SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS
- Change from baseline in PBA-s at Week 26 and 52

3.2.4. Safety Variables and Endpoints

Safety variables and endpoints will include the following:

- AEs throughout the study
- Changes from baseline in QTcF and other ECG parameters throughout the study
- Clinical safety laboratory (clinical chemistry, hematology, and urinalysis) throughout the study
- Changes from baseline C-SSRS and PBA-s throughout the study
- Vital signs throughout the study

3.2.5. Tolerability Variables and Endpoints

Tolerability variables and endpoints will include the following:

- the number (%) of patients who failed to complete the study
- the number (%) of patients who failed to complete the study due to AEs

3.2.6. Pharmacokinetic Variables and Endpoints

The primary PK measure will be determination of plasma concentration of pridopidine. Concentrations will also be incorporated into a pridopidine population PK model and individual exposure for the study patients (C_{max} and AUC) will be calculated.

3.3. Randomization and Blinding

Randomization will be performed by interactive response technology (IRT) using dynamic randomization to balance the treatment arms within centers and neuroleptics use or no use. Patients will be equally assigned to the 5 treatment arms of the study (4 active treatment arms and placebo, allocation ratio of 1:1:1:1:1). Patients that are continuing to the second study period (after week 26) will continue to receive the same treatment as they were randomized to at baseline of the first 26-week study period. Pridopidine capsules sizes differ between the 22.5 and 45 mg dosages, therefore 2 different sizes of placebo capsules will be provided, depending on treatment arm, to maintain blinding. Packaging of all treatment packs will be identical in

appearance in order to maintain blinding throughout each study period. The investigators, the sponsor, and any personnel involved in patients' assessment, monitoring, analysis and data management (excluding the designated Clinical Supplies Chain's personnel), are blinded to the patient assignment until the database is locked for analysis of the first 26-week study period and the treatment assignment revealed. A statistician not assigned to the study will be responsible for reviewing the randomization code.

After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain, designated Pharmacovigilance personnel designated Pharmacovigilance personnel, the Therapeutic Area Head, the Project Champion, and the team members responsible for the population PK and PK/PD analysis will be exposed to the individual patients' treatment assignments. The sponsor study core team that works on the study report and/or design of additional studies and upper management will not be exposed to individual patients' treatment assignments and only be exposed to data summaries by treatments. The investigators, the patient, and any other personnel involved in patients' assessment, monitoring, analysis and data management are blinded to the patient assignment until the database is locked for analysis of the week 52 data. A detailed procedure that will be taken for maintaining the blinding of the study up to week 52, will be specified before the treatment assignment are revealed for analysis of the first 26-week period of the study. This procedure will include a list of people that are allowed to be exposed to safety data summaries by treatments.

Should the DSMB decide to stop the continuation of 1 or more treatment arms, the dynamic randomization algorithm will be adjusted to apply an equal allocation ratio to all approved remaining treatment arms. If an arm is stopped by the DSMB, then any patients currently enrolled in that arm will stop receiving medication immediately but will continue to be followed for adverse events and safety.

Emergency unblinding is discouraged if the knowledge of treatment assignment will not materially change the planned management of a medical emergency. When possible, unblinding should be discussed in advance with the Medical Monitor. Emergency unblinding will be managed through the IRT. Patients whose treatment assignment has been unblinded will be permanently discontinued from treatment. The sponsor and contract research organization (CRO) must be notified immediately if a patient and/or investigator is unblinded during the course of the study. Pertinent information regarding the circumstances of unblinding of a patient's treatment code must be documented in the patient's source documents and case report forms (CRFs).

Details of how the blind is maintained during PK analysis are presented in Section 3.8.

3.4. Study Drugs and Dosage

Study drug (pridopidine and matching placebo) will be administered as described in Sections 3.4.1 and 3.4.2, and as summarized in Table 1.

Table 1: Dose Administration (Capsules are Administered Twice Daily to Give the Total Daily Dose)

	Titration Period				Full Dose Period
Treatment	**Week 1**	**Week 2**	**Week 3**	**Week 4[a]**	**Weeks 4[b] to 52**
Pridopidine 45 mg bid	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 45 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 90 mg)
Pridopidine 67.5 mg bid	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 45 mg Pridopidine 2 × 22.5 mg Placebo (TDD = 90 mg)	1 × 45 mg Pridopidine 2 × 22.5 mg Placebo (TDD = 90 mg)	1 × 22.5 mg Pridopidine 1 × 45 mg Pridopidine 1 × 45 mg Placebo (TDD = 135 mg)
Pridopidine 90 mg bid	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 45 mg Pridopidine 2 × 22.5 mg Placebo (TDD = 90 mg)	1 × 45 mg Pridopidine 1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo (TDD = 135 mg)	1 × 45 mg Pridopidine 1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo (TDD = 135 mg)	2 × 45 mg Pridopidine 1 × 22.5 mg Placebo (TDD = 180 mg)
Pridopidine 112.5 mg bid	1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo 1 × 45 mg Placebo (TDD = 45 mg)	1 × 45 mg Pridopidine 2 × 22.5 mg Placebo (TDD = 90 mg)	1 × 45 mg Pridopidine 1 × 22.5 mg Pridopidine 1 × 22.5 mg Placebo (TDD = 135 mg)	1 × 45 mg Pridopidine 2 × 22.5 mg Pridopidine (TDD = 180 mg)	1 × 22.5 mg Pridopidine 2 × 45 mg Pridopidine (TDD = 225 mg)
Placebo	2 × 22.5 mg Placebo 1 × 45 mg Placebo	2 × 22.5 mg Placebo 1 × 45 mg Placebo	2 × 22.5 mg Placebo 1 × 45 mg Placebo	2 × 22.5 mg Placebo 1 × 45 mg Placebo	1 × 22.5 mg Placebo 2 × 45 mg Placebo

TDD = total daily dose
[a] Excluding Day 28
[b] Day 28 only

3.4.1. Investigational Product and Dosage

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.

The sponsor will provide the study medication. The secondary packaging and labeling of study medication is under the responsibility of the Clinical Supply Chain of the sponsor and is according to EU regulations and ICH guidelines as adopted by the FDA –Good Clinical Practice (E6).

Each medication pack will contain 3 distinct labeled bottles in accordance with the associated treatment arm. Each bottle will contain 30±1 capsules. The 3 bottles will be used to accomplish the dosing of 1 of the 5 treatment arms. During the whole study period, as detailed in Section 3.4.1.1 (titration period) and Section 3.4.1.2 (full dose period), 1 capsule from each of the 3 bottles should be taken by the patient twice a day, ie, 3 capsules in the morning and 3 capsules in the afternoon (7 to 10 hours after the morning dose). There will not be an afternoon dose at the final visit (Week 52/Early Termination). Study drug can be taken irrespective of meals.

Both outer pack and bottles will be labeled with a unique pack number.

The appropriate number of treatment packs will be assigned to patients by using the IRT according to the dosing schedule at Visits 1, 2, 3, 5, 6, 7, 8, 9 and 10 (baseline and Weeks 2, 4, 8, 12, 16, 20, 26 and 39). If tolerability problems occur, patients will be instructed to contact the investigator immediately.

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

3.4.1.1. Weeks 1 to 4 (up to Day 27): Titration Period

Patients randomized to the pridopidine 45 mg bid treatment arm

- Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine)

Patients randomized to the pridopidine 67.5 mg bid treatment arm

- Weeks 1 and 2: Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine)
- Weeks 3 and 4 (up to Day 27): Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg placebo bid (45 mg bid, total daily dose of 90 mg pridopidine)

Patients randomized to the pridopidine 90 mg bid treatment arm

- Week 1: Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine)

- Week 2: Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg placebo bid (45 mg bid, total daily dose of 90 mg pridopidine)
- Weeks 3 and 4 (up to Day 27): Patients will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg pridopidine and 1 capsule of 22.5 mg placebo bid (67.5 mg bid, total daily dose of 135 mg pridopidine)

Patients randomized to the pridopidine 112.5 mg bid treatment arm

- Week 1: Patients will receive 1 capsule of 22.5 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (22.5 mg bid, total daily dose of 45 mg pridopidine)
- Week 2: Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg placebo bid (45 mg bid, total daily dose of 90 mg pridopidine)
- Week 3: Patients will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg pridopidine and 1 capsule of 22.5 mg placebo bid (67.5 mg bid, total daily dose of 135 mg pridopidine)
- Week 4 (up to Day 27): Patients will receive 1 capsule of 45 mg pridopidine and 2 capsules of 22.5 mg pridopidine (90 mg bid, total daily dose of 180 mg pridopidine)

3.4.1.2. Week 4 (Day 28 Only) to Week 52: Full Dose Period

Patients randomized to the pridopidine 45 mg bid treatment arm will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg placebo and 1 capsule of 45 mg placebo bid (total daily dose of 90 mg).

Patients randomized to the pridopidine 67.5 mg bid treatment arm will receive 1 capsule of 45 mg pridopidine, 1 capsule of 22.5 mg pridopidine and 1 capsule of 45 mg placebo bid (total daily dose of 135 mg).

Patients randomized to the pridopidine 90 mg bid treatment arm will receive 2 capsules of 45 mg pridopidine and 1 capsule of 22.5 mg placebo bid (total daily dose of 180 mg).

Patients randomized to the pridopidine 112.5 mg bid treatment arm will receive 2 capsules of 45 mg pridopidine and 1 capsule of 22.5 mg pridopidine bid (total daily dose of 225 mg).

3.4.2. Other Study Drugs and Dosage

Placebo will be presented as white hard gelatin capsules matching the 22.5 mg or 45 mg pridopidine capsules but containing no active ingredient, only the excipients (silicified microcrystalline cellulose and magnesium stearate).

Patients randomized to placebo will receive 3 capsules bid, ie, 3 capsules in the morning and 3 capsules in the afternoon (7 to 10 hours after the morning dose), during the whole study period, as detailed in Section 3.4.2.1 (titration period) and Section 3.4.2.2 (full dose period). There will not be an afternoon dose at the final visit (Week 52/Early Termination).

3.4.2.1. Weeks 1 to 4 (up to Day 27): Titration Period

Patients randomized to placebo arm will receive 2 capsules of 22.5 mg placebo and 1 capsule of 45 mg placebo bid.

3.4.2.2. Week 4 (Day 28 Only) to Week 52: Full Dose Period

Patients randomized to placebo arm will receive 2 capsules of 45 mg placebo and 1 capsule of 22.5 mg placebo bid.

3.5. Duration of Patient Participation

For each patient, the duration of participation is planned to be up to 66 weeks, consisting of a screening period of up to 12 weeks, a 52-week randomized double-blind treatment period (comprised of a 4-week titration and 48-week full dose period), and a 2-week follow-up period following the last dose of study medication.

The total duration of the study is estimated to be approximately 30 months.

3.6. Stopping Rules and Discontinuation Criteria

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, AE). 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 11.1.1, noncompliance, AE).

3.6.1. 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 (see Section 3.6.3).

Patients should be discontinued if any of the following criteria relating to QTcF are met at any visit:

- QTcF >500 msec (based on the mean value from the triplicate ECG measurements);
- QTcF >480 msec with concurrent increase in QTcF >60 msec (ΔQTcF, based on the mean value from the triplicate ECG measurements) from baseline (Day 0);
- If QTcF >480 msec or ΔQTcF >60 msec, a repeat ECG (in triplicate) will be recorded after 7 to 9 days; if the change is confirmed and electrolytes are normal, the patient will be withdrawn.

If the local ECG reading results at the site match any of the above discontinuation criteria, 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), if their body weight decreases to <50 kg, 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.

Additional discontinuation criteria for individual patients, based on suicide ideation or attempt, will be applied. Patients should be discontinued if:

- 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).

3.6.2. Discontinuation of a Treatment Arm

If any of the following conditions related to a treatment arm are met, the DSMB should review the data and consider stopping that treatment arm:

- If ≥20% of the patients in a treatment arm have discontinued dosing based on QTc stopping criteria (as defined in Section 3.6.1), provided there are at least 3 events;
- If the largest placebo-corrected mean change from baseline QTcF (ΔΔQTcF) for a treatment arm exceeds 40 msec;
- If there are findings of concern following review of the relationship between any convulsions and PK data for a treatment arm;
- If >30% of the patients in the treatment arm have discontinued dosing due to intolerable AEs.

These conditions are not discontinuation criteria, but are triggers for a review by the DSMB, who may decide to discontinue the treatment arm following their review.

Two stopping rules based on the occurrence of suicidal attempts and suicidal ideation have been introduced after consultation with members of the study steering committee and DSMB (details in Section 1.5.4):

1. Stopping Rule Based on Suicidal Attempts

Occurrence of more than 2 new cases with suicide attempt after 21 March 2016 in a treatment arm relative to the number of events in patients receiving placebo will trigger discontinuation of the arm and all higher dose arms.

2. Stopping Rule Based on Suicidal Ideation

Occurrence of more than 3 new cases in patients with an adverse event of suicidal ideation or significant suicidal ideation (see definition below) after 21 March 2016 in a treatment arm vs placebo will trigger discontinuation of the arm.

Definition of suicidal ideation case: A suicidal ideation case is defined as grades 4 and 5 of the C-SSRS reported during a site visit, or during safety telephone calls (TCs), or as a reported adverse event or serious adverse event. C-SSRS scores below 4 (e.g., 1, 2 or 3) will not count towards the proposed stopping rule.

3.6.3. Temporary Study Drug Discontinuation

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

The subject 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 electronic Case Report Form (eCRF) and the local clinical management (LCM) should be notified.

Patients who are off drug for less than 5 days can resume IP at the same dose they were taking prior to the drug discontinuation. No titration will be required for these patients.

Patients who are off drug for 5 days or more will be required to titrate again. Patients requiring titration will either repeat the week 3 and 4 titration or they will repeat the week 2, 3, and 4 from the beginning of the study (see Table 1). Sites should discuss the patient status with the Medical Monitor prior to dispensing a titration kit. The investigator and Medical Monitor will decide which titration kits the patient should be dispensed based off the reason for discontinuation of study drug, the patient's medical history, and the patient's tolerability during the initial study drug titration. The IVRS will be updated to dispense the titration kit when requested by the site.

If a patient is off drug for more than 14 days, he/she will not restart study drug treatment. He/she will be asked to continue in the study and follow the visit schedule as outlined in the protocol.

If a patient requires more than 1 titration between week 5 and 52 of the study, he/she will not restart study drug treatment. He/she will be asked to continue in the study and follow the visit schedule as outlined in the protocol.

3.7. Study Drug Supply and Accountability

3.7.1. Study Drug Storage and Security

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

Study drug supplies will be stored securely 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.

3.7.2. Study Drug Distribution and Accountability

Distribution of study drugs will be performed under the sponsor's responsibility.

If the study drug supplies appear to be damaged/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. The Site Investigator/site coordinator is responsible for performing study drug accountability at the site. The Monitor is responsible for the accountability of the returned study drugs.

3.8. Maintenance of Randomization and Blinding

Once a patient meets all inclusion and none of the exclusion criteria and has provided an informed consent at the screening visit, he/she will be assigned a randomization number using an IRT.

Unblinded PK and ECG data may be assessed during the study. The individuals responsible for sample bioanalysis and PK analysis and other responsible staff members supporting the unblinded data review by the DSMB will know who received study drug and who received placebo during the study. The unblinded person responsible for PK analysis will provide concentration data the DSMB in a manner that will not identify individual patients (ie, mean values only or a dummy patient identifier will be linked to an individual patient's concentration data).

The DSMB can request unblinding if deemed necessary for appropriate safety evaluation.

For information about personnel who may be aware of treatment assignments and specification of maintaining the blind procedures after the analysis of the first 26-week study period, see Section 3.3. These individuals will not be involved in conduct of any study procedures or assessment of any AEs.

For an SAE considered related (ie, reasonable possibility; see Section 7.1.4) to the study drug, the sponsor's Pharmacovigilance Department may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, the investigator will remain blinded to treatment.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. Individual treatment codes, indicating the treatment randomization for each randomized patients, will be available to the investigator(s) or pharmacists at the study center via the IRT, both via telephone or internet.

Breaking of the treatment code can be performed by the site without prior approval by the sponsor. If time allows, investigators should consult with the Medical Monitor prior to unblinding a patient. If the code was broken by the investigator, the patient should be discontinued from the study.

If the treatment code is broken, the investigator should document and notify the sponsor immediately.

The circumstances leading to the breaking of the code should be fully documented, in the investigator's study files and in the patient's source documentation. Treatment assignment should remain confidential and should not be recorded in any study documents or source document.

For a serious and unexpected AE considered related to the study drug or study procedure, the sponsor's Global Patient Safety & Pharmacovigilance Department may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, personnel involved in the conduct, analysis, and reporting of the data will remain blinded to treatment.

3.9. 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 CRF. Data may not be recorded directly onto the CRF and considered as source data unless the investigational center obtains written documentation from the sponsor, before the beginning of the study, indicating which data are permitted to be recorded directly onto the CRF.

If data are processed from other institutions (eg, clinical laboratory, ECG central vendor, bioanalytical laboratory, genotyping laboratory etc), 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).

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

3.10. Time Schedule

The study is expected to start in Q1 2014 (first patient enrolled); Q1 2016 (last patient last visit for the first 26-week study period), and to be completed in Q3 2016 (last patient last visit for the second study period).

Approximately 400 patients from approximately 50 investigational centers in multiple countries are planned to be enrolled in the study.

3.11. Study Procedures

Study procedures and assessments with their timing are summarized in Table 2 .

Table 2: Study Procedures and Assessments

TV7820-CNS-20002: Procedures and Assessments	Screening	Titration Period				Full Dose Treatment Period														Follow Up
	First 26-Week Study Period															Second 26-week Study Period				
Visit	**V0[a]**	**V1**	**TC**	**V2**	**TC**	**V3**	**TC**	**V4[a]**	**V5[a]**	**V6[a]**	**V7[a]**	**V8[a]**	**V9[a]**	**TC**	**V10[a]**	**TC**	**TC**	**TC**	**V11[a]**	**V12[a]**
Day	**Maximum 12 weeks**	**0**	**6±3**	**14±3**	**20±3**	**28±4**	**35±3**	**42±5**	**56±5**	**84±7**	**112±7**	**140±7**	**182±7**	**224 ±10**	**273 ±7**	**280-308 ±10**	**315 ±10**	**322-357 ±10**	**364±7**	**378±7**
Procedures and assessments	**Screening**	**BL**	**week 1**	**week 2**	**week 3**	**week 4**	**week 5**	**week 6**	**week 8**	**week 12**	**week 16**	**week 20**	**week 26**	**week 32**	**week 39**	**week 40-44**	**week 45**	**week 46-51**	**week 52**	**week 54**
On-site visit	X	X		X		X		X	X	X	X	X	X		X				X	X
Telephone call			X		X		X							X		X	X	X		
Informed consent	X																			
Demography	X																			
Medical and psychiatric history	X																			
Prior medication history	X																			
Inclusion and exclusion criteria[b]	X	X																		
Randomization		X																		
Clinical laboratory tests (hematology and biochemistry)	X	X		X[c]		X		X	X	X	X	X	X		X				X	X
Urinalysis	X	X				X		X	X	X	X	X	X		X				X	X
Pregnancy test (women of childbearing potential)[d]	X	X				X			X	X	X	X	X		X				X	X
Full physical and neurological examination, including weight (height at screening only)	X	X				X				X			X		X				X	X
ECG	X[e]	X[f]		X[g]		X[f]		X[f]	X[h]	X[f]	X[f]	X[f]	X		X				X[i]	X[j]
Vital signs measurement	X	X		X		X		X	X	X	X	X	X		X				X	X
C-SSRS (Baseline version)	X																			
C-SSRS (Since Last Visit version)		X				X		X	X	X	X	X	X		X	X	X	X	X	
Blood sample for genetic analyses[k]	X																			
UHDRS-TMS	X	X[l]				X[l]			X[l]	X[l]	X[l]	X[l]	X[l]						X[l]	X
mPPT		X[l]				X[l]			X[l]	X[l]	X[l]	X[l]	X[l]						X[l]	
UHDRS-FA		X				X				X		X	X						X	
UHDRS-TFC		X				X				X		X	X						X	
UHDRS-IS	X	X				X				X		X	X						X	
PBA-s		X				X				X			X		X				X	

TV7820-CNS-20002: Procedures and Assessments	Screening	Titration Period				Full Dose Treatment Period														Follow Up
	First 26-Week Study Period															Second 26-week Study Period				
Visit	**V0[a]**	**V1**	**TC**	**V2**	**TC**	**V3**	**TC**	**V4[a]**	**V5[a]**	**V6[a]**	**V7[a]**	**V8[a]**	**V9[a]**	**TC**	**V10[a]**	**TC**	**TC**	**TC**	**V11[a]**	**V12[a]**
Day	**Maximum 12 weeks**	**0**	**6±3**	**14±3**	**20±3**	**28±4**	**35±3**	**42±5**	**56±5**	**84±7**	**112±7**	**140±7**	**182±7**	**224 ±10**	**273 ±7**	**280-308 ±10**	**315 ±10**	**322-357 ±10**	**364±7**	**378±7**
Procedures and assessments	**Screening**	**BL**	**week 1**	**week 2**	**week 3**	**week 4**	**week 5**	**week 6**	**week 8**	**week 12**	**week 16**	**week 20**	**week 26**	**week 32**	**week 39**	**week 40-44**	**week 45**	**week 46-51**	**week 52**	**week 54**
Abbreviated PBA-s																X[m]	X[m]	X[m]		
CIBIS		X																		
CIBIC-Plus						X				X			X						X	
PDS		X				X				X			X						X	
CGI-S		X																		
CGI-C						X				X			X						X	
HD-QoL		X											X						X	
EQ5D-5L		X											X						X	
Walk-12		X				X				X			X						X	
Q-Motor assessments[n]	X	X				X				X			X						X	X
TUG Test		X				X				X			X						X	
Cognitive assessment battery[o]	X	X								X			X						X	
Blood samples for drug concentration		X[f]		X[p]		X[q]		X[q]		X[p]	X[q]	X[p]	X						X[r] (trough)	X[s]
Adverse event inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Benzodiazepines and antidepressants inquiry[t]															X	X	X	X	X	
Alcohol/Illicit drug use inquiry															X	X	X	X	X	
Review of tolerability to study drug prior to dose escalation (if applicable)			X	X	X															
Dispense/collect study drug		X		X		X			X	X	X	X	X		X				X[u]	
Review study compliance & adherence		X		X		X		X	X	X	X	X	X		X	X[v]	X[v]	X[v]	X	
Study drug administration[w x]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	

[a] The procedures and assessments for these visits (V0 and V4-12) may be performed over several days, as long as they are completed within the defined visit window.

[b] Inclusion/exclusion criteria should be met at screening and reviewed on Day 0 before the patient is randomized.

[c] Electrolytes only.

[d] Serum pregnancy test at screening (with urine test if required for confirmation); urine pregnancy test at subsequent time points. An indeterminate reading for the serum pregnancy test should be checked twice (urine test) and the patient referred to a gynecologist if required.

[e] At screening, a single ECG will be performed. If there is evidence of a prolonged QTcF interval at screening (defined as a QTcF interval of >450 msec) then the ECG will be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study.

[f] At the Baseline visit, the predose QTcF will be determined by the average of 3 ECGs (within 10 to 20 minutes of one another), each in triplicate (in total 9 recordings). A postdose ECG will be performed in triplicate 1 to 2 hours after first dosing. PK samples will be collected prior to and 1 to 2 hours after first dose administration at the site. When concomitant to ECG, PK samples will be collected after the ECG recording.

[g] One ECG performed in triplicate prior and 1 to 2 hours post afternoon dose.

[h] ECG is optional on Week 8, unless required by local regulations. It is to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.

[i] On Week 52, a triplicate ECG and PK sample will be collected before the last study (morning) dose.

[j] ECG is optional at the follow up visit, but should be performed for all patients with a previously observed cardiac concern and/or QTc change from baseline.

[k] Including CAG analysis, cytochrome P450 2D6 status, genetic long QT syndrome (assessed only in patients experiencing QT prolongation following study drug administration leading to study discontinuation), or any other genetic analyses related to pridopidine response or Huntington's disease.

[l] Evaluated in priority.

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

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

[o] Includes SDMT, Emotion recognition, Trail Making Test A+B, HVLT-R; Paced Tapping Test and OTS.

[p] On Weeks 2, 12 and 20, PK samples will be collected 1 to 2 hours post afternoon dose. When concomitant to ECG, PK samples will be collected after the ECG recording.

[q] On Weeks 4, 6 and 16, PK samples will be collected prior and 1 to 2 hours post afternoon dose. When concomitant to ECG, PK samples will be collected after the ECG recording.

[r] On the last study day (week 52), the study drug administration will take place on site, after the pre-dose PK sample is obtained.

[s] At the follow up visit, 1 PK sample will be collected. In case of SAE, an additional PK sampling should be aimed to be collected at the closest time to SAE. When concomitant to ECG, PK samples will be collected after the ECG recording.

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

[u] Collection only.

[v] Study adherence is reviewed during the TCs.

[w] Every patient will receive 3 capsules twice daily (bid), ie, 3 capsules in the morning and 3 capsules in the afternoon (7 to 10 hours after the morning dose), during the whole study period. Study drug will not be administered at Early Termination visit. At on-site visits, the afternoon dose will be taken at the site.

[x] Patients, who for safety or tolerability reasons have to stop study drug medication, will be asked to continue in the study and follow the visit schedule as outlined without taking study drug.

V = Visit (on-site); TC = telephone call; BL = Baseline; W = Week; ET = early termination; FU = follow-up; ECG = electrocardiogram; C-SSRS = Columbia-Suicide Severity Rating Scale; UHDRS = Unified Huntington's Disease Rating Scale; CIBIS = Clinician's Interview-based Impression of Severity; CIBIC-Plus = Clinician's Interview-based Impression of Change plus Caregiver Input; CGI-S = Clinical Global Impression of Severity; CGI-C = Clinical Global Impression of Change; TUG = Timed Up and Go; PDS = Physical Disability Scale; mPPT = modified Physical Performance Test; HD-QoL = Huntington's disease Quality of Life; HVLT-R = Hopkins Verbal Learning Test, revised; CAG = cytosine-adenine-guanine; TMS = Total Motor Score; IS = Independence Scale; OTS = One

Touch Stockings of Cambridge, abbreviated 10-trial version; PBA-s = Problem Behaviors Assessment-Short form; SDMT = Symbol Digit Modalities Test; TFC = Total Functional Capacity; FA = Functional Assessment; Q-Motor = Quantitative motor; PK = Pharmacokinetic(s); SAE = serious adverse event

3.11.1. Procedures for Screening and Enrollment (Visit 0)

A signed and dated informed consent form, including consent to genotyping (CAG analysis, CYP2D6 metabolizer status, genetic long QT syndrome for determination in patients who had QT prolongation following study drug administration, or any other genetic analyses related to pridopidine response or HD), will be obtained before screening procedures commence. Patients with a legal guardian should be consented according to local requirements.

Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations.

Testing of the CAG trinucleotide repeat length in the huntingtin gene and CYP2D6 genotype will be done for all patients who have given written informed consent. Patients who refuse to consent to the use of their CAG test results will not be included in the study. The results of genotyping will not be revealed to either the patient or other parties without the patient's consent.

After informed consent is obtained, patients who are screened will be assigned an 8-digit permanent identification number such that all patients from each investigational center are given consecutive identification numbers in successive order of inclusion. The first 2 digits of the screening number will be the number assigned to the country where the investigational center is located, the next 3 digits will be the designated investigator center number, and the last 3 digits will be assigned at the investigator center (e.g., if the number assigned to the country is 01, the 3rd patient screened at center 5 would be given the number of 01005003).

A patient who is screened but not randomized, e.g., because enrollment did not occur within the specified time, or other logistical or operational issues occurred, may be considered for screening again.

Re-screening will be permitted on a case by case basis. A new informed consent form should be signed in any case of re-screening, and screening procedures should be repeated. A new Subject Number will be assigned to the subject.

The screening visit (Visit 0) will take place not more than 12 weeks before the baseline visit. However, the investigator should aim to perform the baseline visit as soon as possible after the screening visit. The following procedures will be performed at the screening visit:

- obtain written informed consent before any other study-related procedures are performed
- review inclusion/exclusion criteria
- review medical and psychiatric history
- review medication history
- collect demographic information
- clinical laboratory tests (hematology, biochemistry, urinalysis)
- serum pregnancy test for women of child-bearing potential only (with urine test if required for confirmation)
- vital signs measurements

- 12-lead ECG (single); if there is evidence of a prolonged QTcF interval at screening (defined as a QTcF interval of >450 msec) then the ECG will be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study. ECGs will be collected after at least 5 minutes of supine rest.
- full physical and neurological examination (including height and weight)
- C-SSRS (baseline version)
- UHDRS-TMS and UHDRS-IS
- Q-Motor assessments
- CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS)
- collect blood sample for CAG analysis, CYP2D6 metabolizer status, genetic long QT syndrome (for determination in patients who had QT prolongation following study drug administration), or any other potential genetic analyses related to pridopidine response or HD
- inform patients of study restrictions and compliance requirements

The procedures and assessments for the screening visit may be performed over several days, as long as they are completed within the defined time period.

3.11.2. Procedures for Baseline Visit (Visit 1)

Patients who meet the inclusion/exclusion criteria at screening (Visit 0) will continue to Visit 1, when baseline evaluations will be conducted. Baseline visit can occur in the morning or afternoon.

The following procedures will be performed at Baseline before the first dose on site:

- review inclusion/exclusion criteria
- vital signs measurements
- inquire about AEs
- inquire about concomitant medication
- full physical and neurological examination (including weight)
- urine pregnancy test for women of child-bearing potential only
- 12-lead ECG in triplicate (performed after at least 5 minutes of supine rest); the predose QTcF will be determined by the average of 3 ECGs (within 10 to 20 minutes of each other), each in triplicate (in total 9 readings).
- C-SSRS (since last visit version)
- UHDRS-TMS
- mPPT

- UHDRS-FA, UHDRS-TFC, UHDRS-IS
- CGI-S
- CIBIS, completed by an independent rater
- PDS
- TUG Test
- HD-QoL
- EQ5D-5L
- Walk-12
- Q-Motor assessments
- CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS)
- PBA-s
- obtain a 4-mL blood sample for plasma drug assay
- dispense study drug (first dose taken at the site)
- review study compliance

UHDRS-TMS and mPPT should be evaluated prior to the other scales.

A patient who does not meet study entry criteria on the basis of results of baseline assessments and is not enrolled in the study will not be considered for screening again. Patients who were considered acceptable for the study on the basis of their UHDRS-TMS and UHDRS-IS results at screening will not be excluded from the study based on their UHDRS-TMS and UHDRS-IS results at baseline.

Patients who continue to meet the inclusion/exclusion criteria will be assigned a permanent unique randomization number and a treatment number (kit, bottle) using an IRT. These 2 newly assigned numbers will be entered into the CRF, and study drug will be dispensed.

The following procedures will be performed at the Baseline visit following administration of the first dose on site:

- 12-lead ECG in triplicate (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest)
- clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)
- obtain a 4-mL blood sample for plasma drug assay (1 to 2 hours after dose administration); samples will be collected as close as possible to, but after the ECG recording.

3.11.3. Procedures During Study Drug Treatment

3.11.3.1. Titration Period (Weeks 0 to 4)

3.11.3.1.1. Telephone Contact at Weeks 1 and 3

Patients will be contacted by telephone on Week 1 (± 3 days) and Week 3 (± 3 days) to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage, and to allow the weekly dose increase during the titration period (see Section 3.4.1.1) that will take place on the following day (if applicable).

3.11.3.1.2. Week 2 (Visit 2)

The following procedures/assessments will be performed at Week 2 (±3 days) (Visit 2); tolerability to the study drug will be evaluated through assessment of AEs and concomitant medication usage, to allow the weekly dose increase during the titration period:

Before Afternoon Dosing:

- AE inquiry
- concomitant medication review
- triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest)
- vital signs measurements
- collect/dispense study drug
- study compliance review

Following Afternoon Dosing:

- triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest)
- clinical laboratory tests (electrolytes only)
- obtain a 4-mL blood sample for plasma drug assay 1 to 2 hours after dose administration; PK samples will be collected as close as possible to, but after the ECG recording.

3.11.3.2. Full Dose Period (Weeks 4 to 52)

3.11.3.2.1. Weeks 4, 6, 8, 12, 16, and 20– (Visits 3 to 8)

The following procedures/assessments will be performed in conjunction with afternoon dosing on Week 4 (±4 days), Week 6 (±5 days), Week 8 (±5 days), Week 12 (±7 days), Week 16 (±7 days), and Week 20 (±7 days):

Before Afternoon Dosing:

- AE inquiry
- concomitant medication review

- Weeks 4, 8, 12, 16 and 20only: urine pregnancy test for women of child-bearing potential only
- Weeks 4 and 12only: full physical and neurological examination (including weight)
- triplicate 12-lead ECG (performed after at least 5 minutes of supine rest) (Note: ECG is optional on Week 8, unless required by local regulations. It is to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation)
- vital signs measurements
- C-SSRS (since last visit version)
- Weeks 4, 6, and 16 only: obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording)
- Weeks 4, 8, 12, 16 and 20 only: collect/dispense study drug
- study compliance review

Following Afternoon Dosing:

- triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest) (Note: ECG is optional on Week 8, unless required by local regulations. It is to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation)
- clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)
- Weeks 4, 6, 12, 16 and 20 only: obtain a 4-mL blood sample for plasma drug assay 1 to 2 hours after dose administration; PK samples will be collected as close as possible to, but after the ECG recording.

In addition, on Weeks 4, 8, 12, 16 and 20, the following efficacy procedures/assessments will be performed, in priority, either before or after the afternoon dose (with the time of the evaluation recorded):

- UHDRS-TMS
- mPPT

In addition to the UHDRS-TMS and mPPT, the following efficacy procedures/assessments will be performed on Weeks 4 and 12 only, either before or after the afternoon dose (with the time of the evaluation recorded), with UHDRS-TMS and mPPT evaluated in priority, as previously stated:

- CIBIC-Plus
- PDS
- UHDRS-FA, UHDRS-TFC, UHDRS-IS – **will also be performed on Week 20**
- CGI-C

- TUG Test
- Walk-12
- Q-Motor assessments
- CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) - **on Week 12 only**
- PBA-s

The procedures and assessments for Visits 4-8 may be performed over several days, as long as they are completed within the defined visit window (±5 days for Visits 4 and 5; ±7 days for Visits 6-8).

3.11.3.2.2. Telephone Contact at Week 5

Patients will be contacted by telephone on Week 5 (±3 days) to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage.

3.11.3.2.3. Week 26 (Visit 9)

The following procedures/assessments will be performed on Week 26 (±7 days) (Visit 9):

- AE inquiry
- concomitant medication review
- clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)
- urine pregnancy test for women of child-bearing potential only
- full physical and neurological examination (including weight)
- triplicate 12-lead ECG (performed after at least 5 minutes of supine rest)
- vital signs measurements
- C-SSRS (since last visit version)
- obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording) (prior to afternoon dose)
- study compliance review
- collect/dispense study drug

The following efficacy procedures/assessments will be performed on Week 26 (Visit 9), before or after dosing (with the time of the evaluation recorded), with UHDRS-TMS and mPPT evaluated in priority:

- UHDRS-TMS
- mPPT
- CIBIC-Plus
- PDS

- UHDRS-FA, UHDRS-TFC, UHDRS-IS
- CGI-C
- TUG Test
- HD-QoL
- EQ5D-5L
- Walk-12
- Q-Motor assessments
- CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS)
- PBA-s

The procedures and assessments for this visit may be performed over several days, as long as they are completed within the defined visit window (±7 days).

3.11.3.2.4. Week 39 (Visit 10)

The following procedures/assessments will be performed on Week 39 (±7 days) (Visit 10):

- AE inquiry
- concomitant medication review (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)
- urine pregnancy test for women of child-bearing potential only
- full physical and neurological examination (including weight)
- triplicate 12-lead ECG (performed after at least 5 minutes of supine rest)
- vital signs measurements
- C-SSRS (since last visit version)
- collect/dispense study drug
- study compliance review
- PBA-s

The procedures and assessments for this visit may be performed over several days, as long as they are completed within the defined visit window (±7 days).

3.11.3.2.5. Telephone Contact at Weeks 32, 40-44, 45 and 46-51

Patients will be contacted by telephone on Week 32 (±10 days) to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage. Between Weeks

40-44, on Week 45 (±10 days) and between Weeks 46-51 to evaluate safety and tolerability to the study drug through assessment of 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

3.11.3.2.6. Week 52 (Visit 11) or Early Termination

The following procedures/assessments will be performed on Week 52 (±7 days) (Visit 11) or at the Early Termination visit:

Before Dosing:

- AE inquiry
- concomitant medication review (including inquiry about changes in use of benzodiazepines and antidepressants)
- inquiry about changes in use of alcohol and illicit drugs
- clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)
- urine pregnancy test for women of child-bearing potential only
- full physical and neurological examination (including weight)
- triplicate 12-lead ECG (performed after at least 5 minutes of supine rest)
- vital signs measurements
- C-SSRS (since last visit version)
- obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording)
- study compliance review
- morning study drug dose administration on-site (Note: study drug will not be administered if Early Termination visit)

After Dosing:

- collect remaining study drug

The following efficacy procedures/assessments will be performed on Week 52 (Visit11), before or after dosing (with the time of the evaluation recorded), with UHDRS-TMS and mPPT evaluated in priority:

- UHDRS-TMS
- mPPT
- CIBIC-Plus
- PDS
- UHDRS-FA, UHDRS-TFC, UHDRS-IS
- CGI-C
- TUG Test
- HD-QoL
- EQ5D-5L
- Walk-12
- Q-Motor assessments
- CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS)
- PBA-s

Note: there will be no afternoon dose on Week 52/Early Termination.

The procedures and assessments for this visit may be performed over several days, as long as they are completed within the defined visit window (±7 days).

3.11.4. Follow-up Visit (Visit 12)

There will be a follow-up visit 2 weeks after the last dose of study drug (Week 54, ±7 days). The following procedures/assessments will be performed:

- AE inquiry
- concomitant medication review
- clinical laboratory tests (hematology, biochemistry, urinalysis)
- urine pregnancy test for women of child-bearing potential only
- full physical and neurological examination (including weight)
- optional triplicate 12-lead ECG (performed after at least 5 minutes of supine rest), should be performed for all patients with a previously observed cardiac concern and/or a clinically significant QTc change from baseline
- vital signs measurements
- UHDRS-TMS
- Q-Motor assessments
- obtain a 4-mL blood sample for plasma drug assay after ECG collection

The procedures and assessments for this visit may be performed over several days, as long as they are completed within the defined visit window (±7 days).

3.11.5. Procedures After Study Drug Treatment/Discontinuation

Patients who participate in the study in compliance with the protocol for at least 26 weeks of double-blind treatment will be considered to have completed the study.

For patients who complete the study or withdraw prematurely, final evaluations will be performed at an end-of treatment visit (Week 52, Visit 11) or on the last day the patient receives the study drug, or as soon as possible thereafter. For patients who do not have a final visit within 7 days after their last dose of study drug, efficacy evaluations (see Section 6) should not be performed. Procedures for patients who withdraw prematurely from the study are described in Section 4.3.

Patients, who for safety or tolerability reasons have to stop study drug medication, will be asked to continue in the study and follow the visit schedule as outlined in the protocol, without taking study drug. Data from these visits will be collected, and included in the statistical analysis as described in Section 9.

Patients with ongoing AEs or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.4, respectively.

3.11.6. 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, AEs, C-SSRS ("Since Last Visit" version) and PBA-s (if visit scheduled to assess psychiatric adverse events), concomitant medications and treatments, and results from procedures or tests).

In case of an SAE, an additional PK sample should be collected at the closest time to SAE.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Inclusion/exclusion criteria should be documented throughout the screening process and the investigator should document review of inclusion/exclusion criteria prior to randomization. The patients should continue to meet inclusion/exclusion criteria at the Baseline visit. If a patient no longer meets inclusion/exclusion criteria at Baseline then the patient will not be eligible for the study. Baseline laboratory values will not be known until after randomization; if there is a finding in the Baseline laboratory values which would cause the patient to be ineligible for the study, the site should review this with the Medical Monitor.

4.1. Patient Inclusion Criteria

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

a. Diagnosis of HD based on clinical features and the presence of ≥36 cytosine-adenosine-guanine (CAG) repeats in the huntingtin gene.
b. Male or female age ≥21 years, with an onset of HD after 18 years' old.
c. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study, including the follow-up period. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, or double barrier contraception, ie, 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.
d. Body weight ≥50 kg.
e. A sum of ≥25 points on the UHDRS-TMS at the screening visit.
f. UHDRS-IS score equal to or less than 90% at the screening visit.
g. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. Patients with a legal guardian should be consented according to local requirements.
h. Willing to provide a blood sample for genetic analyses (including CAG analysis, CYP2D6 status, genetic long QT syndrome in patients who had QT prolongation following study drug administration or any other genetic analyses related to pridopidine response or HD) at the screening visit.
i. Willing and able to take oral medication and able to comply with the study specific procedures.
j. Ambulatory, being able to travel to the study centre, and judged by the investigator as likely to be able to continue to travel for the duration of the study.
k. Availability and willingness of a caregiver, informant or family member to accompany the patient to the clinic at study visits assessing CIBIC-Plus, HD-QoL, and CGI-S/CGI-C. For the purposes of this study, a caregiver is recommended to be someone who attends to the patient at least 2 to 3 times per week for at least 3 hours per occasion, and the suitability of the caregiver should be judged by the investigator.

l. For patients taking allowed antipsychotic, antidepressant or other psychotropic 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.

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. If there is evidence of a prolonged QTcF interval at screening from the initial (single) measurement, then the ECG will be repeated twice, and the mean of the 3 screening 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 a known history of Long QT Syndrome or a first degree relative with this condition.
d. Patients with a history of epilepsy or of seizures within the last 5 years.
e. Have other serious medical illnesses (including but not limited to uncontrolled hypertension, respiratory disease including severe form of asthma, hepatic disease, renal disease, AIDS, unstable psychiatric or other neurologic disorder) which in the opinion of the investigator may put the patient at risk when participating in the study or may influence the results of the study or affect the patient's ability to take part in the study.
f. 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.
g. Patients receiving medications (within the last 6 weeks prior to baseline) 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.
h. Patients receiving medications (within the last 6 weeks prior to baseline) that are metabolized by CYP2D6 and have the potential of reducing seizure threshold (see Section 5.3.2.4).
i. [**Revision 1**] 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.

j. 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.
k. Alcohol and/or drug abuse within the 6 months prior to screening, as defined by Diagnostic and Statistical Manual – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse.
l. Patients with active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the C-SSRS, 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 within 1 year of screening, or patients who, in the opinion of the investigator, present a serious risk of suicide.
m. Patients with known intracranial neoplasms, vascular malformations, history of cerebrovascular accident, or intracranial hemorrhage.
n. **[Revision 1]** Females who are pregnant or breastfeeding.
o. Known allergy to any ingredients of the study medication or placebo (pridopidine, silicified microcrystalline cellulose, magnesium stearate).
p. Previous exposure with pridopidine.
q. Treatment with tetrabenazine within 6 weeks of study baseline.
r. Treatment with any investigational product within 6 weeks of screening or patients planning to participate in another clinical study assessing any investigational product during the study.

4.3. 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 drug at any time. Each investigator also has the right to withdraw a patient from the study drug in the event of intercurrent illness, AEs, pregnancy (see Section 7.3), 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 drug as described in Sections 3.6, 3.11.5, 5.4, 7.1.1 7.1.7, 7.4, and 7.6 .

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 drug 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 AE or a 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(s) must be recorded on the source documentation and transcribed onto the CRF.

Safety evaluations will be performed for all recorded data.

Efficacy evaluations will be performed as described in Section 9.

A patient who is enrolled but does not complete the study will not be replaced.

5. TREATMENT OF PATIENTS

5.1. Study Drugs Administered

Following the baseline visit, patients will be randomly assigned to 1 of 4 pridopidine treatment arms or to the placebo treatment arm. Six capsules will be administered orally (with water) each day; 3 capsules in the morning and 3 capsules in the afternoon (7 to 10 hours after the morning dose). Capsules can be taken with or without food. Following titration, patients will remain at their randomized dosage for the duration of the study (see Sections 3.4.1 and 3.4.2).

Each medication pack will contain 3 distinct labeled bottles containing the study drug and will be provided for patients to take at home, or at the study center when dosing coincides with a study visit (see Section 3.4). Study drug exposure will be measured and compliance to study drug administration will be monitored.

5.2. Restrictions

There are no 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 6 weeks prior to screening and up to the end of the study period, including follow-up, 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 (ie, 1-week washout), to allow enzyme recovery.

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 Adverse Event 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 4.3). If the patient refuses to be seen for further visits, the assessments for Week 52 /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 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.

Allowed antipsychotic medications are olanzapine, quetiapine, thiothixene, acetophenazine, triflupromazine, 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), butriptyline, mianserin, moclobemide, tranylcypromine, buspiron, bupropion, reboxetine, and dibenzepin. Fluvoxamine, trimipramine, and mirtazapine are 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

5.3.2.5. 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 prescribed dosage, timing and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the CRFs.

Each 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. Total Blood Volume

The total volume of blood estimated to be collected from each patient is detailed in Table 3.

Table 3: Total Blood Volume Collected from Each Patient

Type of Assessment	Number of Samples Collected	Volume per Sample	Total Volume for Assessment
Pharmacokinetic	14	4 mL	56 mL
Serum Chemistry	13	10.5 mL[a]	129.5 mL
Hematology	12	***2*** mL	24 mL
Pharmacogenetic Analyses	1	12 mL	12 mL
Total			221.5 mL

[a] The samples are 10.5 mL at all visits, except visit 2 where CK-MB and prolactin are not collected, and thus the volume at this visit is only 3.5 mL.

6. ASSESSMENT OF EFFICACY

Primary and secondary efficacy assessments (UHDRS-TMS and mPPT) will be performed on Visit 1(baseline), Week 4 (Visit 3), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 26 (Visit 9), and Week 52(Visit 11).

Exploratory efficacy assessments will be performed only at Visit 1(baseline), Week 4 (Visit 3), Week 12 (Visit 6), Week 26 (Visit 9), and Week 52(Visit 11); apart from the CAB, which will be performed only at Visit 1 (baseline), Week 12 (Visit 6), Week 26(Visit 9), and Week 52(Visit 11); and UHDRS FA, UHDRS TFC, and UHDRS IS which will also be performed on Week 20 (Visit 8).

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.

UHDRS-TMS and Q-Motor assessments will also be performed at the follow-up visit (Visit 12).

6.1. Primary Efficacy Variable and Endpoint

The primary efficacy variable and endpoint is the change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domain ratings) at Week 26.

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).

6.2. Secondary Efficacy Variable and Endpoint

6.2.1. 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.

6.3. Other Efficacy Variables and Endpoints

Other efficacy variables and endpoints are described in the following sections.

6.3.1. Clinician Interview Based Impression of Change plus Caregiver Input

Global change in HD at Week 26 will be measured using the CIBIS scale at baseline and the CIBIC-Plus scale at subsequent time points. The CIBIC-Plus (version ADCS-CGIC) was

developed, validated, and is commonly used in studies of anti-dementia drugs in Alzheimer's disease (Joffres et al 2000).

An independent rater whose only role in the study is to conduct these global assessments will evaluate the patient's overall disease severity prior to the initiation of study drug. This assessment, known as the CIBIS, rates the patient on a 7-point Likert scale from extremely severe HD to no symptoms of HD.

At each subsequent visit in which the evaluation is performed, the CIBIC-Plus will be administered by the same independent rater, but without knowledge of other endpoint assessments or the AEs experienced by the patient during the study (so as not to confound the rating of CIBIC-Plus as an efficacy measure or to unblind the study). The independent rater is not permitted to discuss the medical condition of the patient with the treating physician. Instead, the independent rater exclusively will consider observations of the patient's cognitive, functional, and behavioral performance obtained through interviewing the patient and the caregiver. The rater then compares those findings to the baseline assessment. The overall impression of change from baseline (CIBIC-Plus) is rated on a 7-point scale: 1 = marked improvement; 2 = moderate improvement; 3 = minimal improvement; 4 = no change; 5 = minimal worsening; 6 = moderate worsening; 7 = marked worsening; all assessments were relative to baseline. A higher score indicates a worsening of global function.

In HD, the inclusion of caregiver input is particularly critical for a global assessment as previous studies have demonstrated that patients have limited awareness and recognition of their deficits. For the purposes of this study, a caregiver is recommended to be someone who attends to the patient at least 2 to 3 times per week for at least 3 hours per occasion, and the suitability of the caregiver should be judged by the investigator. Where possible, the same person should act as a patient's caregiver throughout the study. If this is not possible, a patient should have no more than 2 caregivers 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.

6.3.2. Physical Disability Scale

The PDS will be used during the study as a measure of disability. Patients are scored on a scale from 10 ("Fixed posture requiring total care - gastrotomy, catheterization") to 100 ("Normal; no disease evident") (Myers et al 1991). Scores must end in 0 (e.g., 10%, 20% etc).

6.3.3. UHDRS Functional Assessments

The FA scale of the UHDRS assesses functionality in 25 tasks of daily living (eg, "Could patient engage in gainful employment in his/her accustomed work?"). Each question is answered with 'yes' or 'no'.

6.3.4. Clinical Global Impression of Severity and Change

CGI-S will be assessed at baseline (Visit 1) and CGI-C will be used at all subsequent time points to assess changes from baseline.

The CGI-S scale was initially designed to assess treatment response in patients with mental disorders (Guy 1976) but is now used widely in a range of illnesses. Illness severity is rated by qualified site personnel on a 7-point scale (1 = normal, not at all ill to 7 = among the most extremely ill patients). The assessment is based on qualified site personnel judgment, supported by a comprehensive, semi-structured, patient/caregiver interview.

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

6.3.5. 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).

6.3.6. UHDRS Independence Scale

The independence scale of the UHDRS is a rating scale where the patient's degree of independence is given in percentage, from 10% (tube fed, total bed care) to 100% (no special care needed). Scores must end in 0 or 5 (eg, 10%, 15%, 20% etc). Patients with a UHDRS-IS score >90% at the screening visit will not be eligible for the study.

6.3.7. Patient Reported Outcomes

6.3.7.1. Huntington's Disease Quality of Life

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

HD-QoL will be assessed by both caregiver and patient. 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 caregiver/informant form should be omitted.

6.3.7.2. Walk-12

The Multiple Sclerosis Walking Scale (MSWS-12) was originally developed to measure the impact of multiple sclerosis (MS) on walking. However, as other disabling neurological conditions affect a person's ability to walk, it was adapted to become a generic measure of walking and mobility and renamed the Walk-12. It contains 12 items describing the impact of MS on walking which were generated from 30 MS patient interviews, expert opinion, and literature review (Hobart et al 2003).

6.3.7.3. EQ5D-5L

The EQ-5D 3 level version (EQ-5D-3L) was introduced in 1990 (The EuroQol Group , 1990). It essentially consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In developing the 5L, the 5-dimensional structure of the original EQ-5D-3L was retained but the levels on each dimension were expanded to 5-levels based on qualitative and quantitative studies conducted by the EuroQol Group. The labels for each of the dimensions are: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The EQ-VAS is still an integral part of the EQ-5D-5L but has been adapted to make it more user-friendly. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.

The EQ5D could be completed by the patients with caregiver/informant assistance if needed.

6.3.8. Total Motor Score Subscores

6.3.8.1. UHDRS Hand Movement Score

The hand movement score is defined as the sum of UHDRS domains finger taps, pronate-supinate hands and luria (fist-hand-palm test).

6.3.8.2. UHDRS Gait and Balance Score

The gait and balance score is defined as the sum of UHDRS domains gait, tandem walking and retropulsion pull test.

6.3.8.3. UHDRS Modified Motor Scale

The UHDRS-mMS is defined as the sum of following domains from UHDRS-TMS: dysarthria, tongue protrusion, finger taps, pronate-supinate hands, luria, rigidity, bradykinesia, gait, tandem walking, and retropulsion pull test.

6.3.8.4. UHDRS-Chorea

In the UHDRS, maximal chorea is scored from 0 (absent) to 4 (marked/prolonged) on each of the following items: face, mouth, trunk, right upper extremity, left upper extremity, right lower extremity, and left lower extremity. Maximal chorea is the sum of all scores.

6.3.8.5. UHDRS-Dystonia

In the UHDRS, maximal dystonia is scored from 0 (absent) to 4 (marked/prolonged) on each of the following items: trunk, right upper extremity, left upper extremity, right lower extremity, and left lower extremity. Maximal dystonia is the sum of all scores.

6.3.8.6. TMS Proportion of Responders

The percentage of responders, defined as patients with UHDRS-TMS change from baseline ≤0 at Week 26.

6.3.9. Other Motor Assessments

6.3.9.1. Quantitative Motor Assessments

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 precalibrated and temperature controlled 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. Data analysis will be performed blinded and automated as described in the SAP.

6.3.9.1.1. 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.

6.3.9.1.2. 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.

6.3.9.1.3. 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.

6.3.9.1.4. 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.

6.3.9.2. Timed Up and Go Test

The TUG Test is a simple test used to assess a person's mobility and requires both static and dynamic balance. It uses the time that a person takes to rise from a chair, walk 3 meters, turn around, walk back to the chair, and sit down. During the test, the person is expected to wear their regular footwear and use any mobility aids that they would normally require. The TUG Test is used frequently in the elderly population, as it is easy to administer and can generally be completed by most older adults. The test is quick, requires no special equipment or training, and is easily included as part of the routine medical examination (Podsiadlo and Richardson, 1991). The use of the TUG Test in conjunction with UHDRS has been recommended for clinical studies of HD (Rao et al 2009).

6.3.10. Cognitive Assessment Battery

The following sections describe the tests that will be part of the CAB.

The CAB 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.

6.3.10.1. Symbol Digit Modalities Test

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

6.3.10.2. Emotion Recognition

Emotion recognition of facial expressions of emotions is examined using computerized presentations of photographs depicting 6 basic emotions or a neutral expression. Participants are asked to indicate the emotion expressed in each photograph by selecting from the words fear, disgust, happy, sad, surprise, angry, and neutral (10 stimuli per emotion).

6.3.10.3. Trail Making Tests A and B

Visual attention and task switching are assessed using the Trail Making test, which consists of 25 circles on a standard sheet of paper. For Trails A, participants are required to connect, as quickly as possible, circles containing numbers in ascending numerical order. For Trails B, participants are to connect, as quickly as possible, circles containing numbers and letters, alternating between numbers and letters in ascending order (eg, 1, A, 2, B, 3, C, etc.) (Bowie and Harvey, 2006). Trail A is used only as part of the training.

6.3.10.4. Hopkins Verbal Learning Test, revised

The HVLT-R offers a brief assessment of verbal learning and memory (recognition and recall). It is easy to administer and score and is well tolerated even by significantly impaired individuals. Its use has been validated with brain-disordered populations (eg, Alzheimer's disease, HD, amnestic disorders) as a measure of verbal learning and memory. Each form consists of a list of 12 nouns (targets) with 4 words drawn from each of 3 semantic categories. The semantic categories differ across the 6 forms, but the forms are very similar in their psychometric properties. Raw scores will be derived for Learning Trials 1-3 (i.e., Total Recall) and Trial 4 (e.g., Delayed Recall Trial). The HVLT-R has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well established.

6.3.10.5. Paced Tapping test

Psychomotor function is assessed in a Paced Tapping test. Participants tap on left and right mouse buttons, alternating between thumbs, at 3.0 Hz. They first listen to a tone presented at the desired tapping rate, and then begin tapping to the tone. After 11 taps with the tone, the repetition of the tone is discontinued, and participants attempt to continue tapping at the same rate until the end of the trial (31 taps later).

6.3.10.6. One Touch Stockings of Cambridge

OTS is a spatial planning task which gives a measure of frontal lobe function. OTS is a variant of the Stockings of Cambridge task, and places greater demands on working memory as the participant has to visualize the solution. As with Stockings of Cambridge, the participant is shown 2 displays containing 3 colored balls. The displays are presented in such a way that they can easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam. This arrangement makes the 3-dimensional concepts involved apparent to the participant, and fits with the verbal instructions.

There is a row of numbered boxes along the bottom of the screen. The test administrator first demonstrates to the participant how to use the balls in the lower display to copy the pattern in the upper display, and completes 1 demonstration problem, where the solution requires 1 move. The participant must then complete 3 further problems, 1 each of 2 moves, 3 moves, and 4 moves.

Next, the participant is shown further problems, and must work out in their head how many moves the solutions to these problems require, then touch the appropriate box at the bottom of the screen to indicate their response.

6.3.11. 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 judgment.

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.

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

Methods and timing of assessing efficacy data are discussed in Section 3.11. Procedures for recording efficacy data are discussed in Section 13.1, and methods of analyses are discussed in Section 9.6.4.

7. ASSESSMENT OF SAFETY

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

During the study, an independent DSMB will review unblinded accumulating safety data.

The DSMB will meet monthly until 20 patients from each treatment arm (i.e. a total of 100 patients) have completed two weeks of treatment on full dose (6 weeks in the study). In case of significant emerging safety concerns in 1 or more treatment arms, the DSMB will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatment arm(s) with safety concerns.

Thereafter, the DSMB will decide whether there is a need for additional meetings, and, if needed, will determine when these will take place.

The DSMB will be composed of independent physicians with expertise in the relevant therapeutic field (ie, at least a cardiologist and a neurologist) and other relevant experts, such as a statistician and a PK expert. They will have the right to recommend discontinuation of 1 or more treatment arm(s) for safety reasons.

The DSMB can call a meeting at any time based on safety concerns, and that decisions about discontinuing patients, should that happen, will be explained in a report to all sites and patients.

DSMB sessions can be open or closed. During open sessions, representatives of the sponsor and the Steering Committee may be present and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the DSMB and the designated unblinded statistician (if approved to be present).

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.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

An AE 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 AE occurring after the clinical study patient has signed the informed consent form should be recorded and reported as an AE.

An AE can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the 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 AE. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study will not be considered AEs.

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 duration of the clinical study, the patient should be discontinued from treatment with study drug and 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 AE 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 symptoms of the disease under study or other pre-existing conditions. (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and which occurs during the study should be recorded as an AE.)
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of the 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 an 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 AEs, but will be evaluated to monitor data from patients who do not meet screening criteria.
- 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 AE recording, the study period is defined for each patient as that time period from signature of the informed consent form through to the end of the follow-up period.

All AEs 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 Serious Adverse Event 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 AEs once the study has ended. SAEs 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 query the patient for AEs 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 an SAE, on the Serious Adverse Event Form.

The clinical course of each AE will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or 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 onset and end dates, duration (in case of AE duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each AE must be recorded on the source documentation and transcribed onto the CRF.

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

7.1.3. Severity of an Adverse Event

The severity of each AE 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 AE to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events, which, 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 test 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 test drug. it does not reappear or worsen when the 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 test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	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 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 drug, yet drug-relatedness clearly exists. • it follows a known pattern of response to the test drug.

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

An SAE is an AE occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening AE (ie, 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 means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered SAEs.
- 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 1 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 AE that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious AE.

7.1.5.2. Expectedness

An 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 AE. The reference safety information for this study is the Investigator's Brochure.

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

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), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator 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 AEs once the study has ended. SAEs 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 local safety officer (LSO) or other designated personnel (a CRO in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Pharmacovigilance Department.

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

- study number
- investigator and investigational center identification
- patient number
- patient initials
- onset date and description of AE
- investigator's assessment of the relationship of the AE 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
- 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 AE resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

In the US, the investigator must ensure that the IRB is also informed of the event, in accordance with local regulations. In the EU, the sponsor or its designee must ensure that the IEC is also informed of the event, in accordance with local regulations.

Each report of an 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 EU countries, the sponsor's Pharmacovigilance Department will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/XML file to the LSO for local submission to the regulatory authorities and IEC/IRBs and investigators, according to regulations. In non-EU countries, the LSO (USA Pharmacovigilance /Canadian LSO) will be responsible for submission of the MedWatch form 3500/CIOMS form/XML file to the regulatory authorities. In non-EU countries, SAEs should be reported by the sponsor to investigators. Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures.

The blinding will be maintained for the people who are involved directly in the study. Therefore, in case of a suspected unexpected serious adverse reaction (SUSAR), only the LSO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

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 7.3).

7.1.5.3.2. Sponsor Responsibility

If a serious unexpected AE 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.

In addition to notifying the investigators and regulatory authorities, 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 AEs 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 AE may be withdrawn from the study at any time at the discretion of the investigator. If a patient is withdrawn wholly or in part because of an AE, both the AE page and termination page of the CRF will be completed at that time.

In addition, a blood sample will be obtained 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 AEs. Additional reports must be provided when requested.

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

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 are discontinued from treatment may continue their participation in the study and perform the scheduled visits and assessments, while off study drug.

7.1.8. Medical Emergencies

Medical emergencies must be reported to the individual identified in the clinical study personnel contact information section of this protocol.

Equipment, supplies, and properly skilled medical personnel must be accessible for an AE requiring immediate treatment. Any dose of study drug (whether the investigational product, reference therapy, or a placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. When the identification of the study drug must be known, the investigator must follow the procedures outlined in Section 3.8.

7.1.9. Protocol Deviations Because of an Adverse Event

If a patient experiences an AE or medical emergency, departures from the protocol visit and dosing schedule will not necessarily be considered a reason for withdrawal, and will be considered 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 Medical Monitor, will decide whether the patient should continue to participate in the study. Any departures from the protocol because of AEs must be noted on the CRF and in source documents, along with the reason for such departures.

7.2. Tolerability

Tolerability will be evaluated in terms of the number (%) of patients who failed to complete the study and the number (%) of patients who failed to complete the study due to AEs.

7.3. Pregnancy

All pregnancies (pregnancies in women participating in the study and in 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 an SAE (see Section 7.1.5.3).

Any patient becoming pregnant during the study will be withdrawn. All patients (or partners of patients) who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of

age), including spontaneous or voluntary termination, 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 will be reported as an AE 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 an SAE.
- For an elective abortion due to developmental anomalies, report as an SAE.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form.

7.4. Clinical Laboratory Tests

All clinical laboratory test results outside of the reference range will be interpreted by the investigator as belonging to 1 of the following categories:

- abnormal but not a clinically significant worsening
- abnormal and a clinically significant worsening

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 AE, and monitored as described in Section 7.1.2. An AE 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.

Clinical laboratory tests (serum chemistry including electrolytes, hematology and urinalysis) will be performed at screening (Visit 0), baseline (Visit 1), Week 2 (Visit 2; electrolytes only), Week 4 (Visit 3), Week 6 (Visit 4), Week 8(Visit 5), Week 12(Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 26(Visit 9), Week 39 (Visit 10) and Week 52 (Visit 11) or Early Termination, and at the follow-up visit. Clinical laboratory tests will be performed using a central laboratory, as identified in the Laboratory Procedures Manual provided in the study file documents.

Specific laboratory tests to be performed are listed below.

7.4.1. Serum Chemistry

The following serum chemistry tests will be performed:

- calcium
- phosphorus
- sodium
- magnesium
- potassium
- chloride
- bicarbonate or carbon dioxide

- glucose
- blood urea nitrogen
- creatinine
- cholesterol
- uric acid
- ALT
- AST
- lactate dehydrogenase
- gamma-glutamyl transpeptidase (GGT)
- alkaline phosphatase
- creatine phosphokinase (in case of elevated creatine phosphokinase, the MB fraction should be measured)
- total protein
- albumin
- total bilirubin
- direct bilirubin
- indirect bilirubin
- prolactin

Patients with serum potassium, magnesium and/or calcium levels outside of the central laboratory's reference range at the screening visit will be excluded from the study. Repeat testing is allowed (up to a maximum of 3 tests) if required to establish if values are within normal range.

7.4.2. 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

7.4.3. Urinalysis

Urinalysis will include testing for the following:

- protein
- glucose
- ketones
- blood (hemoglobin)
- pH
- specific gravity
- leukocyte esterase
- microscopic
  - bacteria
  - RBCs
  - WBCs
  - casts
  - crystals

7.4.3.1. Pregnancy Tests

Human chorionic gonadotropin (HCG) serum test will be performed for all women of childbearing age at screening (Visit 0). An indeterminate reading for the serum pregnancy test should be checked twice (urine test) and the patient referred to a gynecologist if required; no study drug will be administered until this is resolved. HCG urine tests will be performed for all women of childbearing age at baseline (Visit 1), Week 4 (Visit 3), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 26 (Visit 9), Week 39 (Visit 10), and Week 52 (Visit 11) or Early Termination, at the follow-up visit, and if clinically indicated at any other time.

Any patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.3.

7.5. Vital Signs

Vital signs will be measured at screening (Visit 0), baseline (Visit 1), Week 2 (Visit 2), Week 4 (Visit 3), Week 6 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 26 (Visit 9), Week 39 (Visit 10), Week 52 (Visit 11) or Early Termination, and at the follow-up visit. Vital signs include the following: pulse, blood pressure (supine and standing), body temperature.

Before pulse and blood pressure are measured, the patient must be in a supine position and resting for at least 5 minutes. Thereafter, blood pressure should be measured again after standing for 2 minutes. Where applicable, measurements should be taken prior to blood being drawn for clinical laboratory evaluations. The same 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 clinically significant change (worsening) from a baseline value will be considered an AE, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

7.6. Electrocardiography

A single resting 12-lead ECG will be conducted after at least 5 minutes of supine rest at screening (Visit 0). If there is evidence of a prolonged QTcF interval at screening (defined as a QTcF interval of >450 msec) then the ECG will be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study.

At the Baseline visit, the predose QTcF will be determined by the average of 3 ECGs (within 10 to 20 minutes of one another), each in triplicate (in total 9 recordings). A postdose ECG will be performed in triplicate 1 to 2 hours after first dosing.

ECGs will be performed in triplicate prior to dosing on site and 1 to 2 hours after dosing on site at Week 2 (Visit 2), Week 4 (Visit 3), Week 6 (Visit 4), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 26 (Visit 9), and Week 39 (Visit 10). On Week 52 (Visit 11) or Early Termination, a triplicate ECG will be performed before the morning dose. At the discretion of the investigator, 12-lead ECG measurements can also be performed on Week 8 (Visit 5) where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.

ECG will also be performed in triplicate at the follow-up visit only for patients with a previously observed cardiac concern and/or QTc change from baseline.

The patient must be in a supine position and resting for at least 5 minutes prior to each ECG measurement. Where applicable, ECG measurements should be taken prior to vital sign measurements and blood being drawn for clinical laboratory or PK evaluations.

A qualified physician at the central ECG vendor will be responsible for interpreting the ECG. However, every ECG should be reviewed immediately at site in order to detect any QTcF prolongation of potential clinical concern and allow dosing.

If the local ECG reading results at the site match any of the discontinuation criteria (see Section 3.6.1), 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.

Evaluation of the screening ECG(s) for inclusion in the study can be performed locally, ie, the interpretation from the central ECG vendor is not required for inclusion. Any ECG finding that is judged by the investigator or the physician from the central ECG vendor as a clinically significant change (worsening) compared with a baseline value will be considered an AE,

recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

Details of dose discontinuation criteria related to QTc prolongation are presented in Section 3.6.1.

7.7. Physical and Neurological Examinations

Physical and neurological examinations, including weight, will be performed at screening (Visit 0), baseline (Visit 1), Week 4 (Visit 3), Week 12 (Visit 6), Week 26 (Visit 9), Week 39(Visit 10), and Week 52 (Visit 11) or Early Termination, and at the follow-up visit. Any physical or neurological examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an AE, recorded on the CRF, and monitored as described in Section 7.1.2.

Height will be measured at the screening visit only.

7.8. Other Safety Measures and Variables

7.8.1. 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, 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].

7.8.2. 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 baseline (Visit 1), Week 4 (Visit 3), Week 6 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 26 (Visit 9), Week 39 (Visit 10), and Week 52 (Visit 11) or Early Termination. The C-SSRS will also be assessed during the week 40-44 telephone call, the Week 45 telephone call, and the Week 46-51 telephone call. 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

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

PBA-s suicidality scores 1 and 2 may be handled by study investigator/neurologist with a consultancy with psychiatrists where necessary per investigator’s medical judgment.

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 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

Methods and timing of assessing safety data are discussed in Section 3.11. Procedures for recording safety data are discussed in Section 13.1 and methods of analyses are discussed in Section 9.8.2.

Furthermore, all AEs will be reviewed on a periodic basis (eg, scheduled safety reviews) as data become available (see Section 7).

8. ASSESSMENT OF PHARMACOKINETICS AND PHARMACOGENOMICS

8.1. Pharmacokinetic Variables

The primary PK measure will be determination of plasma concentration of pridopidine. Concentrations will also be incorporated into a pridopidine population PK model and individual exposure for the study patients (C_{max} and AUC) will be calculated.

8.1.1. Blood Sampling and Handling

Blood samples (4 mL each) will be collected for the determination of plasma concentrations via venipuncture or indwelling catheter in the morning before study drug administration at the following visits:

Titration Period

- Baseline – prior and 1 to 2 hours post first dose
- Week 2 – 1 to 2 hours post afternoon dose

Full Treatment Dose Period

- Week 4 – pre afternoon dose and 1 to 2 hours post afternoon dose
- Week 6 – pre afternoon dose and 1 to 2 hours post afternoon dose
- Week 12 – 1 to 2 hours post afternoon dose
- Week 16 – pre afternoon dose and 1 to 2 hours post afternoon dose
- Week 20 – 1 to 2 hours post afternoon dose
- Week 26 – prior to afternoon dose
- Week 52 – prior to morning dose
- Follow-up visit (Week 54)

A total of 14 samples will be drawn from each patient for PK analysis.

In case of an SAE, the aim will be to collect an additional PK sample at the closest time possible to the SAE.

The date and time of each PK sample and the dates and times of the last drug administration prior to any collected PK sample will be recorded on the source documentation and transcribed onto the CRF. Only major deviations (>5%) from the scheduled blood sampling time points will be commented on the respective page of the CRF.

When ECG evaluation is scheduled at the same time as blood collection, ECG will be performed before blood collection.

Samples will be collected in potassium ethylene diamine tetra acetate-containing tubes. Immediately following collection, samples will be cooled and centrifuged within 45 minutes at approximately 4°C at 1500 × g for 15 minutes. The plasma will then be transferred into

2 polypropylene tubes (first aliquot [Set A] and back-up [Set B]) and stored below -20°C until bioanalysis.

Sample labels should include the study number, patient randomization number, nominal collection time, set (A or B), and indication that they are pharmacokinetic samples.

8.1.2. Shipment of Samples

Plasma samples for all patients will be shipped from the investigational center to the central laboratory or bioanalytical laboratory identified in the front matter of this protocol, where they will be stored until shipped to the sponsor or its designee for analysis. Samples will be stored in an upright position at –20ºC until assayed. The laboratory will be notified before the shipment of the samples and will be sent the shipping information when the samples are shipped.

Set A samples will be transported, frozen with sufficient dry ice for 4 days, by next-day courier to the laboratory identified in the front matter of this protocol.

Set B samples will either be sent to the same laboratory as that for Set A on a subsequent day by next-day courier, or be retained at the investigational center until the study is completed and the clinical study report has been issued (unless shipment to another facility is requested by the sponsor). Instructions as to the disposition of the Set B samples will be provided by the sponsor.

Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

8.1.3. Analysis of Samples

Samples will be analyzed using an appropriate validated method for pridopidine and its main metabolite TV-45065 (previously called ACR30). The lower limits of quantification for pridopidine and TV-45065 in plasma are approximately 1.6 to 1.8 ng/mL and 1.5 to 1.9 ng/mL, respectively. Incurred sample reanalysis may be performed.

8.2. Pharmacogenomic Variables

A blood sample (12 mL) will be collected in 2 dipotassium ethylenediaminetetraacetic acid (K2EDTA) plastic tubes at the screening visit for genetic analyses. Analyses will include CAG repeats, CYP2D6 status, and genetic long QT syndrome (assessed only in patients experiencing QT prolongation following study drug administration leading to study discontinuation). Additionally, any subpopulation of patients that responds differently to drug (in terms of exposure, efficacy, tolerability, or safety) should be investigated for genetic association, with the exact analysis selected according to the study results. Samples will be stored for a period of up to 15 years and then destroyed.

Tubes will be labeled only with patient coded number and patient initials (or dummy initials). The sample can be traced or linked back to the patient only by the investigator or investigational center staff. Coded samples must not carry personal identifiers (such as name or social security number).

Pharmacogenetic samples will be sent to the laboratory within 72 hours from collection in ambient. If DNA extraction is not performed at the laboratory within 24 hours, the samples should be stored at -70ºC until DNA extraction is performed. After DNA extraction, the samples

will be stored either at –20ºC or –70ºC and will be labeled with a new code, so genetic data will not be recorded with patient number or initials

9. STATISTICS

9.1. Study Design and Randomization

This is a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of pridopidine treatment in patients with HD. Patients will be randomly assigned to receive treatment with pridopidine at a dosage of 45, 67.5, 90, or 112.5 mg bid or a matching placebo in a 1:1:1:1:1 ratio. Randomization will be as described in Section 3.3.

The duration of the first study period is 26 weeks and the primary and secondary efficacy analyses will be performed at week 26. Patients that are continuing to the second study period (after week 26 and up to week 52) will continue to receive the same treatment as they were randomized to at baseline of the first study period. All endpoints evaluation at week 52 will be for exploratory purposes.

After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain designated Pharmacovigilance personnel, the Therapeutic Area Head, the Project Champion, and the team members responsible for the population PK and PK/PD analysis will be exposed to the individual patients' treatment assignments. The sponsor study core team that works on the study report and/or design of additional studies and upper management will not be exposed to individual patients' treatment assignments and only be exposed to data summaries by treatments. The investigators, the patient, and any other personnel involved in patients' assessment, monitoring, analysis, and data management are blinded to the patient assignment until the database is locked for analysis of the week 52 data. A detailed procedure that will be taken for maintaining the blinding of the study up to week 52, will be specified before the treatment assignment are revealed for analysis of the first 26-week study period. This procedure will include a list of people that are allowed to be exposed to safety data summaries by treatments.

9.2. Sample Size and Power Considerations

It is estimated that approximately 80 patients per arm will enable a power of 84% to detect a beneficial effect of 4.0 points or more in the change from baseline in UHDRS-TMS of an active pridopidine arm compared to placebo at week 26, assuming SD of 8.5 (as estimated from the MermaiHD [ACR16C008] study) and type I error of 5%.

Eighty patients per arm will enable a power of 71% to detect a beneficial effect of 2.0 points or more in the change from baseline in mPPT of an active pridopidine arm compared to placebo, assuming SD of 5.0.

9.3. Analysis Sets/Populations

9.3.1. Analysis Sets/Populations for the First Study Period (26 Weeks)

9.3.1.1. Intent-to-Treat Population (ITT)

The intent-to-treat (ITT) population will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. The ITT analysis set will include efficacy observations that were measured up to week 26.

9.3.1.2. Safety Population (SP)

The safety population (SP) will include all randomized patients who receive at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually received, regardless of the treatment to which they were randomized. The SP analysis set will include safety observations that were measured up to week 26.

9.3.1.3. Pharmacokinetic Population (PK)

The pharmacokinetic population (PK) will include all randomized patients who received at least 1 dose of study drug and had sufficient plasma concentration results available to allow the intended PK analysis. Patients will be assigned to the treatment actually received regardless of the treatment assignment. The PK analysis set will include observations that were measured up to week 26.

9.3.1.4. Full Analysis Set (FAS)

The full analysis set (FAS) will include all patients in the ITT population who received at least 1 dose of study drug and have at least 1 post baseline efficacy assessment. The FAS analysis set will include efficacy observations that were measured up to week 26.

9.3.1.5. Full Analysis Set On Study Drug (FASOD)

The full analysis set on study drug (FASOD) will include all patients in the ITT population who received at least 1 dose of study drug and have at least 1 post baseline efficacy assessment. The FASOD analysis set will include efficacy observations that were measured up to week 26 and for patients that discontinue study drug, the FASOD will include all efficacy observations that were measured under study drug. All other efficacy observations measured after study drug discontinuation will be excluded from the FASOD analysis set.

9.3.1.6. Completers Analysis Set (CO)

The completers analysis set (CO) will include all patients in the ITT population who completed all visits up to week 26. The CO analysis set will include observations that were measured up to week 26.

9.3.2. Analysis Sets/Populations for the Second Study Period (52 Weeks)

9.3.2.1. Intent-to-Treat Population for the 52 weeks Analyses (ITT2)

The Intent-to-Treat Population for the 52 weeks analyses (ITT2) will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. The ITT2 analysis set will include efficacy observations that were measured up to week 54.

9.3.2.2. Safety Population for the 52 weeks Analyses (SP2)

The safety population for the 52 weeks analyses (SP2) will include all randomized patients who received at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually received, regardless of the treatment to which they were randomized. The SP2 will include safety observations that were measured up to week 54.

9.3.2.3. Pharmacokinetic Population for the 52 weeks Analyses (PK2)

The Pharmacokinetic Population for the 52 weeks Analyses PK2 population will include all randomized patients who received at least 1 dose of study drug and had sufficient plasma concentration results available to allow the intended PK analysis. Patients will be assigned to the treatment actually received regardless of the treatment assignment. The PK2 analysis set will include observations that were measured up to week 52.

9.3.2.4. Full Analysis Set for the 52 weeks Analyses (FAS2)

The full analysis set for the 52 weeks analyses (FAS2) will include all patients in the ITT2 population who received at least 1 dose of study drug and have at least 1 post baseline efficacy assessment. The FAS2 analysis set will include efficacy observations that were measured up to week 54.

9.4. Data Handling Conventions

For all variables, only the observed data from the patients will be used in the statistical analyses. Repeated measures models will be used to estimate treatment effects at weeks 26 and 52.

9.5. Study Populations

The ITT and ITT2 populations will be used for all study population summaries for the 26 and 52-week analyses respectively unless otherwise noted. Summaries will be presented by treatment group and for all patients with available data.

The SP and SP2 analyses sets will be used for safety variables for the 26 and 52-week analyses respectively.

The FAS and FAS2 analyses sets will be used for efficacy variables for the 26 and 52-week analyses respectively.

The primary efficacy variable at week 26 will be analyzed also in the Completers and FASOD analysis sets.

The secondary efficacy variable at week 26 will be analyzed also in the FASOD analysis set.

9.5.1. Patient Disposition

Data from patients screened, patients screened but not treated, patients in the safety population and FAS, patients who complete the study, and patients who withdraw from the study 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.

9.5.2. Demographic and Baseline Characteristics

Patient demographic and baseline characteristics will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number, mean, SD, standard error, 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.

9.6. Efficacy Analysis

The primary and secondary efficacy endpoints will be evaluated at week 26.

Other efficacy endpoints will be evaluated at week 26 and week 52 and will be performed for exploratory purposes.

9.6.1. Primary Efficacy Variable

The primary efficacy variable for this study is the change from baseline in the UHDRS-TMS at Week 26.

9.6.2. Secondary Efficacy Variable

The secondary efficacy analysis variable for this study is the change from baseline in the mPPT at Week 26.

9.6.3. Other Efficacy Variables

Global Functional Scales:

- Change from baseline in the mPPT at Week 52
- CIBIC-Plus global score at Week 26 and 52 as compared to baseline (rated by an independent investigator)
- Change from baseline in the PDS score at Week 26 and 52
- Change from baseline in UHDRS-FA at Week 26 and 52
- CGI-C at Week 26 and 52 as compared to baseline (rated by the qualified site personnel)
- Change from baseline in UHDRS-TFC at Week 26 and 52
- Change from baseline in UHDRS-IS at Week 26 and 52

Patient Reported Outcomes:

- Change from baseline in HD-QoL at Week 26 and 52

- Change from baseline in EQ5D-5L at Week 26 and 52
- Change from baseline in Walk-12 at Week 26 and 52

UHDRS-TMS and Subscores:

- Change from baseline in the UHDRS-TMS at Week 52
- Change from baseline in hand movement score at Week 26 and 52
- Change from baseline in Gait and balance score at Week 26 and 52
- Change from baseline in UHDRS-mMS at Week 26 and 52
- Change from baseline in UHDRS-Chorea at Week 26 and 52
- Change from baseline in UHDRS-Dystonia at Week 26 and 52
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea items
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Dystonia items
- Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea and Dystonia items
- Responders, defined as patients with UHDRS-TMS change from baseline ≤0 at Week 26/early termination visit prior to week 26

Other Motor Assessments:

- Change from baseline in Q-Motor measurements at Week 26 and 52
- Change from baseline in the TUG Test at Week 26 and 52

Cognitive/Psychiatric Assessments:

- Change from baseline in CAB at Week 26 and 52
- Change from baseline in PBA-s at Week 26 and 52 (also part of safety assessments)

9.6.4. Planned Method of Analysis

The FAS and FAS2 (see Section 9.3.1.4 and Section 9.3.2.4) will be used for all the 26- and 52-week efficacy analyses respectively. Summaries will be presented by treatment group.

9.6.4.1. Primary Efficacy Analysis

The comparison of pridopidine dose group of 45 mg bid to placebo will serve as a bridging comparison to the legacy pridopidine studies (ACR16C008 [MermaiHD] and ACR16C009 [HART]), where the pridopidine dose of 45 mg bid was the maximal dose. This comparison to historical data will be performed descriptively.

In addition, any treatment group that will be discontinued due to safety issues will not be formally tested for efficacy and hence not controlled for type I error.

The primary efficacy endpoint analysis will be performed on the FAS analysis set that includes efficacy observations measured up to week 26.

The change from baseline in UHDRS-TMS up to week 26 will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in study by treatment interaction, center, neuroleptic use or no use, and baseline UHDRS-TMS score. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model does not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge, then a simpler covariance structure with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) [ARH(1)], Heterogeneous Compound Symmetry (CSH), Autoregressive(1) [AR(1)], and Compound Symmetry (CS). The estimated means at the Week 26 visit of the change from baseline in UHDRS-TMS will be compared between the active treatment arms (the arms from: 67.5, 90, or 112.5 mg bid that are not discontinued due to safety issues) and the placebo arm.

9.6.4.2. Sensitivity Analysis

A sensitivity analysis to evaluate if the observed effect in UHDRS-TMS is driven by the Chorea UHDRS-TMS sub-score, the Dystonia UHDRS-TMS sub-score, or the Involuntary Movements (Chorea + Dystonia) UHDRS-TMS sub-score will be performed according to the following:

Three variables will be calculated:

- The change from baseline to Week 26 in the sum of the UHDRS-TMS items except the Chorea items
- The change from baseline to Week 26 in the sum of the UHDRS-TMS items except the Dystonia items
- The change from baseline to Week 26 in the sum of the UHDRS-TMS items except the Chorea and Dystonia items

These variables will be analyzed in the same way as the primary efficacy endpoint except that the variable evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.

Additional sensitivity analysis will be performed for change from baseline in UHDRS-TMS on the completers and FASOD analysis sets

9.6.4.3. Secondary Efficacy Variable Analyses

Any statistically significant dose that will be observed in the primary analysis will continue to be tested for the secondary endpoint at an alpha level of 5%.

The secondary efficacy endpoint analysis will be performed on the FAS analysis set that includes efficacy observations measured up to week 26.

The change from baseline in mPPT up to week 26 will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in study by treatment interaction, center, neuroleptic use or no use, and baseline mPPT score. The unstructured covariance matrix for repeated

observations within patients will be used. In case that the model does not converge, the ML estimation method will be used instead of the default REML. If the model still does not converge, then a simpler covariance structure with less parameters will be used, according to the following order: ARH(1), CSH, AR(1), and CS. The estimated means at the Week 26 visit of the change from baseline in mPPT will be compared between the active treatment arms and the placebo arm.

9.6.4.4. Other Efficacy Variables Analyses

The odds of responders will be compared between the active groups and the placebo group using logistic regression analysis (SAS® LOGISTIC procedure) stratified by center using the STRATA sub-command with the following effects: treatment group, neuroleptic use or no use and baseline UHDRS-TMS score.

The change from baseline in HD-QoL and in EQ5D-5L at Week 26 and Week 52/Early Termination will be analyzed using an Analysis of Covariance (ANCOVA) Model. The model will include the following fixed effects: treatment, center, neuroleptic use or no use, and baseline HD-QoL or EQ5D-5L score. The last observation carried forward (LOCF) will be applied for these endpoints for early terminated subjects.

The other efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.

For CIBIC-Plus, the CIBIS score at baseline will be included in the model instead of baseline UHDRS-TMS.

For CGI-C, the CGI-S score at baseline will be included in the model instead of baseline UHDRS-TMS.

9.6.4.5. Exposure Response Analyses

An analysis of correlation between C_{max}/AUC and efficacy and safety measures will be performed.

9.6.4.6. Pooling of Small Centers

Centers with low number of patients will be pooled according to geographical region.

Details will be provided in the Blinded Data Review Meeting minutes.

The pooled center variable will be used in all statistical models that include center as covariate.

9.7. Multiple Comparisons and Multiplicity

The Hochberg's Step-Up method for multiple comparisons between treatment arms in combination with the hierarchical method between the primary efficacy endpoint and the secondary efficacy endpoint, will be used to maintain the experiment-wise type I error of 5% level.

The comparison of pridopidine dose group of 45 mg bid to placebo will serve as a bridging comparison to the legacy pridopidine studies (ACR16C008 [MermaiHD] and ACR16C009 [HART]), where the pridopidine dose of 45 mg bid was the maximal dose. Hence, only a

maximum of 3 multiple dose comparisons to placebo will be performed and controlled for type I error in this study: 67.5, 90, and 112.5 mg bid. First, the Hochberg method will be applied for the comparisons of the 3 (or less) active doses (67.5, 90, and 112.5 mg bid) to placebo. Then, using the hierarchical method, any statistically significant dose will continue to be tested for the secondary endpoint at an alpha level of 5%.

In addition, any treatment group that will be discontinued due to safety issues will not be formally tested for efficacy and hence not controlled for type I error.

9.8. Safety Variables and Analysis

9.8.1. Safety Variables

The overall safety and tolerability of pridopidine treatment will be assessed throughout the study by evaluating AEs and the following additional safety variables:

- clinical laboratory tests
- vital signs
- 12-lead ECG
- C-SSRS
- PBA-s

9.8.2. Safety Analysis

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 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 (ie, reasonable possibility; see Section 7.1.4) (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.

For continuous variables, descriptive statistics (n, mean, SD, standard error, 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 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.

9.9. Pharmacokinetic Analysis

Plasma concentration data on pridopidine and the main metabolite TV-45065 will be presented by descriptive statistics by dose of pridopidine and also by CYP2D6 metabolizer status. Concentrations will be also incorporated into a pridopidine's population PK model and individual exposure for the study patients (C_{max} and AUC) will be calculated.

9.10. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic and pharmacodynamic data (selected efficacy and safety parameters) will be included in population analyses. Details of these analyses will be reported separately.

9.11. Planned Interim Analysis

No interim analysis is planned for this study.

9.12. 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 complete statistical plan, the clinical study report, or any combination of these, as appropriate.

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.

Each investigator must maintain the original records (ie, 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 3.9).

Each 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

Protocol amendments must be prepared by the sponsor or designee and approved by the sponsor, Competent Authorities (if applicable), Central IEC/IRB and/or each respective site's IEC/IRB (if applicable), prior to implementation.

Changes to the protocol can only be made by an approved protocol amendment. In case of urgent safety amendment, the ICH GCP guideline should be followed.

For clinical trial sites located in EU Member States, the procedures outlined in Directive 2001/20/EC, Article 10(a), are applicable.

11.1.2. Protocol Deviations

Any significant deviation from the protocol will be considered a protocol violation. Protocol violations include nonadherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, or GCP guidelines; 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. 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.

11.2. Information to Study Personnel

Each 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). Each 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 standard operating procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and each investigator. The main responsibilities of the study monitors are to visit each 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 monitors will contact each 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, to include specific electronic source documentation [see Section 3.9]) 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. Each 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 clinical.productcomplaints@tevapharm.com 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 serious adverse event 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 serious adverse event 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 serious adverse event, 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 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.

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

12. ETHICS

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. 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 writing in a consent form, which will be signed and personally dated by the patient. Patients with a legal guardian should be consented according to local requirements.

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 they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understood by the patient will be given to all patients.

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 gives written approval or a favorable opinion.

12.3. Confidentiality Regarding Study Patients

Each investigator must assure 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 (eg, initials and 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/EC, Article 10(c); for other countries, local regulations will be followed.

12.5. Registration of the Clinical Study

This clinical study will be registered on clinical trials registry websites according to Teva standard procedures.

13. DATA HANDLING, DATA QUALITY ASSURANCE, 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 21 CFR Part 11. Before used to capture data from this study, the CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study. Before using the CDMS, all users will receive training on the system and any study-specific training. Subsequent to the training, the users will be provided with individual system access rights.

Data will be collected at the study center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent according to the data source. The patient's 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 study center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

If data are processed from other institutions (eg, central laboratory, central image center, electronic diary data), the results should be sent to the study center, where they are retained but not entered into the CRF. These results may also be sent electronically to the sponsor (or organization performing data management) for direct entry into the clinical database (see Section 3.9). Laboratory test results will not be added to the CRF unless otherwise noted in the protocol.

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

13.2. Data Quality Assurance

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

CRFs 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. For each instance of data modifications, the system requires a reason for the change. The system 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. Investigator Responsibilities

All records related to the study (ie, source data, source documents, CRFs [see Section 3.9], data results from other institutions [see Section 13.1], copies of protocols and protocol amendments, drug accountability forms, correspondence, patient identification lists, signed informed consent forms, and other essential documents) must be retained until the sponsor notifies the institution, in writing, that records may be destroyed.

If the sponsor has not provided written notification of records destruction after 10 years from study completion (or earlier in the case of an institution closing), and the institution determines the study record retention is unduly burdensome, the institution may submit a written request to the sponsor at least 60 days before the planned disposition of the study records. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between the sponsor and each investigator. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to the sponsor.

13.3.2. Sponsor Responsibilities

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

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

14. FINANCING AND INSURANCE

A separate financial agreement will be made between each principal investigator and the sponsor before the study drug is delivered.

This clinical study is insured in accordance with the corresponding local legal provisions.

The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions.

Excluded from the insurance cover are, inter alia, damages to health and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), each investigator will provide the sponsor with financial information required to complete Form FDA 3454. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

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 for registration and posting of results.

The sponsor is responsible for preparing a clinical study report. The final report is signed by the sponsor and, if applicable, by the principal investigators and the coordinating investigator.

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

All unpublished information given to the investigators 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 "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as established by the International Committee of Medical Journal Editors (www.ICMJE.org). Authorship will be restricted to parties who have editorial or conceptual input to protocol design, collection of data and/or analysis, interpretation of data, and manuscript preparation. 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 application(s) 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.

16. SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT

16.1. PROTOCOL AMENDMENT 05 DATED 31 MARCH 2016

The primary reason for this global amendment is to implement additional precautionary safety measures to make every effort to ensure the safety of the patients in the TV7820-CNS-20002 (PRIDE-HD) study, following the observation of certain psychiatric adverse events. These measures include (but are not limited to) the addition of 2 telephone calls for safety evaluation (at weeks 40-44 and 46-51) including C-SSRS and an abbreviated PBA-s assessment. Suicidal thoughts and ideations have now been defined as protocol-defined adverse events for expedited reporting. Additional discontinuation criteria for individual patients and stopping rules for treatment arms were implemented.

Further clarifications related to study conduct were implemented in this amendment.

Table 2 (Study Procedures and Assessments) and Figure 1 (Overall Study Schema) have also been revised to reflect the amended study design and the changes described below.

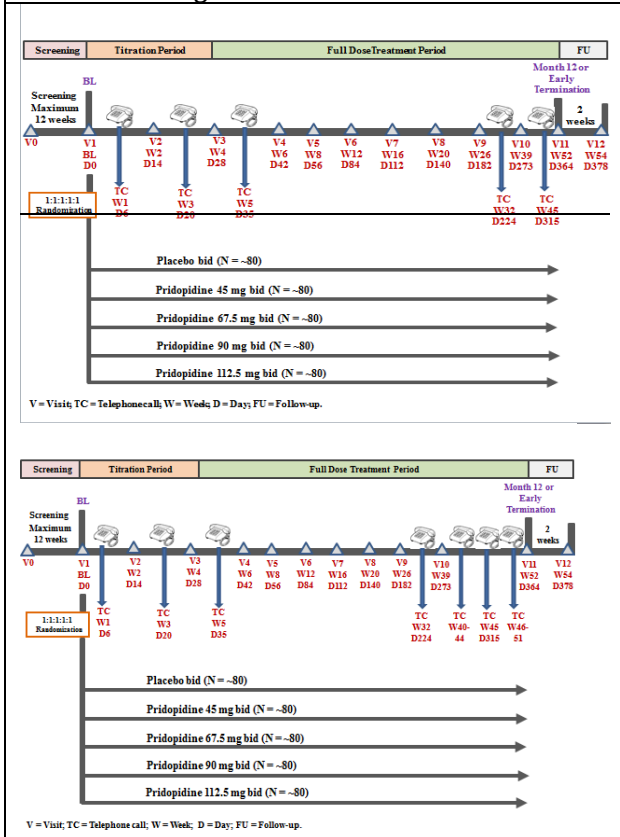
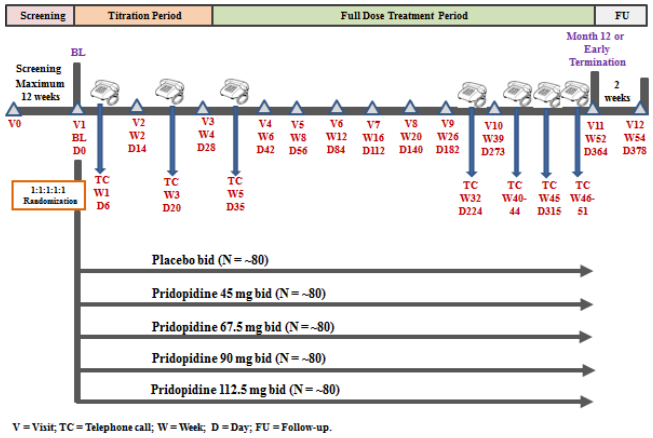
The revisions listed below have been made to the protocol (and protocol synopsis, as appropriate) and are considered substantial by the Teva Authorized Representative.

A comparison table showing substantive changes from the Amendment 04 to Amendment 05 is provided below. Previous text is presented in the column titled "Original text with changes shown", and the revised or new text is presented in the column titled "new wording". Revised or new text is shown in bold italics and deletions are shown in strike-through.

Original text with changes shown	New wording	Reason / Justification for change
COVER PAGE (other sections affected by this change: Investigator Agreement)		
~~Jonathan Isaacsohn, MD, Chief Medical Officer~~ ~~Global Research and Development,~~ ~~Teva Pharmaceutical Industries, Ltd.~~ ***Spyros Papapetropoulos, MD, PhD,*** ***Vice President, Global Head Clinical Development,*** ***Neurodegenerative Diseases*** ***Global Specialty Development,*** ***Teva Branded Pharmaceutical Products R&D, Inc.***	Spyros Papapetropoulos, MD, PhD, Vice President, Global Head Clinical Development, Neurodegenerative Diseases Global Research and Development, Teva Branded Pharmaceutical Products R&D, Inc.	Change in sponsor's authorized signatory. .
Sponsor's Medical Expert ~~Spyridon (Spyros) Papapetropoulos,~~ ***Igor Grachev***, MD, PhD ~~Global Head, Neurodegeneration,~~Senior Director, Clinical Development Leader NDD Teva Branded Pharmaceutical Products R&D, Inc. Tel: +1-610-727-~~6044~~***6462***	**Sponsor's Medical Expert** Igor Grachev, MD, PhD Senior Director, Clinical Development Leader NDD Teva Branded Pharmaceutical Products R&D, Inc. Tel: +1-610-727-6462	Change of medical expert.
1 BACKGROUND INFORMATION		
Section 1.5.4		
1.5.4 Psychiatric Adverse Events Reflecting Suicidal Behavior ***The DSMB for the PRIDE-HD study held an unscheduled meeting on 29 February 2016, and follow-up meetings on 04 March 2016 and 12 March 2016, to review psychiatric adverse events. Upon initial review of safety data from PRIDE-HD and Open PRIDE-HD, the DSMB raised questions regarding certain psychiatric AEs, including depression, suicidal ideation, and suicide attempts observed in the PRIDE-HD study. In the ongoing PRIDE-HD study (n=408 patients), 4 patients had serious adverse events of suicidal attempts and 2 patients had a serious adverse event of suicidal ideation. In addition, 6 patients had adverse events of suicidal ideation: 4 cases were mild and 2 moderate in severity/intensity. In the ongoing Open-PRIDE-HD study, there has been 1 serious adverse event of suicidal ideation in a patient. These patients were discontinued from treatment with study medication but were permitted to continue in the study.*** ***The data reviewed suggested that the overall rate of***	**1.5.4 Psychiatric Adverse Events Reflecting Suicidal Behavior** The DSMB for the PRIDE-HD study held an unscheduled meeting on 29 February 2016, and follow-up meetings on 04 March 2016 and 12 March 2016, to review psychiatric adverse events. Upon initial review of safety data from PRIDE-HD and Open PRIDE-HD, the DSMB raised questions regarding certain psychiatric AEs, including depression, suicidal ideation, and suicide attempts observed in the PRIDE-HD study. In the ongoing PRIDE-HD study (n=408 patients), 4 patients had serious adverse events of suicidal attempts and 2 patients had a serious adverse event of suicidal ideation. In addition, 6 patients had adverse events of suicidal ideation: 4 cases were mild and 2 moderate in severity/intensity. In the ongoing Open-PRIDE-HD study, there has been 1 serious adverse event of suicidal ideation in a patient. These patients were discontinued from treatment with study medication but were permitted to continue in the study. The data reviewed suggested that the overall rate of suicidality events reported in PRIDE-HD and Open PRIDE-HD were comparable to previous experience in HD trials. Nevertheless, following full review and discussion, Teva and members of the	Newly-added text to reflect psychiatric adverse event findings in the PRIDE-HD and Open PRIDE-HD studies.

Original text with changes shown	New wording	Reason / Justification for change
suicidality events reported in PRIDE-HD and Open PRIDE-HD were comparable to previous experience in HD trials. Nevertheless, following full review and discussion, Teva and members of the PRIDE-HD Steering Committee proposed an increase in safety monitoring for psychiatric AEs in both studies, which was approved by the DSMB (March 12th meeting). An expert HD psychiatrist (Dr. Erik van Duijn) also issued a letter in support of the proposed monitoring plan. ***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 and Section 3.6.2), including updated individual patient stopping rules (Section 3.6.1), while the sponsor closely monitors psychiatric AEs in all pridopidine studies for emergence of any potential safety signal.*** ***No new safety signal has been identified and no significant information has been obtained for the previously identified risks associated with use of pridopidine.***	PRIDE-HD Steering Committee proposed an increase in safety monitoring for psychiatric AEs in both studies, which was approved by the DSMB (March 12th meeting). An expert HD psychiatrist (Dr. Erik van Duijn) also issued a letter in support of the proposed monitoring plan. 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 and Section 3.6.2), including updated individual patient stopping rules (Section 3.6.1), while the sponsor closely monitors psychiatric AEs in all pridopidine studies for emergence of any potential safety signal. No new safety signal has been identified and no significant information has been obtained for the previously identified risks associated with use of pridopidine.	
3 STUDY DESIGN		
Section 3.1		
.... During the full treatment dose period (Weeks 4-52), there will be a total of 9 on-site visits at Weeks 4, 6, 8, 12, 16, 20, 26, 39 and 52 (or at early termination) and a phone call on Weeks 5, 32 ***between Weeks 40-44***, ***on Week 45 and between Weeks 46-51*** ~~and 45~~ . Visits and procedures during the full dose period will be scheduled around the afternoon dose, with the exception of Week 52 where only the morning dose is administered. During the phone call at Weeks 5 ***and*** 32 ~~and 45~~ inquiries about AEs and concomitant medication will be conducted. ***During the phone calls between Weeks 40-44, on Week 45 and between Weeks 46-51, 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***	.... During the full treatment dose period (Weeks 4-52), there will be a total of 9 on-site visits at Weeks 4, 6, 8, 12, 16, 20, 26, 39 and 52 (or at early termination) and a phone call on Weeks 5, 32 between Weeks 40-44, on Week 45 and between Weeks 46-51. Visits and procedures during the full dose period will be scheduled around the afternoon dose, with the exception of Week 52 where only the morning dose is administered. During the phone call at Weeks 5 and 32 inquiries about AEs and concomitant medication will be conducted. During the phone calls between Weeks 40-44, on Week 45 and between Weeks 46-51, 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	Per increased safety measures, two safety evaluation telephone calls were added and PBA-s assessment was added at Week 39.

Original text with changes shown	New wording	Reason / Justification for change
obsessive-compulsive behaviors) will be conducted. ... At Weeks 4, 12, 26 and 52, in addition to safety assessments and the UHDRS-TMS and mPPT, the CIBIC-Plus will be rated by an independent rater, while another qualified site personnel will assess the PDS, the CGI-C, the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, and the PBA-s. ***The PBA-s will also be assessed at Week 39.*** UHDRS-TMS and mPPT should be evaluated prior to the other scales.	conducted. ... At Weeks 4, 12, 26 and 52, in addition to safety assessments and the UHDRS-TMS and mPPT, the CIBIC-Plus will be rated by an independent rater, while another qualified site personnel will assess the PDS, the CGI-C, the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, and the PBA-s. The PBA-s will also be assessed at Week 39. UHDRS-TMS and mPPT should be evaluated prior to the other scales.	

Original text with changes shown	New wording	Reason / Justification for change
Section 3.1 – Figure 1		
 		Figure revised to reflect updated study design with additional safety telephone calls.
Section 3.2.4		
Safety variables and endpoints will include the following: • AEs throughout the study • Changes from baseline in QTcF and other ECG parameters throughout the study • Clinical safety laboratory (clinical chemistry, hematology, and urinalysis) throughout the study • Changes from baseline C-SSRS ***and PBA-s*** throughout the study	Safety variables and endpoints will include the following: • AEs throughout the study • Changes from baseline in QTcF and other ECG parameters throughout the study • Clinical safety laboratory (clinical chemistry, hematology, and urinalysis) throughout the study • Changes from baseline C-SSRS and PBA-s throughout the study	The PBA-s is also a safety variable in this study.

Original text with changes shown	New wording	Reason / Justification for change
• Vital signs throughout the study	• Vital signs throughout the study	
Section 3.3 (Other sections affected by this change: 9.1)		
... After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain ~~and~~ designated Pharmacovigilance personnel, ***the Therapeutic Area Head, the Project Champion, and the team members responsible for the population PK and PK/PD analysis*** will be exposed to the individual patients' treatment assignments. ...	After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain ~~and~~ designated Pharmacovigilance personnel, the Therapeutic Area Head, the Project Champion, and the team members responsible for the population PK and PK/PD analysis will be exposed to the individual patients' treatment assignments. ...	Text revised to reflect unblinding of additional personnel to data following the 26-week database lock.
Section 3.6.1		
Additional discontinuation criteria for individual patients, based on suicide ideation or attempt, will be applied. Patients should be discontinued if: • ***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).***	Additional discontinuation criteria for individual patients, based on suicide ideation or attempt, will be applied. Patients should be discontinued if: • 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).	Implementation of additional discontinuation criteria for individual patients based on suicidal ideations and attempts.
Section 3.6.2		
... ***Two stopping rules based on the occurrence of suicidal attempts and suicidal ideation have been introduced after consultation with members of the study steering committee and DSMB (details in Section 1.5.4):*** ***1. Stopping Rule Based on Suicidal Attempts*** ***Occurrence of more than 2 new cases with suicide attempt after 21 March 2016 in a treatment arm relative to the number of events in patients receiving placebo will trigger discontinuation of the arm and all higher dose arms.*** ***2. Stopping Rule Based on Suicidal Ideation***	... Two stopping rules based on the occurrence of suicidal attempts and suicidal ideation have been introduced after consultation with members of the study steering committee and DSMB (details in Section 1.5.4): 1. Stopping Rule Based on Suicidal Attempts Occurrence of more than 2 new cases with suicide attempt after 21 March 2016 in a treatment arm relative to the number of events in patients receiving placebo will trigger discontinuation of the arm and all higher dose arms. 2. Stopping Rule Based on Suicidal Ideation	As a safety measure, two stopping rules based on the occurrence of suicidal attempts and suicidal ideation, have been introduced.

Original text with changes shown	New wording	Reason / Justification for change
Occurrence of more than 3 new cases in patients with an adverse event of suicidal ideation or significant suicidal ideation (see definition below) after 21 March 2016 in a treatment arm vs placebo will trigger discontinuation of the arm. ***Definition of suicidal ideation case: A suicidal ideation case is defined as grades 4 and 5 of the C-SSRS reported during a site visit, or during safety telephone calls (TCs), or as a reported adverse event or serious adverse event. C-SSRS scores below 4 (e.g., 1, 2 or 3) will not count towards the proposed stopping rule.***	Occurrence of more than 3 new cases in patients with an adverse event of suicidal ideation or significant suicidal ideation (see definition below) after 21 March 2016 in a treatment arm vs placebo will trigger discontinuation of the arm. Definition of suicidal ideation case: A suicidal ideation case is defined as grades 4 and 5 of the C-SSRS reported during a site visit, or during safety telephone calls (TCs), or as a reported adverse event or serious adverse event. C-SSRS scores below 4 (e.g., 1, 2 or 3) will not count towards the proposed stopping rule.	
Section 3.8		
Unblinded PK and ECG data may be assessed during the study. The individuals responsible for sample bioanalysis and PK analysis and other responsible staff members supporting the unblinded data review by the DSMB will know who received study drug and who received placebo during the study ~~but will not have access to any clinical data~~. The unblinded person responsible for PK analysis will provide concentration data to ~~other staff members~~ ***the DSMB*** in a manner that will not identify individual patients (ie, mean values only or a dummy patient identifier will be linked to an individual patient's concentration data). The DSMB can request unblinding if deemed necessary for appropriate safety evaluation. For information about personnel who may be aware of treatment assignments and specification of maintaining the blind procedures after the analysis of the first 26-week study period, see Section 3.3. These individuals will not be involved in conduct of any study procedures or assessment of any AEs. ~~The sponsor personnel involved in the safety and efficacy analysis of the study will remain blinded to the treatment allocation.~~	Unblinded PK and ECG data may be assessed during the study. The individuals responsible for sample bioanalysis and PK analysis and other responsible staff members supporting the unblinded data review by the DSMB will know who received study drug and who received placebo during the study. The unblinded person responsible for PK analysis will provide concentration data to the DSMB in a manner that will not identify individual patients (ie, mean values only or a dummy patient identifier will be linked to an individual patient's concentration data). The DSMB can request unblinding if deemed necessary for appropriate safety evaluation. For information about personnel who may be aware of treatment assignments and specification of maintaining the blind procedures after the analysis of the first 26-week study period, see Section 3.3. These individuals will not be involved in conduct of any study procedures or assessment of any AEs.	Text revised to reflect unblinding of some personnel to data following the 26-week database lock.
Section 3.11 – Table 2		
Urinalysis was not listed as performed at Visit 10 (Week 39)	An "X" was added to the urinalysis row at Visit 10 (Week 39) to show this procedure is required at this visit.	Corrected per issued administrative letter; for consistency with protocol sections 3.11.3.2.4 and 7.4

Original text with changes shown	New wording	Reason / Justification for change
(Not applicable)	Additional safety evaluation telephone calls were added at Weeks 40-44 and 46-51, and relevant assessments performed were marked with an "X".	Newly-added telephone calls as part of the increased safety measures.
(Not applicable)	New row added titled "Abbreviated PBA-s" to denote subset of PBA-s questions relevant to suicidality that will be assessed during the safety evaluation telephone calls.	Clarification.
(Not applicable)	Rows for benzodiazepines and antidepressants inquiry and for alcohol and illicit drug use inquiry were added to the table. These assessments will be performed at V10, Week 40-44 TC, Week 45 TC, Week 46-51 TC and V11.	As part of the increased safety measures, screening for changes in use of medications, alcohol and drugs, which have been associated with suicidality in HD, will be performed
(Not applicable)	C-SSRS assessment was added to the Week 45 telephone contact and additional safety TCs	Implemented as part of the increased safety measures,
(Not applicable)	PBA-s assessment was added at Week 39 (Visit 10), at Week 45 and the additional safety TCs.	Implemented as part of the increased safety measures,
Review study compliance ***& adherence***	Review study compliance & adherence	Study adherence is reviewed during the telephone calls at Weeks 40-44, Week 45 and Weeks 6-51.
(new text) ***Footnote m. The safety telephone calls will include an abbreviated PBA-s (a subset of PBA questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation and obsessive compulsive behaviors).***	Footnote m. The safety telephone calls will include a subset of The safety telephone calls will include an abbreviated PBA-s (a subset of PBA questions on depressed mood, suicidal ideation, anxiety, irritability, loss of motivation and obsessive compulsive behaviors).	Newly added footnote per increased safety monitoring measures.
Footnote t. This information will be collected as part of concomitant medication inquiry.	Footnote t. This information will be collected as part of concomitant medication inquiry.	Newly added footnote per increased safety monitoring measures.
Footnote v. Study adherence is reviewed during these telephone calls.	Footnote v. Study adherence is reviewed during these telephone calls.	Newly-added footnote for clarification.
Section 3.11.3.2.4		
The following procedures/assessments will be performed on Week 39 (±7 days) (Visit 10): • AE inquiry • concomitant medication review ***(including inquiry about changes in use of benzodiazepines and***	The following procedures/assessments will be performed on Week 39 (±7 days) (Visit 10): • AE inquiry • concomitant medication review (including inquiry about changes in use of benzodiazepines and antidepressants)	As part of the increased safety measures, screening for changes in use of medications, alcohol and drugs, which have been

Original text with changes shown	New wording	Reason / Justification for change
antidepressants) • ***inquiry about changes in use of alcohol and illicit drugs*** • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis) • ... • ***PBA-s***	• inquiry about changes in use of alcohol and illicit drugs • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis) • ... • PBA-s	associated with suicidality in HD, will be performed. PBA-s assessment was added at Week 39.
Section 3.11.3.2.5		
3.11.3.2.5 Telephone Contact at Weeks 32, *40-44*, ~~and~~ 45 and *46-51* Patients will be contacted by telephone on Week 32 (±10 days) ~~and Week 45 (±10 days)~~ to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage. ***Between Weeks 40-44, on Week 45 (±10 days) and between Weeks 46-51, patients will be contacted by telephone to evaluate safety and tolerability to the study drug through assessment of*** ~~AEs and concomitant medication usage~~ ***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	**3.11.3.2.5 Telephone Contact at Weeks 32, 40-44, 45 and 46-51** Patients will be contacted by telephone on Week 32 (±10 days) to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage. Between Weeks 40-44, on Week 45 (±10 days) and between Weeks 46-51, patients will be contacted by telephone to evaluate safety and tolerability to the study drug through assessment of 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	Per increased safety measures, 2 safety evaluation telephone calls were added.
Section 3.11.3.2.6		
The following procedures/assessments will be performed on Week 52 (±7 days) (Visit 11) or at the Early Termination visit: <u>Before Dosing:</u> • AE inquiry • concomitant medication review (***including inquiry***	The following procedures/assessments will be performed on Week 52 (±7 days) (Visit 11) or at the Early Termination visit: <u>Before Dosing:</u> • AE inquiry • concomitant medication review (including inquiry about changes in use of benzodiazepines and antidepressants)	As part of the increased safety measures, screening for changes in use of medications, alcohol and drugs, which have been associated with suicidality in

Original text with changes shown	New wording	Reason / Justification for change
about changes in use of benzodiazepines and antidepressants) • ***inquiry about changes in use of alcohol and illicit drugs*** • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)	• inquiry about changes in use of alcohol and illicit drugs • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)	HD, will be performed.
Section 3.11.6.		
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, AEs, ***C-SSRS ("Since Last Visit" version) and PBA-s (if visit scheduled to assess psychiatric adverse events,)*** concomitant medications and treatments, and results from procedures or tests). In case of an SAE, an additional PK sample should be collected at the closest time to SAE.	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, AEs, C-SSRS ("Since Last Visit" version) and PBA-s (if visit scheduled to assess psychiatric adverse events) concomitant medications and treatments, and results from procedures or tests). In case of an SAE, an additional PK sample should be collected at the closest time to SAE.	Additional safety assessments that may be performed during an unscheduled visit.
6 ASSESSMENT OF EFFICACY		
Section 6.3.11		
... ***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***	... 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	Increased safety monitoring of patients with positive C-SSRS or PBA-s suicidal ideation scores.

Original text with changes shown	New wording	Reason / Justification for change
>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. ...	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 ASSESSMENT OF SAFETY		
Section 7.1.1		
… ~~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 him or herself, the patient should be referred for **immediate** psychiatric evaluation and an AE/SAE should be reported.~~ ***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 duration of the clinical study, the patient should be discontinued from treatment with study drug and 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.***	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 duration of the clinical study, the patient should be discontinued from treatment with study drug and 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.	Clarification regarding patients with psychiatric adverse events reflecting suicidal behavior.
Section 7.1.6.		
~~No protocol-defined adverse events for expedited reporting were identified for this study.~~ 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	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	Suicidal ideations or attempts are now protocol-defined adverse events for expedited reporting.

Original text with changes shown	New wording	Reason / Justification for change
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).	monitoring (see Section 7.1.7).	
Section 7.1.7		
... ***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 are discontinued from treatment may continue their participation in the study and perform the scheduled visits and assessments, while off study drug.***	... 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 are discontinued from treatment may continue their participation in the study and perform the scheduled visits and assessments, while off study drug.	Clarification regarding patients who report adverse events of suicidal behavior or ideation.
Section 7.8.1.		
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, 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]***.	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, 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].	As part of the increased safety measures, screening for changes in use of medications, alcohol and drugs, which have been associated with suicidality in HD, will be performed.
(New footnote)	[2] In accordance with the American Psychiatric Associations 2003	Clarification.

Original text with changes shown	New wording	Reason / Justification for change
[2] In accordance with the American Psychiatric Associations 2003 Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors.	Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors.	
Section 7.8.2		
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 baseline (Visit 1), Week 4 (Visit 3), Week 6 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), ~~and~~ Week 26 (Visit 9), Week 39 (Visit 10), and Week 52 (Visit 11) or Early Termination. ***The C-SSRS will also be assessed during the week 40-44 telephone call, the Week 45 telephone call, and the Week 46-51 telephone call.*** 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. ... ***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 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***	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 baseline (Visit 1), Week 4 (Visit 3), Week 6 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6), Week 16 (Visit 7), Week 20 (Visit 8), Week 26 (Visit 9), Week 39 (Visit 10), and Week 52 (Visit 11) or Early Termination. The C-SSRS will also be assessed during the week 40-44 telephone call, the Week 45 telephone call, and the Week 46-51 telephone call. 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. ... 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 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.	Increased C-SSRS assessment and safety monitoring of patients with positive C-SSRS or PBA-s suicidal ideation scores.

Original text with changes shown	New wording	Reason / Justification for change
be referred for psychiatric evaluation per the investigator's medical judgment.		
9 STATISTICS		
Section 9.1.		
... After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain and designated Pharmacovigilance personnel, ***the Therapeutic Area Head, the Project Champion, and the team members responsible for the population PK and PK/PD analysis*** will be exposed to the individual patients' treatment assignments. ...	After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain and designated Pharmacovigilance personnel, the Therapeutic Area Head, the Project Champion, and the team members responsible for the population PK and PK/PD analysis will be exposed to the individual patients' treatment assignments. ...	Text revised to reflect unblinding of additional personnel to data following the 26-week database lock.
Section 9.6.3.		
... Cognitive/Psychiatric Assessments: • Change from baseline in CAB at Week 26 and 52 • Change from baseline in PBA-s at Week 26 and 52 ***(also part of safety assessments)***	... Cognitive/Psychiatric Assessments: • Change from baseline in CAB at Week 26 and 52 • Change from baseline in PBA-s at Week 26 and 52 (also part of safety assessments)	Clarification.
Section 9.8.1		
The overall safety and tolerability of pridopidine treatment will be assessed throughout the study by evaluating AEs and the following additional safety variables: • clinical laboratory tests • vital signs • 12-lead ECG • C-SSRS • ***PBA-s***	The overall safety and tolerability of pridopidine treatment will be assessed throughout the study by evaluating AEs and the following additional safety variables: • clinical laboratory tests • vital signs • 12-lead ECG • C-SSRS • PBA-s	The PBA-s is also a safety variable in this study.

16.2. ADMINISTRATIVE LETTER DATED 04 FEBRUARY 2016

TV7820-CNS-20002
The Pride-HD Study
EMBRACING CHALLENGES

TEVA Global R&D

February 4, 2016

RE: TV7820-CNS-20002

Administrative changes to the protocol

The purpose of this administrative letter is to notify sites of a change to the clinical study protocol with amendment 04 dated 12 January 2015, related to urinalysis at Visit 10.

For consistency, Table 2 is being updated to require urinalysis at Visit 10 (Week 39). The change is being made to ensure consistency between the table and the different sections of the protocol (Sections 3.11.3.2.4 and 7.4).

This administrative letter will be an addendum to protocol TV7820-CNS-20002 amendment 04 dated 12 January 2015 and Local Protocol Amendment 01 for Denmark dated 19 February 2015, and is not considered a substantial amendment. The affected sections of the protocol will be updated during the next protocol amendment.

If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

Sincerely,

Igor Grachev, MD, PhD
Senior Director, Global Clinical Development Leader NDD
Global Research and Development
Teva Branded Pharmaceutical Products R&D, Inc.

Page **1** of **1**

16.3. ADMINISTRATIVE LETTER DATED 03 AUGUST 2015

August 3, 2015

RE: TV7820-CNS-20002

Administrative changes to the protocol

The purpose of this administrative letter is to notify sites of a change to the protocol amendment 4 dated 12 January 2015, related to electrocardiograms (ECG) at V9 and V10 as well as a change in the Sponsor's Medical Expert.

For consistency, section 7.6 is being updated to only require a triplicate 12-lead ECG prior to dosing at visit 9 (week 26) and visit 10 (week 39). At the discretion of the investigator, an additional 12 -lead ECG measurement can also be performed where there are clinical circumstances that justify an additional ECG (eg, patients with a previous episode of hypokalemnia without QT prolongation) or where required by local regulation. The change is being made to ensure consistency between the different sections of the protocol (sections 3.11.3.2.3 and 3.11.3.2.4).

The Sponsor's Medical Expert located on the cover page of the protocol is being updated. Spyridon Papapetropoulos, MD, PhD has been replaced by Igor Grachev, MD, PhD. Dr. Grachev's contact information is listed below:

Igor Grachev, MD, PhD
Senior Director, Global Clinical Development Lead
Neurodegeneration
Teva Branded Pharmaceutical Products R&D, Inc.
Tel: 610-727-6462

This administrative letter will be an addendum to protocol TV7820-CNS-20002 amendment 4 dated 12-Jan-15 and Local Protocol Amendment 01 for Denmark dated 19-Feb-2015, and is not considered a substantial amendment. The affected sections of the protocol will be updated during the next protocol amendment.

If you have any questions, please contact the study personnel designated for protocol issues on the Clinical Study Personnel Contact Information page of the protocol.

Sincerely,

Spyros Papapetropoulos, MD, PhD
VP Glob Head Clinical Dev NDD
Global Research and Development
Teva Pharmaceuticals

Page 1 of 1

16.4. PROTOCOL AMENDMENT 04 DATED 12 JANUARY 2015

The revisions listed below have been made to the protocol, and synopsis as appropriate, and are considered substantial by the sponsor's Authorized Representative.

The primary reason for this amendment is to extend the study treatment period to 52 weeks instead of the previous 26 weeks, in order to collect long-term safety data from the range of pridopidine doses in HD patients. Two on-site visits, at weeks 39 and 52, were added. During these visits, various procedures and assessments will be performed as detailed in Table 2. Also, 2 telephone calls have been added (at weeks 32 and 45) between the on-site visits during the second study period. The sections pertaining to statistical endpoints and analyses have been updated to reflect the extension of the study duration. Also, clarifications regarding various aspects of study conduct have been introduced.

For clarification and due to the allowed time windows for the visits and telephone calls, references to study days throughout the protocol text have been replaced by references to weeks/visits.

Throughout the document, the references have been edited and formatted to include the author name(s) and publication year, and the corresponding numbering has been removed.

Substantive changes from Amendment 03 to Amendment 04 are provided below.

Previous text is presented in the column titled "Previous approved wording"; revised or new text is presented in bold italics and deletions are struck through in the column titled "Amended or new wording" and the reason or justification for the change is presented in the column titled "Reason/Justification for change". If text was relocated within the same section of the protocol but was not revised, the change is not shown in the comparison table**.**

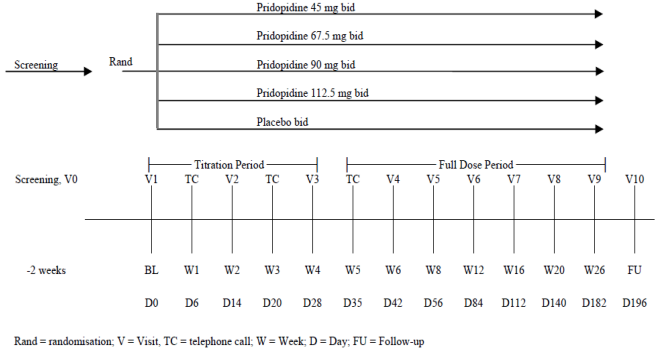
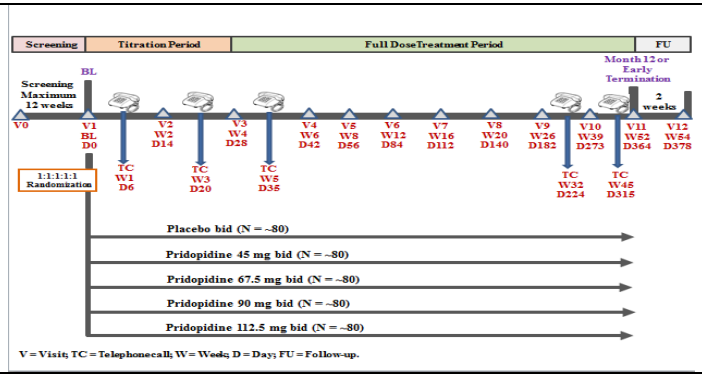
Previous approved wording	Amended or new wording	Reason/Justification for change
COVER PAGE		
(Not applicable)	***PRIDE-HD – Pridopidine Dose Evaluation in Huntington's Disease***	Addition of the study acronym and definition.
Sponsor's Global Clinical Leader Anna Wickenberg, PhD Global Clinical Leader, CNS & Pain TA Teva Pharmaceutical Industries Ltd. Tel: +46 72 721 9122	~~**Sponsor's Global Clinical Leader**~~ ~~Anna Wickenberg, PhD~~ ~~Global Clinical Leader,~~ ~~CNS & Pain TA~~ ~~Teva Pharmaceutical Industries Ltd.~~ ~~Tel: +46 72 721 9122~~	Updated to reflect change in the study clinical leadership.
Sponsor's Medical Expert: Jonathan Isaacsohn, MD Chief Medical Officer Global Research and Development Teva Pharmaceutical Industries, Ltd. Tel: +972 3 926 7249	Sponsor's Medical Expert ~~Jonathan Isaacsohn, MD~~ ~~Chief Medical Officer~~ ~~Global Research and Development~~ ~~Teva Pharmaceutical Industries, Ltd.~~ ~~Tel: +972 3 926 7249~~ ***Spyridon Papapetropoulos, MD, PhD*** ***Global Head, Neurodegeneration,*** ***Clinical Development*** ***Teva Branded Pharmaceutical Products R&D, Inc.*** ***Tel: +1-610-727-6044***	Updated to reflect change in the study clinical leadership.
CLINICAL LABORATORY AND OTHER DEPARTMENTS AND INSTITUTIONS		
Pending: Information will be included in the Trial Master File	~~**Pending: Information will be included in the Trial Master File**~~ ***Central Laboratory*** ***Quest Diagnostics Clinical Laboratories, Inc.*** ***27027 Tourney Road*** ***Suite 2E Valencia, CA 91355*** ***USA*** ***Quest Diagnostics Limited Unit B1*** ***Parkway West Industrial Estate Cranford Lane – Heston*** ***Middlesex TW5 9QA*** ***UK*** ***Quest Diagnostics Nichols Institute*** ***33608 Ortega Highway*** ***San Juan Capistrano, CA 92675-2042*** ***USA***	This section was updated to include the vendors and service providers for this study.

Previous approved wording	Amended or new wording	Reason/Justification for change
	Tan Tock Seng Hospital Dept of Laboratory ***Medicine Level 2*** ***Podium Block Tan Tock Seng Hospital*** ***11 Jalan Tan Tock Seng 308433*** ***SINGAPORE*** ***<u>Central Electrocardiogram Evaluation</u>*** ***eResearchTechnology, Inc.*** ***1818 Market Street 10th floor*** ***Philadelphia, Pa 19103*** ***USA*** ***<u>Web and Phone Integrated Interactive Response Technology</u>*** ***Parexel International*** ***Suite 3 Kelvin House*** ***Kelvin Way*** ***Crawley*** ***West Sussex*** ***RH10 9WE*** ***UK*** ***<u>Computer-Based Rating System</u>*** ***QuantiMedis GmbH*** ***Marientalstrasse 43*** ***48149 Münster*** ***Germany*** ***Stout Neuropsych Pty Ltd*** ***44 Stewart Street*** ***Ormond VIC 3204*** ***Australia*** ***<u>Bioanalytical Pharmacokinetics Evaluation</u>*** ***CRS Clinical Research Services*** ***Richard-Wagner-Strasse 20*** ***67269 Grünstadt*** ***Germany***	

Previous approved wording	Amended or new wording	Reason/Justification for change
	Collaborator ***European Huntington's Disease Network*** ***Oberer Eselsberg 45/1*** ***D-89081 Ulm*** ***Germany*** ***Huntington Study Group, LTD*** ***2604 Elmwood Avenue*** ***Suite 335*** ***Rochester, NY 14618***	
LIST OF ABBREVIATIONS		
(Not applicable)	***CO – Completers analysis set*** ***FASOD – Full Analysis Set on Study Drug*** ***SP – Safety Population*** ***PK – Pharmacokinetic Population***	Newly-added abbreviations.
1 BACKGROUND INFORMATION		
Section 1.3.2		
As per 01 May 2013, 853 patients with HD have been enrolled in clinical studies with pridopidine, with 621 patients receiving pridopidine in doses ranging from 20 to 90 mg daily.	As per ~~01 May 2013~~***18 November 2014***, ~~853~~ ***866*** patients with HD have been enrolled in clinical studies with pridopidine, with ~~621~~ ***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.***	Updated exposure to pridopidine in patients with Huntington's disease.
Section 1.4.2		
It should be noted that there was no titration period in the MAD study while a 1-month progressive titration will be implemented in the present study, which should decrease the risk of dizziness.	It should be noted that there was no titration period in the MAD study while a 1-month progressive titration ~~will be~~ ***is*** implemented in the present study, which should decrease the risk of dizziness.	Changed to reflect that the study is ongoing.
Section 1.5		
Pridopidine has been shown to have a benign safety profile, similar to placebo, in doses so far tested in patients with HD. Hence it is 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 will be used in the present study.	Pridopidine has been shown to have a benign safety profile, similar to placebo, in doses so far tested in patients with HD. Hence it is 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 ~~will be~~ ***are*** used in the present study.	Changed to reflect that the study is ongoing.

Previous approved wording	Amended or new wording	Reason/Justification for change
2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES		
Section 2.2		
The other secondary objectives are as follows: • To evaluate the safety and tolerability of a range of pridopidine doses in patients with HD during 26 weeks of treatment • To explore the PK of pridopidine in the study population • To investigate the relationship between exposure to pridopidine and outcome measures (eg, clinical efficacy and toxicity parameters)	The other secondary objectives are as follows: • To evaluate the safety and tolerability of a range of pridopidine doses in patients with HD during ~~26 weeks of treatment~~ ***the entire 52-week study period.*** • To explore the PK of pridopidine in the study population • To investigate the relationship between exposure to pridopidine and outcome measures (eg, clinical efficacy and toxicity parameters)	Objective changed to reflect the extension of the study.
3 STUDY DESIGN		
Section 3.1		
Patients will be equally randomized (1:1:1:1:1) to receive pridopidine 45, 67.5, 90, or 112.5 mg or placebo bid for 26 weeks, including a 4-week progressive titration period. ... During titration (Days 0 to 27), there will be 2 on-site visits: at Day 0 (baseline) and at Day 14. There will be additional phone calls on Days 6 and 20. ... Phone calls on Days 6 and 20will be performed to inquire about AEs and concomitant medications, and to allow the weekly dose increase on the following day. During the on-site visit at Day 14, before the afternoon dose of the study drug, a blood sample will be taken for electrolyte monitoring; if hypokalemia is observed, dosing will be interrupted 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. Vital signs will be assessed in addition to the inquiry about AEs and concomitant medications. Twelve-lead ECGs will be performed in triplicate 1 to 2 hours after the afternoon dose of study drug on Day 14, followed by collection of a PK sample. During the full treatment dose period (Days 28 to 182), there	Patients will be equally randomized (1:1:1:1:1) to receive pridopidine 45, 67.5, 90, or 112.5 mg or placebo bid for ~~26~~ ***52*** weeks, including a 4-week progressive titration period. ... During titration (Days 0 to 27), there will be 2 on-site visits: at ~~Day 0~~ ***Visit 1*** (baseline) and at ~~Day 14~~ ***Week 2***. There will be additional phone calls on ~~Days 6 and 20~~ ***Weeks 1 and 3***. ... Phone calls on ~~Days 6 and 20~~ ***Weeks 1 and 3*** will be performed to inquire about AEs and concomitant medications, and to allow the weekly dose increase on the following day. During the on-site visit at ~~Day 14~~ ***Week 2***, before the afternoon dose of the study drug, a blood sample will be taken for electrolyte monitoring; if hypokalemia is observed, dosing will be interrupted 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***. Vital signs will be assessed in addition to the inquiry about AEs and concomitant medications. Twelve-lead ECGs will be performed in triplicate 1 to 2 hours after the afternoon dose of study drug on ~~Day 14~~ ***Week 2***, followed by collection of a PK sample. During the full treatment dose period (~~Days 28 to 182~~***Weeks 4 to***	Treatment period revised to reflect extension. Days of assessments and procedures modified to reflect changes in time points; all references to days changed to Weeks and Visits (throughout protocol). Day of final visit updated.

Previous approved wording	Amended or new wording	Reason/Justification for change
will be a total of 7 on-site visits at Days 28, 42, 56, 84, 112, 140, and 182 (or at early termination) and a phone call on Day 35. Visits and procedures during the full dose period will be scheduled around the afternoon dose, with the exception of Day 182 where only the morning dose is administered. During the phone call at Day 35, inquiries about AEs and concomitant medication will be conducted. At each of the on-site visits, safety variables will be assessed, including triplicate ECG evaluation before and 1 to 2 hours after dose administration at the site (ECG is optional on Day 56), and clinical laboratory evaluations. PK sampling for determination of the levels of pridopidine and TV-45065 will be done on Days 28, 42, and 112 (before and 1 to 2 hours after the afternoon dose), on Days 84 and 140 (1 to 2 hours after the afternoon dose), and on Day 182 (before the morning dose). When concomitant to ECG, PK samples will be collected after the ECG recording. At days 28, 56, 84, 112, 140, and 182, in addition to safety assessments, the UHDRS-TMS and the mPPT will be assessed by qualified site personnel. At Days 28, 84, and 182, in addition to safety assessments and the UHDRS-TMS and mPPT, the CIBIC-Plus will be rated by an independent rater, while another qualified site personnel will assess the PDS, the CGI-C, the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, and the PBA-s. UHDRS-TMS and mPPT should be evaluated prior to the other scales. ... The CAB will be performed on days 84 and 182 only. The HD-QoL and EQ5D scales will be completed on Day 182 only. Patients who complete all scheduled visits will have final procedures and assessments performed at the final visit (Day 182). Patients who withdraw from the study before completing the evaluation period will have the Day 182	***52***), there will be a total of ~~7~~ ***9*** on-site visits at ~~Days 28, 42, 56, 84, 112, 140, and 182~~***Weeks 4, 6, 8, 12, 16, 20, 26, 39 and 52*** (or at early termination) and a phone call on ~~Day 35~~ ***Weeks 5, 32 and 45***. Visits and procedures during the full dose period will be scheduled around the afternoon dose, with the exception of ~~Day 182~~ ***Week 52*** where only the morning dose is administered. During the phone call at ~~Day 35~~ ***Weeks 5, 32 and 45***, inquiries about AEs and concomitant medication will be conducted. At each of the on-site visits, safety variables will be assessed, including triplicate ECG evaluation before and 1 to 2 hours after dose administration at the site (ECG is optional on ~~Day 56~~***Week 8***), and clinical laboratory evaluations. PK sampling for determination of the levels of pridopidine and TV-45065 will be done on ~~Days 28, 42, and 112~~ ***Weeks 4, 6, and 16*** (before and 1 to 2 hours after the afternoon dose), on ~~Days 84 and 140~~ ***Weeks 12 and 20*** (1 to 2 hours after the afternoon dose), ***on Week 26 (before the afternoon dose)*** and on ~~Day 182~~ ***Week 52*** (before the morning dose). When concomitant to ECG, PK samples will be collected after the ECG recording. At ~~days 28, 56, 84, 112, 140, 182~~***Weeks 4, 8, 12. 16, 20, 26 and 52,*** in addition to safety assessments, the UHDRS-TMS and the mPPT will be assessed by qualified site personnel. At ~~Days 28, 84, and 182~~ ***Weeks 4, 12, 26 and 52***, in addition to safety assessments and the UHDRS-TMS and mPPT, the CIBIC-Plus will be rated by an independent rater, while another qualified site personnel will assess the PDS, the CGI-C, the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, and the PBA-s. UHDRS-TMS and mPPT should be evaluated prior to the other scales. ... The CAB will be performed on ~~days 84 and 182~~ ***Weeks 12, 26 and 52*** only. The HD-QoL and EQ5D scales will be completed on ~~Day182~~ ***Weeks 26 and 52*** only. Patients who complete all scheduled visits will have final	

Previous approved wording	Amended or new wording	Reason/Justification for change
procedures and assessments performed at their final visit.	procedures and assessments performed at the final visit (~~Day 182~~***Week 52***). Patients who withdraw from the study before completing the evaluation period will have the ~~Day 182~~ **Week 52** procedures and assessments performed at their final visit.	
The procedures and assessments for visits V0 and V4-10 may be performed over several days, as long as they are completed within the defined visit window.	The procedures and assessments for visits V0 and V4-~~10~~ ***12*** may be performed over several days, as long as they are completed within the defined visit window.	Revision of sentence to include all visits.
Section 3.1 – Figure 1		
		Figure revised to reflect the 12 week screening period, the extension of the study to 52 weeks and the additional visits and telephone calls.
Section 3.2 (Other sections affected by this change: 9.6)		
(Not applicable)	***The primary and secondary efficacy endpoints will be evaluated at week 26.*** ***Other efficacy endpoints will be evaluated at week 26 and week 52 and will be performed for exploratory purposes.***	New text to clarify endpoint evaluation.
Section 3.2.3 (Other sections affected by this change: 9.6.3)		
Global Functional Scales: • CIBIC-Plus global score at Week 26 as compared to baseline (rated by an independent investigator) • Change from baseline in the PDS score at Week 26 • Change from baseline in UHDRS-FA at Week 26 • CGI-C at Week 26 as compared to baseline (rated by qualified site personnel) • Change from baseline in UHDRS-TFC at	**Global Functional Scales:** • ***Change from baseline in the mPPT at Week 52*** • CIBIC-Plus global score at Week 26 ***and 52*** as compared to baseline (rated by an independent investigator) • Change from baseline in the PDS score at Week 26 ***and 52*** • Change from baseline in UHDRS-FA at Week 26 ***and 52*** • CGI-C at Week 26 ***and 52*** as compared to baseline (rated by qualified site personnel)	Endpoints modified and/or added to reflect the study extension and the additional time point.

Previous approved wording	Amended or new wording	Reason/Justification for change
Week 26 • Change from baseline in UHDRS-IS at Week 26 **Patient Reported Outcomes:** • Change from baseline in HD-QoL at Week 26 • Change from baseline in EQ5D-5L at Week 26 • Change from baseline in Walk-12 at Week 26 **UHDRS-TMS Subscores:** • Change from baseline in hand movement score (defined as the sum of UHDRS domains finger taps, pronate-supinate hands and luria [fist-hand-palm test]) at Week 26 • Change from baseline in Gait and balance score (defined as the sum of UHDRS domains gait, tandem walking and retropulsion pull test) at Week 26 • Change from baseline in UHDRS-mMS (defined as the sum of UHDRS domains dysarthria, tongue protrusion, finger taps, pronate-supinate hands, luria, rigidity, bradykinesia, gait, tandem walking, retropulsion pull test) at Week 26 • Change from baseline in UHDRS-Chorea at Week 26 • Change from baseline in UHDRS-Dystonia at Week 26 • Responders, defined as patients with UHDRS-TMS change from baseline ≤0 at Week 26 **Other Motor Assessments:** • Change from baseline in Q-Motor measurements at Week 26 including digitomotography (speeded index finger tapping), dysdiadochomotography (pronation/supination hand tapping), manumotography and choreomotography (grip force and chorea analysis) and pedomotography (speeded foot	• Change from baseline in UHDRS-TFC at Week 26 ***and 52*** • Change from baseline in UHDRS-IS at Week 26 ***and 52*** **Patient Reported Outcomes:** • Change from baseline in HD-QoL at Week 26 ***and 52*** • Change from baseline in EQ5D-5L at Week 26 ***and 52*** • Change from baseline in Walk-12 at Week 26 ***and 52*** **UHDRS-TMS *and* Subscores:** • ***Change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week 52*** • Change from baseline in hand movement score (defined as the sum of UHDRS domains finger taps, pronate-supinate hands and luria [fist-hand-palm test]) at Week 26 ***and 52*** • Change from baseline in Gait and balance score (defined as the sum of UHDRS domains gait, tandem walking and retropulsion pull test) at Week 26 ***and 52*** • Change from baseline in UHDRS-mMS (defined as the sum of UHDRS domains dysarthria, tongue protrusion, finger taps, pronate-supinate hands, luria, rigidity, bradykinesia, gait, tandem walking, retropulsion pull test) at Week 26 ***and 52*** • Change from baseline in UHDRS-Chorea at Week 26 ***and 52*** • Change from baseline in UHDRS-Dystonia at Week 26 ***and 52*** • ***Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea items*** • ***Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Dystonia items*** • ***Change from baseline to Week 26 and 52 in the sum of the UHDRS-TMS items except the Chorea and***	

Previous approved wording	Amended or new wording	Reason/Justification for change
tapping) • Change from baseline in the TUG Test at Week 26 **Cognitive/Psychiatric Assessments:** • Change from baseline in CAB at Week 26: SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS • Change from baseline in PBA-s at Week 26	***Dystonia items*** • Responders, defined as patients with UHDRS-TMS change from baseline ≤0 at Week 26***/early termination visit prior to week 26*** **Other Motor Assessments:** • Change from baseline in Q-Motor measurements at Week 26 ***and 52*** including digitomotography (speeded index finger tapping), dysdiadochomotography (pronation/supination hand tapping), manumotography and choreomotography (grip force and chorea analysis) and pedomotography (speeded foot tapping) • Change from baseline in the TUG Test at Week 26 ***and 52*** **Cognitive/Psychiatric Assessments:** • Change from baseline in CAB at Week 26 ***and 52***: SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS • Change from baseline in PBA-s at Week 26 ***and 52***	
Section 3.3 (Other sections affected by this change: 9.1)		
Randomization will be performed by interactive response technology (IRT) using dynamic randomization to balance the treatment arms within centers and neuroleptics use or no use. Patients will be equally assigned to the 5 treatment arms of the study (4 active treatment arms and placebo, allocation ratio of 1:1:1:1:1). Pridopidine capsules sizes differ between the 22.5 and 45 mg dosages, therefore 2 different sizes of placebo capsules will be provided, depending on treatment arm, to maintain blinding. Packaging of all treatment packs will be identical in appearance in order to maintain blinding throughout each study period. The investigators, the sponsor, and any personnel involved in patients' assessment, monitoring, analysis and data management (excluding the designated Clinical Supplies Chain's personnel), are blinded to the patient assignment until the database is locked for analysis and the treatment assignment revealed. A statistician not assigned to the study will be responsible for reviewing the	Randomization will be performed by interactive response technology (IRT) using dynamic randomization to balance the treatment arms within centers and neuroleptics use or no use. Patients will be equally assigned to the 5 treatment arms of the study (4 active treatment arms and placebo, allocation ratio of 1:1:1:1:1). ***Patients that are continuing to the second study period (after week 26) will continue to receive the same treatment as they were randomized to at baseline of the first 26-week study period.*** Pridopidine capsules sizes differ between the 22.5 and 45 mg dosages, therefore 2 different sizes of placebo capsules will be provided, depending on treatment arm, to maintain blinding. Packaging of all treatment packs will be identical in appearance in order to maintain blinding throughout each study period. The investigators, the sponsor, and any personnel involved in patients' assessment, monitoring, analysis and data management (excluding the designated Clinical Supplies Chain's personnel), are blinded to the patient assignment until the database is locked for analysis ***of***	Clarification regarding doses of patients continuing in the extension. New text regarding blinding and statistical analysis of the 6-month (26-week) and the 12-month (52-week) data, respectively. Clarification regarding patients in treatment arm which is stopped by DSMB.

Previous approved wording	Amended or new wording	Reason/Justification for change
randomization code. Should the DSMB decide to stop the continuation of 1 or more treatment arms, the dynamic randomization algorithm will be adjusted to apply an equal allocation ratio to all approved remaining treatment arms.	***the first 26-week study period*** and the treatment assignment revealed. A statistician not assigned to the study will be responsible for reviewing the randomization code. ***After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain and designated Pharmacovigilance personnel will be exposed to the individual patients' treatment assignments. The sponsor study core team that works on the study report and/or design of additional studies and upper management will not be exposed to individual patients' treatment assignments and only be exposed to data summaries by treatments. The investigators, the patient, and any other personnel involved in patients' assessment, monitoring, analysis and data management are blinded to the patient assignment until the database is locked for analysis of the week 52 data. A detailed procedure that will be taken for maintaining the blinding of the study up to week 52, will be specified before the treatment assignment are revealed for analysis of the first 26-week period of the study. This procedure will include a list of people that are allowed to be exposed to safety data summaries by treatments.*** Should the DSMB decide to stop the continuation of 1 or more treatment arms, the dynamic randomization algorithm will be adjusted to apply an equal allocation ratio to all approved remaining treatment arms. ***If an arm is stopped by the DSMB, then any patients currently enrolled in that arm will stop receiving medication immediately but will continue to be followed for adverse events and safety.***	
Section 3.4 – Table 1 (Other sections affected by this change: 3.4.1.2; 3.4.2.2)		
In the Table Header: Full Dose Period Weeks 4 to 26	In the Table Header: Full Dose Period Weeks 4 to ~~26~~***52***	Changed to reflect the extension of the full-dose study period.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 3.4.1		
… There will not be an afternoon dose at the final visit (Day 182/Early Termination). Study drug can be taken irrespective of meals. Both outer pack and bottles will be labeled with a unique pack number. The appropriate number of treatment packs will be assigned to patients by using the IRT according to the dosing schedule at Visits 1, 2, 3, 5, 6, 7, and 8 (Days 0, 14, 28, 56, 84, 112, and 140). If tolerability problems occur, patients will be instructed to contact the investigator immediately.	… There will not be an afternoon dose at the final visit (~~Day 182~~ ***Week 52***/Early Termination). Study drug can be taken irrespective of meals. Both outer pack and bottles will be labeled with a unique pack number. The appropriate number of treatment packs will be assigned to patients by using the IRT according to the dosing schedule at Visits 1, 2, 3, 5, 6, 7, ~~and~~ 8, ***9 and 10*** ~~(Days 0, 14, 28, 56, 84, 112, and 140)~~ ***(Baseline and Weeks 2, 4, 8, 12, 16, 20, 26 and 39)***. If tolerability problems occur, patients will be instructed to contact the investigator immediately.	Assignment and dispensing of drug changed to reflect the extension of the full-dose study period.
Section 3.5		
For each patient, the duration of participation is planned to be up to 40 weeks, consisting of a screening period of up to 12 weeks, a 26-week randomized double-blind treatment period (comprised of a 4-week titration and 22-week full dose period), and a 2-week follow-up period following the last dose of study medication. The total duration of the study is estimated to be approximately 15 months.	For each patient, the duration of participation is planned to be up to ~~40~~ ***66*** weeks, consisting of a screening period of up to 12 weeks, a ~~26~~ ***52***-week randomized double-blind treatment period (comprised of a 4-week titration and ~~22~~ ***48***-week full dose period), and a 2-week follow-up period following the last dose of study medication. The total duration of the study is estimated to be approximately ~~15~~ ***30*** months.	Changed to reflect the extension of the study duration.
Section 3.6.1		
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. … Patients should also be discontinued if they experience a seizure or convulsions (regardless of the relationship to treatment), if their body weight decreases to <50 kg, and/or if creatinine clearance decreases to <60 mL/min (calculated using the Cockcroft-Gault equation).	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 (see Section 3.6.3.*** ***…*** Patients should also be discontinued if they experience a seizure or convulsions (regardless of the relationship to treatment), if their body weight decreases to <50 kg, 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.***	Clarification that patients who have been off drug for over 14 days should not restart treatment, in accordance with Section 3.6.3, but will be asked to continue in the study. Clarification that the creatinine clearance test may be repeated if deemed clinically appropriate.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 3.6.3		
If a patient requires more than 1 titration between week 5 and 26 of the study, he/she will not restart study drug treatment. He/she will be asked to continue in the study and follow the visit schedule as outlined in the protocol.	If a patient requires more than 1 titration between week 5 and ~~26~~ ***52*** of the study, he/she will not restart study drug treatment. He/she will be asked to continue in the study and follow the visit schedule as outlined in the protocol.	Clarification to allow only 1 titration during the entire study period.
Section 3.8		
For information about personnel who may be aware of treatment assignments, see Section 3.3.These individuals will not be involved in conduct of any study procedures or assessment of any AEs. The sponsor personnel involved in the safety and efficacy analysis of the study will remain blinded to the treatment allocation.	For information about personnel who may be aware of treatment assignments ***and specification of maintaining the blind procedures after the analysis of the first 26-week study period***, see Section 3.3. These individuals will not be involved in conduct of any study procedures or assessment of any AEs. The sponsor personnel involved in the safety and efficacy analysis of the study will remain blinded to the treatment allocation.	Clarification.
Section 3.10		
The study is expected to start in Q1 2014 (first patient enrolled) and be completed in Q3 2015 (last patient last visit).	The study is expected to start in Q1 2014 (first patient enrolled); ***Q1 2016 (last patient last visit for the first 26-week study period),*** and ***to*** be completed in Q3 ~~2015~~ ***2016*** (last patient last visit ***for the second study period***)	Changed to reflect updated planned study period.
Section 3.11 – Table 2		
Table of Study Procedures and Assessments.	The table was replaced to include the study procedures and assessments performed during the added on-site visits (Weeks 39 and 52) and telephone calls to patients (Weeks 32 and 45).	Table modified to reflect study extension. At week 39, safety procedures will be performed; at Week 52, safety and efficacy procedures will be performed. During the TCs patients will be asked about adverse events and concomitant medications.
Section 3.11 – Table 2		
a. The procedures and assessments for these visits (V0 and V4-10) may be performed over several days, as long as they are completed within the defined visit window.	a. The procedures and assessments for these visits (V0 and V4-~~10~~***12***) may be performed over several days, as long as they are completed within the defined visit window.	Changed to reflect updated number of study visits.
Section 3.11 – Table 2		
i. On Day 182, a triplicate ECG and PK sample will be collected before the last study (morning) dose.	i. On ~~Day 182~~***Week 52***, a triplicate ECG and PK sample will be collected before the last study (morning) dose.	Footnote revised and moved to Week 52 (Visit 11) to

Previous approved wording	Amended or new wording	Reason/Justification for change
		reflect new time point of last study visit.
Section 3.11 – Table 2		
(Not applicable)	***q. On the last study day (week 52), the study drug administration will take place on site, after the pre-dose PK sample is obtained.***	Newly added footnote for clarification.
Section 3.11.3.2.3		
3.11.3.2.3. Week 26 – Day 182 (Visit 9) or Early Termination The following procedures/assessments will be performed on Day 182 (±7 days) at Week 26 (Visit 9) or at the Early Termination visit: <u>Before Dosing:</u> • AE inquiry • concomitant medication review • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis) • urine pregnancy test for women of child-bearing potential only • full physical and neurological examination (including weight) • triplicate 12-lead ECG (performed after at least 5 minutes of supine rest) • vital signs measurements • C-SSRS (since last visit version) • obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording) • study compliance review • morning study drug dose administration (Note: study drug will not be administered if Early Termination visit) <u>After Dosing:</u> • collect remaining study drug The following efficacy procedures/assessments will be performed on Day 182 (Visit 9), before or after dosing (with	**3.11.3.2.3 Week 26 – ~~Day 182~~ (Visit 9) ~~or Early Termination~~** The following procedures/assessments will be performed on ~~Day 182~~ ***Week 26*** (±7 days) ~~at Week 26~~ (Visit 9) ~~or at the Early Termination visit~~: ~~<u>Before Dosing:</u>~~ • AE inquiry • concomitant medication review • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis) • urine pregnancy test for women of child-bearing potential only • full physical and neurological examination (including weight) • triplicate 12-lead ECG (performed after at least 5 minutes of supine rest) • vital signs measurements • C-SSRS (since last visit version) • obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording) ***(prior to afternoon dose)*** • study compliance review • ~~morning study drug dose administration (Note: study drug will not be administered if Early Termination visit)~~ ~~<u>After Dosing:</u>~~ • collect/dispense ~~remaining~~ study drug The following efficacy procedures/assessments will be performed on ~~Day 182~~ ***Week 26*** (Visit 9), before or after dosing (with the time of the evaluation recorded), with UHDRS-TMS and mPPT	Following the extension of the study, week 26 is no longer the final study visit/early termination visit.

Previous approved wording	Amended or new wording	Reason/Justification for change
the time of the evaluation recorded), with UHDRS-TMS and mPPT evaluated in priority: • UHDRS-TMS • mPPT • CIBIC-Plus • PDS • UHDRS-FA, UHDRS-TFC, UHDRS-IS • CGI-C • TUG Test • HD-QoL • EQ5D-5L • Walk-12 • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) • PBA-s Note: there will be no afternoon dose .on Day 182/Early Termination.	evaluated in priority: • UHDRS-TMS • mPPT • CIBIC-Plus • PDS • UHDRS-FA, UHDRS-TFC, UHDRS-IS • CGI-C • TUG Test • HD-QoL • EQ5D-5L • Walk-12 • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) • PBA-s ~~Note: there will be no afternoon dose .on Day 182/Early Termination.~~	
Section 3.11.3.2.4		
(Not applicable)	***3.11.3.2.4 Week 39 (Visit 10)*** ***The following procedures/assessments will be performed on Week 39 (±7 days) (Visit 10):*** • ***AE inquiry*** • ***concomitant medication review*** • ***clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)*** • ***urine pregnancy test for women of child-bearing potential only*** • ***full physical and neurological examination (including weight)*** • ***triplicate 12-lead ECG (performed after at least 5 minutes of supine rest)***	New section added to depict procedures performed on Week 39 (Visit 10).

Previous approved wording	Amended or new wording	Reason/Justification for change
	• ***vital signs measurements*** • ***C-SSRS (since last visit version)*** • ***collect/dispense study drug*** • ***study compliance review*** ***The procedures and assessments for this visit may be performed over several days, as long as they are completed within the defined visit window (±7 days).***	
Section 3.11.3.2.5		
(Not applicable)	***Patients will be contacted by telephone on Week 32 (±10 days) and Week 45 (±10 days) to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage.***	New section added to depict telephone calls to patients at Weeks 32 and 45 (mid-way between the on-site visits during the second study period).
Section 3.11.3.2.6		
(Not applicable)	***The following procedures/assessments will be performed on Week 52 (±7 days) (Visit 11) or at the Early Termination visit:*** ***<u>Before Dosing:</u>*** • ***AE inquiry*** • ***concomitant medication review*** • ***clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)*** • ***urine pregnancy test for women of child-bearing potential only*** • ***full physical and neurological examination (including weight)*** • ***triplicate 12-lead ECG (performed after at least 5 minutes of supine rest)*** • ***vital signs measurements*** • ***C-SSRS (since last visit version)*** • ***obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording)*** • ***study compliance review*** • ***morning study drug dose administration on-site***	New section added to depict procedures performed on Week 52 (Visit 11) or Early Termination (occurring after week 26).

Previous approved wording	Amended or new wording	Reason/Justification for change
	(Note: study drug will not be administered if Early Termination visit) ***<u>After Dosing:</u>*** • ***collect remaining study drug*** ***The following efficacy procedures/assessments will be performed on Week 52 (Visit 11), before or after dosing (with the time of the evaluation recorded), with UHDRS-TMS and mPPT evaluated in priority:*** • ***UHDRS-TMS*** • ***mPPT*** • ***CIBIC-Plus*** • ***PDS*** • ***UHDRS-FA, UHDRS-TFC, UHDRS-IS*** • ***CGI-C*** • ***TUG Test*** • ***HD-QoL*** • ***EQ5D-5L*** • ***Walk-12*** • ***Q-Motor assessments*** • ***CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS)*** • ***PBA-s*** ***Note: there will be no afternoon dose on Week 52/Early Termination.*** ***The procedures and assessments for this visit may be performed over several days, as long as they are completed within the defined visit window (±7 days).***	
Section 3.11.4		
3.11.4 Follow Up Visit There will be a follow-up visit 2 weeks after the last dose of study drug (Day 196, ±7 days). The following procedures/assessments will be performed. ...	3.11.4 Follow Up Visit ***(Visit 12)*** There will be a follow-up visit 2 weeks after the last dose of study drug (~~Day 196~~ ***Week 54***, ±7 days). The following procedures/assessments will be performed. ...	Revised to reflect updated week in which the visit takes place.

<table>
<tr><th>Previous approved wording</th><th>Amended or new wording</th><th>Reason/Justification for change</th></tr>
<tr><td colspan="3">Section 3.11.5</td></tr>
<tr><td>For patients who complete the study or withdraw prematurely, final evaluations will be performed at the Week 26/Early Termination visit (Visit 9).</td><td><s>For patients who complete the study or withdraw prematurely, final evaluations will be performed at the Week 26/Early Termination visit (Visit 9).</s> For patients who complete the study or withdraw prematurely, final evaluations will be performed at an end-of treatment visit (Week 52, Visit 11) or on the last day the patient receives the study drug, or as soon as possible thereafter.</td><td>Clarification regarding performance of final evaluations.</td></tr>
<tr><td colspan="3">4 SELECTION AND WITHDRAWAL OF PATIENTS</td></tr>
<tr><td>i.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).</td><td>i. [Revision 1] 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.</td><td>Clarification that the creatinine clearance test may be repeated if deemed clinically appropriate.</td></tr>
<tr><td>n. Females who are pregnant or lactating.</td><td>n. [Revision 1] Females who are pregnant or <s>lactating</s> breastfeeding.</td><td>Clarification.</td></tr>
<tr><td colspan="3">5 TREATMENT OF PATIENTS</td></tr>
<tr><td colspan="3">Section 5.3</td></tr>
<tr><td>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 4.3). If the patient refuses to be seen for further visits, the assessments for Week 26 (Day 182)/Early Termination should be performed, as far as possible (at least attempts to capture information on AEs and concomitant medication).</td><td>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 4.3). If the patient refuses to be seen for further visits, the assessments for Week <s>26 (Day 182)</s>52/Early Termination should be performed, as far as possible (at least attempts to capture information on AEs and concomitant medication).</td><td>Revised to reflect updated week in which the visit takes place.</td></tr>
<tr><td colspan="3">Section 5.5</td></tr>
<tr><td>
Table 3: Total Blood Volume Collected from Each Patient
<table>
<tr><th>Type of Assessment</th><th>Number of Samples Collected</th><th>Volume per Sample</th><th>Total Volume for Assessment</th></tr>
<tr><td>Pharmacokinetic</td><td>13</td><td>4 mL</td><td>52 mL</td></tr>
<tr><td>Serum Chemistry</td><td>11</td><td>10.5 mL</td><td>115.5 mL</td></tr>
<tr><td>Hematology</td><td>9</td><td>3 mL</td><td>27 mL</td></tr>
<tr><td>Pharmacogenetic Analyses</td><td>1</td><td>12 mL</td><td>12 mL</td></tr>
<tr><td>Total</td><td></td><td></td><td>206.5 mL</td></tr>
</table>
</td><td>
Table 3: Total Blood Volume Collected from Each Patient
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<tr><th>Type of Assessment</th><th>Number of Samples Collected</th><th>Volume per Sample</th><th>Total Volume for Assessment</th></tr>
<tr><td>Pharmacokinetic</td><td><s>13</s> 14</td><td>4 mL</td><td><s>52</s> 56 mL</td></tr>
<tr><td>Serum Chemistry</td><td><s>11</s> 13</td><td>10.5 mL[a]</td><td><s>115.5</s> 129.5 mL</td></tr>
<tr><td>Hematology</td><td>9<s>12</s></td><td><s>3</s> 2 mL</td><td><s>27</s>24 mL</td></tr>
<tr><td>Pharmacogenetic Analyses</td><td>1</td><td>12 mL</td><td>12 mL</td></tr>
<tr><td>Total</td><td></td><td></td><td><s>206.5</s> 221.5 mL</td></tr>
</table>
[a] The samples are 10.5 mL at all visits, except visit 2 where CK-MB and prolactin are not collected, and thus the volume at this visit is only 3.5 mL.
</td><td>The table was updated and corrected to reflect the number of samples and the volumes collected.</td></tr>
</table>

Previous approved wording	Amended or new wording	Reason/Justification for change
6 ASSESSMENT OF EFFICACY		
Primary and secondary efficacy assessments (UHDRS-TMS and mPPT) will be performed on Day 0 (Visit 0, baseline), Day 28 (Visit 3), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), and Day 182 (Visit 9). Exploratory efficacy assessments will be performed only at Day 0 (Visit 0, baseline), Day 28 (Visit 3), Day 84 (Visit 6), and Day 182 (Visit 9); apart from the CAB, which will be performed only at Day 0 (Visit 0, baseline), Day 84 (Visit 6), and Day 182 (Visit 9); and UHDRS FA, UHDRS TFC, and UHDRS IS which will also be performed on Day 140. Except for Day 0, 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. UHDRS-TMS and Q-Motor assessments will also be performed at the follow-up visit.	Primary and secondary efficacy assessments (UHDRS-TMS and mPPT) will be performed on ~~Day 0 (~~Visit ~~0~~1~~,~~ ***(***baseline), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 56~~ ***Week 8*** (Visit 5), ~~Day 84~~ ***Week 12*** (Visit 6), ~~Day 112~~ ***Week 16*** (Visit 7), ~~Day 140~~***Week 20*** (Visit 8), ~~Day 182~~ ***Week 26*** (Visit 9) ***and Week 52 (Visit 11)***. Exploratory efficacy assessments will be performed only at ~~Day 0 (~~Visit ~~0~~***1 (***baseline), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 84~~ ***Week 12*** (Visit 6), ~~and~~ ~~Day 182~~ ***Week 26*** (Visit 9), ***and Week 52 (Visit 11)***; apart from the CAB, which will be performed only at ~~Day~~ 0 (Visit ~~0~~***1 (***baseline), ~~Day 84~~ ***Week 12*** (Visit 6), ~~and~~ ~~Day 182~~ ***Week 26***(Visit 9), ***and Week 52 (Visit 11)***; and UHDRS FA, UHDRS TFC, and UHDRS IS which will also be performed on ~~Day 140~~ ***Week 20 (Visit 8)***. Except for ~~Day 0~~ ***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. UHDRS-TMS and Q-Motor assessments will also be performed at the follow-up visit ***(Visit 12)***.	Changed to reflect updated number of study visits for these assessments.
Section 6.3.1		
Global change in HD at Week 26 will be measured using the CIBIS scale at baseline (Day 0) and the CIBIC-Plus scale at subsequent time points. The CIBIC-Plus (version ADCS-CGIC) was developed, validated, and is commonly used in studies of anti-dementia drugs in Alzheimer's disease.[23] … At each subsequent visit in which the evaluation is performed (Visits 3, 6, and 9), the CIBIC-Plus will be administered by the same independent rater, but without knowledge of other endpoint assessments or the AEs experienced by the patient during the study (so as not to confound the rating of	Global change in HD at Week 26 will be measured using the CIBIS scale at baseline ~~(Day 0)~~ and the CIBIC-Plus scale at subsequent time points. The CIBIC-Plus (version ADCS-CGIC) was developed, validated, and is commonly used in studies of anti-dementia drugs in Alzheimer's disease.[23] … At each subsequent visit in which the evaluation is performed ~~(Visits 3, 6, and 9)~~, the CIBIC-Plus will be administered by the same independent rater, but without knowledge of other endpoint assessments or the AEs experienced by the patient during the study (so as not to confound the rating of CIBIC-Plus as an efficacy measure or to unblind the study).	Reference to specific time points was removed. The visits at which the assessment is performed is detailed in Table 2.

Previous approved wording	Amended or new wording	Reason/Justification for change
CIBIC-Plus as an efficacy measure or to unblind the study). …	**…**	
Section 6.3.4		
CGI-S will be assessed at baseline (Day 0) and CGI-C will be used at all subsequent time points (Visits 3, 6, and 9) to assess changes from baseline.	CGI-S will be assessed at baseline (~~Day 0~~***Visit 1)*** and CGI-C will be used at all subsequent time points ~~(Visits 3, 6, and 9)~~ to assess changes from baseline.	Reference to specific time points was removed. The visits at which the assessment is performed is detailed in Table 2.
7 ASSESSMENT OF SAFETY		
Section 7.4 (Other sections affected by this change: Table 2)		
… Clinical laboratory tests (serum chemistry including electrolytes, hematology and urinalysis) will be performed at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2; electrolytes only), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), Day 182 (Visit 9) or Early Termination, and at the follow-up visit. …	… Clinical laboratory tests (serum chemistry including electrolytes, hematology and urinalysis) will be performed at screening (Visit 0), baseline (Visit 1), ~~Day 14~~ ***Week 2*** (Visit 2; electrolytes only), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 42~~ ***Week 6*** (Visit 4), ~~Day 56~~ ***Week 8*** (Visit 5), ~~Day 84~~***Week 12*** (Visit 6), ~~Day 112~~ ***Week 16*** (Visit 7), ~~Day 140~~ ***Week 20*** (Visit 8), ~~Day 182~~ ***Week 26*** (Visit 9), ***Week 39 (Visit 10), and Week 52 (Visit 11)*** or Early Termination, and at the follow-up visit. …	Revised to reflect updated number of study visits at which clinical laboratory tests are taken.
Section 7.4.3.1 (Other sections affected by this change: Table 2)		
HCG urine tests will be performed for all women of childbearing age at baseline (Visit 1), Day 28 (Visit 3), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), Day 182 (Visit 9) or Early Termination, at the follow-up visit, and if clinically indicated at any other time.	HCG urine tests will be performed for all women of childbearing age at baseline (Visit 1), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 56~~***Week 8*** (Visit 5), ~~Day 84~~ ***Week 12*** (Visit 6), ~~Day 112~~ ***Week 16*** (Visit 7), ~~Day 140~~ ***Week 20*** (Visit 8), ~~Day 182~~ ***Week 26*** (Visit 9)***, Week 39 (Visit 10), and Week 52 (Visit 11)*** or Early Termination, at the follow-up visit, and if clinically indicated at any other time.	Revised to reflect updated number of study visits at which HCG urine tests are performed.
Section 7.5 (Other sections affected by this change: Table 2)		
Vital signs will be measured at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), Day 182 (Visit 9) or Early Termination, and at the follow-up visit. Vital signs include the following: pulse, blood pressure (supine and standing), body temperature.	Vital signs will be measured at screening (Visit 0), baseline (Visit 1), ~~Day 14~~ ***Week 2*** (Visit 2), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 42~~ ***Week 6*** (Visit 4), ~~Day 56~~ ***Week 8*** (Visit 5), ~~Day 84~~ ***Week 12*** (Visit 6), ~~Day 112~~***Week 16*** (Visit 7), ~~Day 140~~ ***Week 20*** (Visit 8), ~~Day 182~~ ***Week 26*** (Visit 9)***, Week 39 (Visit 10), Week 52 (Visit 11)*** or Early Termination, and at the follow-up visit. Vital signs include the following: pulse, blood pressure (supine and standing), body temperature.	Revised to reflect updated number of study visits at which vital signs are assessed.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 7.6 (Other sections affected by this change: Table 2)		
ECGs will be performed in triplicate prior to dosing on site and 1 to 2 hours after dosing on site at Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8). On Day 182 (Visit 9) or Early Termination, a triplicate ECG will be performed before the morning dose. At the discretion of the investigator, 12-lead ECG measurements can also be performed on Day 56 (Visit 5) where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.	ECGs will be performed in triplicate prior to dosing on site and 1 to 2 hours after dosing on site at ~~Day 14~~ ***Week 2*** (Visit 2), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 42~~ ***Week 6*** (Visit 4), ~~Day 84~~ ***Week 12*** (Visit 6), ~~Day 112~~ ***Week 16*** (Visit 7), ~~Day 140~~ ***Week 20*** (Visit 8), ***Week 26 (Visit 9), and Week 39 (Visit 10)***. On ~~Day~~ ~~182~~ ***Week 52 (Visit 11)*** or Early Termination, a triplicate ECG will be performed before the morning dose. At the discretion of the investigator, 12-lead ECG measurements can also be performed on ~~Day 56~~ ***Week 8*** (Visit 5) where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.	Revised to reflect updated number of study visits at which ECGs are performed.
Section 7.7 (Other sections affected by this change: Table 2)		
Physical and neurological examinations, including weight, will be performed at screening (Visit 0), baseline (Visit 1), Day 28 (Visit 3), Day 84 (Visit 6), Day 182 (Visit 9) or Early Termination, and at the follow-up visit.	Physical and neurological examinations, including weight, will be performed at screening (Visit 0), baseline (Visit 1), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 84~~ ***Week 12*** (Visit 6), ~~Day 182~~ ***Week 26*** (Visit 9)***, Week 39 (Visit 10), and Week 52 (Visit 11)*** or Early Termination, and at the follow-up visit.	Revised to reflect updated number of study visits at which physical examinations are performed.
Section 7.8.2		
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".[34] The C-SSRS Baseline version will be completed at screening (Visit 0), while the C-SSRS Since Last Visit version will be completed at baseline (Visit 1), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), and Day 182 (Visit 9) or Early Termination. …	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". [34] The C-SSRS Baseline version will be completed at screening (Visit 0), while the C-SSRS Since Last Visit version will be completed at baseline (Visit 1), ~~Day 28~~ ***Week 4*** (Visit 3), ~~Day 42~~ ***Week 6*** (Visit 4), ~~Day 56~~ ***Week 8*** (Visit 5), ~~Day 84~~ ***Week 12*** (Visit 6), ~~Day 112~~ ***Week 16*** (Visit 7), ~~Day 140~~ ***Week 20*** (Visit 8), ~~and Day 182~~ ***Week 26 (Visit 9), Week 39 (Visit 10), and Week 52 (Visit 11)*** or Early Termination. …	Revised to reflect updated number of study visits at which the C-SSRS is performed.

Previous approved wording	Amended or new wording	Reason/Justification for change
8 ASSESSMENT OF PHARMACOKINETICS AND PHARMACOGENOMICS		
Section 8.1.1		
… Titration Period • Day 0 (baseline) – prior and 1 to 2 hours post first dose • Day 14 – 1 to 2 hours post afternoon dose Full Treatment Dose Period • Day 28 – pre afternoon dose and 1 to 2 hours post afternoon dose • Day 42 – pre afternoon dose and 1 to 2 hours post afternoon dose • Day 84 – 1 to 2 hours post afternoon dose • Day 112 – pre afternoon dose and 1 to 2 hours post afternoon dose • Day 140 – 1 to 2 hours post afternoon dose • Day 182 – prior to morning dose • Follow-up visit A total of 13 samples will be drawn from each patient for PK analysis.	… Titration Period • ~~Day 0 (~~baseline~~)~~ – prior and 1 to 2 hours post first dose • ~~Day 14~~ ***Week 2*** – 1 to 2 hours post afternoon dose Full Treatment Dose Period • ~~Day 28~~ ***Week 4*** – pre afternoon dose and 1 to 2 hours post afternoon dose • ~~Day 42~~ ***Week 6*** – pre afternoon dose and 1 to 2 hours post afternoon dose • ~~Day 84~~ ***Week 12*** – 1 to 2 hours post afternoon dose • ~~Day 112~~ ***Week 16*** – pre afternoon dose and 1 to 2 hours post afternoon dose • ~~Day 140~~ ***Week 20*** – 1 to 2 hours post afternoon dose • ~~Day 182~~ ***Week 26*** – ***prior to the afternoon dose*** ~~prior to morning dose~~ • ***Week 52 – prior to morning dose*** • Follow-up visit ***(Week 54)*** A total of ~~13~~ ***14*** samples will be drawn from each patient for PK analysis.	Revised to reflect updated time points and number of PK samples collected.
9 STATISTICS		
Section 9.1 (Other sections affected by this change: 3.3)		
This is a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of pridopidine treatment in patients with HD. Patients will be randomly assigned to receive treatment with pridopidine at a dosage of 45, 67.5, 90, or 112.5 mg bid or a matching placebo in a 1:1:1:1:1 ratio. Randomization will be as described in Section 3.3.	This is a double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of pridopidine treatment in patients with HD. Patients will be randomly assigned to receive treatment with pridopidine at a dosage of 45, 67.5, 90, or 112.5 mg bid or a matching placebo in a 1:1:1:1:1 ratio. Randomization will be as described in Section 3.3. ***The duration of the first study period is 26 weeks and the primary and secondary efficacy analyses will be performed at week 26. Patients that are continuing to the second study period (after week 26 and up to week 52) will continue to receive the same treatment as they were randomized to at baseline of the first study period. All endpoints evaluation at week 52 will be for exploratory purposes.***	New text for clarification regarding blinding and statistical analysis following the extension of the study to 52 weeks.

Previous approved wording	Amended or new wording	Reason/Justification for change
	After the data base is cleaned and locked for the analysis of the first 26-week study period and treatment assignment are revealed, only the clinical programmer, the study statistician, a statistician not assigned to the study that is responsible for reviewing the randomization code and the designated Clinical Supplies Chain and designated Pharmacovigilance personnel will be exposed to the individual patients' treatment assignments. The sponsor study core team that works on the study report and/or design of additional studies and upper management will not be exposed to individual patients' treatment assignments and only be exposed to data summaries by treatments. The investigators, the patient, and any other personnel involved in patients' assessment, monitoring, analysis, and data management are blinded to the patient assignment until the database is locked for analysis of the week 52 data. A detailed procedure that will be taken for maintaining the blinding of the study up to week 52, will be specified before the treatment assignment are revealed for analysis of the first 26-week study period. This procedure will include a list of people that are allowed to be exposed to data summaries by treatments.	
Section 9.2		
It is estimated that approximately 80 patients per arm will enable a power of 84% to detect a beneficial effect of 4.0 points or more in the change from baseline in UHDRS-TMS of an active pridopidine arm compared to placebo, assuming SD of 8.5 (as estimated from the MermaiHD [ACR16C008] study) and type I error of 5%.	It is estimated that approximately 80 patients per arm will enable a power of 84% to detect a beneficial effect of 4.0 points or more in the change from baseline in UHDRS-TMS of an active pridopidine arm compared to placebo ***at week 26***, assuming SD of 8.5 (as estimated from the MermaiHD [ACR16C008] study) and type I error of 5%.	Clarification that the primary endpoint is the change from baseline at Week 26.
Section 9.3.		
(Not applicable)	Creation of two subheadings 9.3.1 [Analysis Sets/Populations for the First Study Period (26 Weeks)] and 9.3.2 [Analysis Sets/Populations for the Second Study Period (52 Weeks)].	To differentiate and define the population sets used to analyze the data from the first and second study periods, respectively.
Section 9.3.1		
9.3.1 Intent-to-Treat Population The intent-to-treat (ITT) population will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were	***9.3.1.1*** **Intent-to-Treat Population *(ITT)*** The intent-to-treat (ITT) population will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which	Definition and clarification of the population sets used to analyze the data from the first study period.

Previous approved wording	Amended or new wording	Reason/Justification for change
randomized, regardless of which treatment they actually received. **9.3.2 Safety Population** The safety population will include all randomized patients who receive at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually receive, regardless of the treatment to which they were randomized. **9.3.3 Pharmacokinetic Population** The PK population will include all randomized patients who received at least 1 dose of study drug and had sufficient plasma concentration results available to allow the intended PK analysis. Patients will be assigned to the treatment actually received regardless of the treatment assignment. **9.3.4 Full Analysis Set (FAS)** The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment. For patients that discontinue study drug, the FAS will include all efficacy observations that were measured under study drug and the closest next available single observation measured after study drug discontinuation. All other efficacy observations measured after study drug discontinuation will be excluded from the full analysis set, for these patients. **9.3.5 Follow-Up Analysis Set (FUAS)** The Follow-Up Analysis Set (FUAS) 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. **9.3.6 Completers Analysis Set** The completers analysis set will include all patients in the ITT population who completed the study.	treatment they actually received. ***The ITT analysis set will include efficacy observations that were measured up to week 26.*** ***9.3.1.2*** **Safety Population *(SP)*** The safety population ***(SP)*** will include all randomized patients who receive at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually received, regardless of the treatment to which they were randomized. ***The SP analysis set will include safety observations that were measured up to week 26.*** ***9.3.1.3*** Pharmacokinetic Population ***(PK)*** The ***pharmacokinetic population*** (PK) will include all randomized patients who received at least 1 dose of study drug and had sufficient plasma concentration results available to allow the intended PK analysis. Patients will be assigned to the treatment actually received regardless of the treatment assignment. ***The PK analysis set will include observations that were measured up to week 26.*** ***9.3.1.4*** Full Analysis Set (FAS) The full analysis set (FAS) will include all patients in the ITT population who received at least 1 dose of study drug and have at least 1 post baseline efficacy assessment. ***The FAS analysis set will include efficacy observations that were measured up to week 26.*** ~~For patients that discontinue study drug, the FAS will include all efficacy observations that were measured under study drug and the closest next available single observation measured after study drug discontinuation. All other efficacy observations measured after study drug discontinuation will be excluded from the full analysis set, for these patients.~~ **9.3.1.5 *Full Analysis Set On Study Drug ~~Follow-Up Analysis Set (FUAS~~FASOD)*** ~~The Follow-Up Analysis Set (FUAS) 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.~~ ***The full analysis set on study drug (FASOD) will include all***	

Previous approved wording	Amended or new wording	Reason/Justification for change
	patients in the ITT population who received at least 1 dose of study drug and have at least 1 post baseline efficacy assessment. The FASOD analysis set will include efficacy observations that were measured up to week 26 and for patients that discontinue study drug, the FASOD will include all efficacy observations that were measured under study drug. All other efficacy observations measured after study drug discontinuation will be excluded from the FASOD analysis set. **9.3.1.6 Completers Analysis Set *(CO)*** The completers analysis set ***(CO)*** will include all patients in the ITT population who completed ~~the study~~ ***all visits up to week 26. The CO analysis set will include observations that were measured up to week 26.***	
Section 9.3.2		
(Not applicable)	***9.3.3.1 Intent-to-Treat Population for the 52 weeks Analyses (ITT2)*** ***The Intent-to-Treat Population for the 52 weeks analyses (ITT2) will include all randomized patients. In this population, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. The ITT2 analysis set will include efficacy observations that were measured up to week 54.*** ***9.3.3.2 Safety Population for the 52 weeks Analyses (SP2)*** ***The safety population for the 52 weeks analyses (SP2) will include all randomized patients who received at least 1 dose of study drug. In this population, treatment will be assigned based upon the treatment patients actually received, regardless of the treatment to which they were randomized. The SP2 will include safety observations that were measured up to week 54.*** ***9.3.3.3 Pharmacokinetic Population for the 52 weeks Analyses (PK2)*** ***The Pharmacokinetic Population for the 52 weeks Analyses PK2 population will include all randomized patients who received at least 1 dose of study drug and had sufficient plasma concentration results available to allow the intended PK analysis. Patients will be assigned to the treatment actually received***	New text added to define the population sets that will be used to analyze the data from the second study period.

Previous approved wording	Amended or new wording	Reason/Justification for change
	regardless of the treatment assignment. The PK2 analysis set will include observations that were measured up to week 52. ***9.3.3.4 Full Analysis Set for the 52 weeks Analyses (FAS2)*** ***The full analysis set for the 52 weeks analyses (FAS2) will include all patients in the ITT2 population who received at least 1 dose of study drug and have at least 1 post baseline efficacy assessment. The FAS2 analysis set will include efficacy observations that were measured up to week 54.***	
Section 9.4		
For all variables, only the observed data from the patients will be used in the statistical analyses. Repeated measures models will be used to estimate treatment effects at the end of the double blind treatment.	For all variables, only the observed data from the patients will be used in the statistical analyses. Repeated measures models will be used to estimate treatment effects at ~~the end of the double blind treatment~~ ***weeks 26 and 52.***	Clarification of data analysis time points.
Section 9.5		
9.5 Study Population The ITT population will be used for all study population summaries unless otherwise noted. Summaries will be presented by treatment group and for all patients. The Safety population will be used for safety variables. The FAS will be used for efficacy variables. The FUAS will be used for efficacy variables sensitivity analyses. The primary efficacy variable will be analyzed also in the Completers analysis set.	**9.5 Study Populations** The ITT ***and ITT2*** populations will be used for all study population summaries ***for the 26 and 52-week analyses respectively*** unless otherwise noted. Summaries will be presented by treatment group and for all patients ***with available data***. The ~~Safety population~~ ***SP and SP2 analyses sets*** will be used for safety variables ***for the 26 and 52-week analyses respectively***. The FAS ***and FAS2 analyses sets*** will be used for efficacy variables ***for the 26 and 52-week analyses respectively***. ~~The FUAS will be used for efficacy variables sensitivity analyses.~~ The primary efficacy variable ***at week 26*** will be analyzed also in the Completers ***and FASOD*** analysis set***s***. ***The secondary efficacy variable at week 26 will be analyzed also in the FASOD analysis set.***	Section updated to clarify and explain the analysis sets for the variables in the study periods.
Section 9.6 (Other sections affected by this change: 3.2)		
(Not applicable)	***The primary and secondary efficacy endpoints will be evaluated at week 26.*** ***Other efficacy endpoints will be evaluated at week 26 and week 52***	New text to clarify endpoint evaluation.

Previous approved wording	Amended or new wording	Reason/Justification for change
	and will be performed for exploratory purposes.	
Section 9.6.4		
The FAS (see Section 9.3.4) will be used for all efficacy analyses. Summaries will be presented by treatment group	The FAS ***and FAS2*** (see Section ~~9.3.4~~ ***9.3.1.4 and Section 9.3.2.4***) will be used for all ***the 26 and 52-week*** efficacy analyses ***respectively***. Summaries will be presented by treatment group.	Clarification regarding analysis sets for efficacy analysis of both study periods.
Section 9.6.4.1		
... The change from baseline in UHDRS-TMS will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). ...	***...*** ***The primary efficacy endpoint analysis will be performed on the FAS analysis set that includes efficacy observations measured up to week 26.*** The change from baseline in UHDRS-TMS ***up to week 26*** will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). ...	Clarification regarding primary efficacy variable analysis.
Section 9.6.4.2		
Additional sensitivity analysis will be performed for change from baseline in UHDRS-TMS on the FUAS population, including efficacy observations measured after study drug discontinuation.	Additional sensitivity analysis will be performed for change from baseline in UHDRS-TMS on the ~~FUAS~~ ***completers and FASOD*** ~~population~~ ***analysis sets***~~, including efficacy observations measured after study drug discontinuation.~~	Clarification regarding sensitivity analysis.
Section 9.6.4.3		
… The change from baseline in mPPT will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). …	… ***The secondary efficacy endpoint analysis will be performed on the FAS analysis set that includes efficacy observations measured up to week 26.*** The change from baseline in mPPT ***up to week 26*** will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). …	Clarification regarding secondary efficacy variable analysis.
Section 9.6.4.4		
The change from baseline in HD-QoL and in EQ5D-5L at week 26/Early Termination will be analyzed using an Analysis of Covariance (ANCOVA) Model. The model will include the following fixed effects: treatment, center, neuroleptic use or no use, and baseline HD-QoL or EQ5D-5L score. The last observation carried forward (LOCF) will be applied for these endpoints for early terminated subjects.	... The change from baseline in HD-QoL and in EQ5D-5L at week 26~~/Early Termination~~ ***and week 52/Early Termination*** will be analyzed using an Analysis of Covariance (ANCOVA) Model. The model will include the following fixed effects: treatment, center, neuroleptic use or no use, and baseline HD-QoL or EQ5D-5L score. The last observation carried forward (LOCF) will be applied for	Clarification regarding other efficacy variable (HD-QoL and EQ5D-5L) analysis.

Previous approved wording	Amended or new wording	Reason/Justification for change
	these endpoints for early terminated subjects. ...	
Section 9.10		
(Not applicable)	***9. 10 Pharmacokinetic and Pharmacodynamic Analyses*** ***Pharmacokinetic and pharmacodynamic data (selected efficacy and safety parameters) will be included in population analyses. Details of these analyses will be reported separately.***	Newly added section regarding pharmacokinetic and pharmacodynamics analyses. Consequently, the numbering of the two subsequent headings in this section has changed.
11 QUALITY CONTROL AND QUALITY ASSURANCE		
Section 11.4		
(Not applicable)	***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 clinical.productcomplaints@tevapharm.com within 48 hours of becoming aware of the issue.***	New subsection added per regulatory authority request and change in Sponsor template.

Previous approved wording	Amended or new wording	Reason/Justification for change
	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 serious adverse event 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***	

Previous approved wording	Amended or new wording	Reason/Justification for change
	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 serious adverse event 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 serious adverse event, 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.***	
REFERENCES (Other sections affected by this change: 1.4.5; 1.5.2)		
19. Exploratory Population Pharmacokinetic Modeling and Simulations With Pridopidine (Report Number: CP-13-013). Pharsight Consulting Services, 10 July 2013.	~~19. Exploratory Population Pharmacokinetic Modeling and Simulations With Pridopidine (Report Number: CP-13-013). Pharsight Consulting Services, 10 July 2013.~~	This report was deleted from reference list and referenced as a footnote within the text.

16.5. PROTOCOL AMENDMENT 03 DATED 16 SEPTEMBER 2014

The revisions listed below have been made to the protocol, and synopsis as appropriate, and are considered substantial by the sponsor's Authorized Representative.

The primary reasons for this amendment are 1) the extension of the period between screening and baseline visit to 12 weeks, to allow a switch in concomitant drugs if deemed medically justified and for the benefit of the patient by the investigator, and 2) modification of the inclusion criterion f, to allow patients with an independence score of 90 to enter the study. Modifications to some inclusion and exclusion criteria have been made as result of this change. Also, clarifications regarding various aspects of study conduct have been introduced.

Substantive changes from Amendment 02 to Amendment 03 are provided below.

Previous text is presented in the column titled "Previous approved wording"; revised or new text is presented in bold italics and deletions are struck through in the column titled "Amended or new wording" and the reason or justification for the change is presented in the column titled "Reason/Justification for change". If text was relocated within the same section of the protocol but was not revised, the change is not shown in the comparison table**.**

Changes previously notified in administrative letters issued following the distribution of protocol TV7820-CNS-20002 Amendment 02 have also been included.

Previous approved wording	Amended or new wording	Reason/Justification for change
CLINICAL STUDY PERSONNEL CONTACT INFORMATION		
EU Sites: Dr. Marianne Giuffra (Located in Germany) Office Phone (between 9-5pm CET): +49 6103 904-1760 24/7 Hotline: Phone No.: +49 6103 904-1953 e-mail: marianne.giuffra@iconplc.com Australian Sites: Dr. Romillie Cruz (Located in Singapore) Cell Phone: +65 6895-8256 24/7 Hotline Phone No: +65 6896-0378 e-mail: Romillie.Cruz@iconplc.com US and Canadian Sites: Dr. Ricardo Nunez (Located in the US) Office Phone (between 9-5 EST): +1 215 616 5089 24/7 Hotline Phone No: +1 888-723-9952 e-mail: Ricardo.Nunez@iconplc.com	EU Sites: ~~Dr.~~ Marianne Giuffra, ***MD*** (Located in Germany) Office Phone (between 9-5pm CET): +49 6103 904-1760 24/7 Hotline: Phone No.: +49 6103 904-1953 e-mail: marianne.giuffra@iconplc.com Australian Sites: ~~Dr. Romillie Cruz~~ ~~(Located in Singapore)~~ ~~Cell Phone: +65 6895-8256~~ ~~24/7 Hotline Phone No: +65 6896-0378~~ ~~e-mail: Romillie.Cruz@iconplc.com~~ ***Jerome Gonzaga, MD*** ***(Located in the Philippines)*** ***Office Phone: +63 2 230 5701*** ***Cell Phone: +63 917 537 3862*** ***24/7 Hotline Phone No: +65 6896-0378*** ***e-mail: Jerome.Gonzaga@iconplc.com*** US and Canadian Sites: ~~Dr. Ricardo Nunez~~ ~~(Located in the US)~~ ~~Office Phone (between 9-5 EST): +1 215 616 5089~~ ~~24/7 Hotline Phone No: +1 888-723-9952~~ ~~e-mail: Ricardo.Nunez@iconplc.com~~ ***Margaret Zalewski, MD*** ***(Located in the East Coast of US)*** ***Office Phone (between 9-5ET): +215 616 4969*** ***24/7 Hotline Phone No: +1 888-723-9952*** ***e-mail: Margaret.Zalewski@iconplc.com*** ***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 ICON Call-Center: Telephone: +1 919 674 5468***	Contact details for medical issues updated.

Previous approved wording	Amended or new wording	Reason/Justification for change
	[Toll (not free of charge) telephone number allowing a global reach from both landlines and mobile phones] ***On the following internet page (https://icophone.iconplc.com), 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.***	
Netherlands: dso.nl@tevapharmachemie.com	Netherlands: ~~dso.nl@tevapharmachemie.com~~ ***dso.nl@Tevanederland.com***	Updated contact details for Netherlands address for notifications of SAEs.
1 BACKGROUND INFORMATION		
Section 1.7 (Other sections affected by this change: 3.1		
The study population will consist of male or female patients aged ≥21 years and with body weight ≥50 kg, with HD diagnoses obtained with the identification of HD clinical features and confirmed by the presence of ≥36 CAG repeats in the huntingtin gene.	The study population will consist of male or female patients aged ≥21 years and with body weight ≥50 kg, ~~with HD diagnoses obtained with the identification of HD clinical features and confirmed by the presence of ≥36 CAG repeats in the huntingtin gene~~***, with diagnosis of HD based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene.***	Clarification.
3 STUDY DESIGN		
Section 3.1 (Other sections affected by this change: 3.5)		
After having signed an informed consent, including consent to provide a blood sample for genetic analyses, patients will be screened for a period of up to 2 weeks in order to determine whether they are eligible to participate into the study.	After having signed an informed consent, including consent to provide a blood sample for genetic analyses, patients will be screened for a period of up to ~~2~~ ***12*** weeks in order to determine whether they are eligible to participate in the ***study. The investigator should aim to perform the baseline visit as soon as possible after the screening visit.***	Longer period between screening and baseline visit, to allow a switch in concomitant drugs if deemed by the investigator as medically justified and for patient benefit.
Section 3.1 (Other sections affected by this change: 3.11.2; 7.7, Table 2)		
At the baseline visit, before the first dose of study drug, the Clinician's Interview Based Impression of Severity (CIBIS) will be rated by an independent rater, while another qualified	At the baseline visit, before the first dose of study drug, the Clinician's Interview Based Impression of Severity (CIBIS) will be rated by an independent rater, while another qualified site personnel	A full physical and neurological examination has been added at the baseline

Previous approved wording	Amended or new wording	Reason/Justification for change
site personnel will assess the mPPT, the Clinical Global Impression of Severity (CGI-S), the Timed Up and Go (TUG) Test, the Physical Disability Scale (PDS), the UHDRS-TMS, the UHDRS-FA, the UHDRS-IS, the UHDRS Total Functional Capacity (TFC), the CAB (as defined in Section 6.3.10), and the Problem Behaviors Assessment-Short form (PBA-s). The patient will fill the Walk-12 and the HD-Quality of life scale (HD-QoL), the EQ5D, and Q-Motor assessments will be performed. UHDRS-TMS and mPPT should be evaluated prior to the other scales.	will assess the mPPT, the Clinical Global Impression of Severity (CGI-S), the Timed Up and Go (TUG) Test, the Physical Disability Scale (PDS), the UHDRS-TMS, the UHDRS-FA, the UHDRS-IS, the UHDRS Total Functional Capacity (TFC), the CAB (as defined in Section 6.3.10), and the Problem Behaviors Assessment-Short form (PBA-s). ***A full physical and neurological examination, including weight, will be performed.*** The patient will fill the Walk-12 and the HD-Quality of life scale (HD-QoL), the EQ5D, and Q-Motor assessments will be performed. UHDRS-TMS and mPPT should be evaluated prior to the other scales.	visit as the maximum screening period has been extended.
Section 3.1 (Other sections affected by this change: Table 2; 3.11.1; 3.11.3.2.1; 3.11.3.2.3; 3.11.4)		
(Not applicable)	***The procedures and assessments for visits V0 and V4-10 may be performed over several days, as long as they are completed within the defined visit window.***	Clarification regarding performance of study assessments.
Section 3.2.3 (Other sections affected by this change: 9.6.3)		
• CGI-C at Week 26 as compared to baseline (rated by the qualified site personnel and the patient)	• CGI-C at Week 26 as compared to baseline (rated by the qualified site personnel ~~and the patient~~)	Clarification that the patient will not be rating the CGI-C at week 26.
Section 3.5 (Other sections affected by this change: 3.1)		
For each patient, the duration of participation is planned to be up to 30 weeks, consisting of a screening period of up to 2 weeks, a 26-week randomized double-blind treatment period (comprised of a 4-week titration and 22-week full dose period), and a 2-week follow-up period following the last dose of study medication.	For each patient, the duration of participation is planned to be up to ~~30~~ ***40*** weeks, consisting of a screening period of up to ~~2~~ ***12*** weeks, a 26-week randomized double-blind treatment period (comprised of a 4-week titration and 22-week full dose period), and a 2-week follow-up period following the last dose of study medication.	Longer period between screening and baseline visit, to allow a switch in concomitant drugs if deemed by the investigator as medically justified and for patient benefit.
Section 3.6.1		
Patients should be discontinued if any of the following criteria relating to QTcF are met: • QTcF >500 msec (based on the mean value from the triplicate ECG measurements); • QTcF >480 msec with concurrent increase in QTcF >60 msec (ΔQTcF, based on the mean value from the triplicate ECG measurements) from baseline (Day 0);	Patients should be discontinued if any of the following criteria relating to QTcF are met ***at any visit***: • QTcF >500 msec (based on the mean value from the triplicate ECG measurements); • QTcF >480 msec with concurrent increase in QTcF >60 msec (ΔQTcF, based on the mean value from the triplicate ECG measurements) from baseline (Day 0); • If QTcF >480 msec or ΔQTcF >60 msec, a repeat	Clarification regarding discontinuation of patients due to QTcF prolongation.

Previous approved wording	Amended or new wording	Reason/Justification for change
• If QTcF >480 msec or ΔQTcF >60 msec, a repeat ECG (in triplicate) will be recorded after 7 to 9 days; if the change is confirmed and electrolytes are normal, the patient will be withdrawn.	ECG (in triplicate) will be recorded after 7 to 9 days; if the change is confirmed and electrolytes are normal, the patient will be withdrawn.	
Section 3.6.3		
(Not applicable)	***3.6.3 Temporary Study Drug Discontinuation*** ***Temporary discontinuation is defined as missing more than 5 consecutive days of the study drug.*** ***The subject 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 electronic Case Report Form (eCRF) and the local clinical management (LCM) should be notified.*** ***Patients who are off drug for less than 5 days can resume IP at the same dose they were taking prior to the drug discontinuation. No titration will be required for these patients.*** ***Patients who are off drug for 5 days or more will be required to titrate again. Patients requiring titration will either repeat the week 3 and 4 titration or they will repeat the week 2, 3, and 4 from the beginning of the study (see Table 1). Sites should discuss the patient status with the Medical Monitor prior to dispensing a titration kit. The investigator and Medical Monitor will decide which titration kits the patient should be dispensed based off the reason for discontinuation of study drug, the patient's medical history, and the patient's tolerability during the initial study drug titration. The IVRS will be updated to dispense the titration kit when requested by the site.*** ***If a patient is off drug for more than 14 days, he/she will not restart study drug treatment. He/she will be asked to continue in***	New subheading and text added to provide instruction on how patients who temporarily discontinue study drug should resume dosage.

Previous approved wording	Amended or new wording	Reason/Justification for change
	the study and follow the visit schedule as outlined in the protocol. If a patient requires more than 1 titration between week 5 and 26 of the study, he/she will not restart study drug treatment. He/she will be asked to continue in the study and follow the visit schedule as outlined in the protocol.	
Section 3.8		
For an SAE considered related (ie, reasonable possibility; see Section 7.1.4) to the study drug, the sponsor's Pharmacovigilance Department may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, the investigator will remain blinded to treatment but the sponsor's clinical project physician/clinical leader may be unblinded to treatment in order to decide on the action taken as described in Section 3.6.	For an SAE considered related (ie, reasonable possibility; see Section 7.1.4) to the study drug, the sponsor's Pharmacovigilance Department may independently request that the treatment code be revealed (on a case-by-case basis). If this occurs, the investigator will remain blinded to treatment ~~but the sponsor's clinical project physician/clinical leader may be unblinded to treatment in order to decide on the action taken as described in Section 3.6~~.	Clarification regarding revealing of treatment codes in case of a related SAE.
In the event of an emergency, if it is necessary to know what treatment a specific patient has received, the investigator may determine the patient's treatment using IRT, after consulting the sponsor. In an extreme emergency, if the investigator is unable to contact the sponsor, the investigator may determine the patient's treatment using IRT without prior authorization. When this occurs, the investigator must contact the individual identified in the clinical study personnel contact information section of this protocol immediately; the patient will be withdrawn from the study, and the event will be recorded on the study completion record. Proper documentation must be maintained when a treatment code is revealed.	~~In the event of an emergency, if it is necessary to know what treatment a specific patient has received, the investigator may determine the patient's treatment using IRT, after consulting the sponsor. In an extreme emergency, if the investigator is unable to contact the sponsor, the investigator may determine the patient's treatment using IRT without prior authorization. When this occurs, the investigator must contact the individual identified in the clinical study personnel contact information section of this protocol immediately; the patient will be withdrawn from the study, and the event will be recorded on the study completion record. Proper documentation must be maintained when a treatment code is revealed.~~ ***In case of a serious adverse event, pregnancy, or in cases when knowledge of the study drug assignment is needed to make treatment decisions, the investigator may unblind the patient's drug assignment as deemed necessary, mainly in emergency situations. Individual treatment codes, indicating the treatment randomization for each randomized patients, will be available to the investigator(s) or pharmacists at the study center via the IRT, both via telephone or internet.*** ***Breaking of the treatment code can be performed by the site without prior approval by the sponsor. If time allows,***	This section has been revised following input from health authorities to clearly describe that the investigator can unblind the treatment code in an emergency situation without prior approval of the sponsor.

Previous approved wording	Amended or new wording	Reason/Justification for change
	investigators should consult with the Medical Monitor prior to unblinding a patient. If the code was broken by the investigator, the patient should be discontinued from the study. ***If the treatment code is broken, the investigator should document and notify the sponsor immediately.*** ***The circumstances leading to the breaking of the code should be fully documented, in the investigator's study files and in the patient's source documentation. Treatment assignment should remain confidential and should not be recorded in any study documents or source document.***	
Section 3.10		
The study is expected to start in Q1 2014 (first patient enrolled) and be completed in Q2 2015 (last patient last visit).	The study is expected to start in Q1 2014 (first patient enrolled) and be completed in ~~Q2~~ ***Q3*** 2015 (last patient last visit).	Slower recruitment than originally projected.
Section 3.11 – Table 2 (Other sections affected by this change: 3.1; 3.11.1)		
Days of screening are listed as -14 to -1.	Days of screening changed to a maximum of 12 weeks.	Longer period between screening and baseline visit.
Section 3.11 – Table 2 (Other sections affected by this change: 3.11.3.1.1)		
TC performed on Day 6 and Day 20.	TC performed on Day 6***±3*** days and on Day 20***±3 days.***	Window of ±3days was added to the TC visits.
Section 3.11 – Table 2 (Other sections affected by this change: 3.1; 3.11.2, 7.7)		
Full physical and neurological examination, including weight, performed at screening (V0), week 4 (V3), week 12 (V6), week 26/early termination (V9) and follow up.	Full physical and neurological examination, including weight, performed at screening (V0), ***baseline (V1);*** week 4 (V3), week 12 (V6), week 26/early termination (V9) and follow up.	A full physical and neurological examination has been added at the baseline visit, as the maximum screening period has been extended.
Section 3.11 – Table 2 (Other sections affected by this change: 3.1; 3.11.1; 3.11.3.2.1-3.11.3.2.3; 3.11.4)		
(Not applicable)	a. The procedures and assessments for these visits (V0 and V4-10) may be performed over several days, as long as they are completed within the defined visit window.	New footnote; Clarification regarding performance of study assessments. Consequently all footnote letters have changed due to the addition of this new footnote.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 3.11 – Table 2 (Other sections affected by this change: 3.11.3.2.1)		
g. ECG is optional on Day 56, to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.	h. ECG is optional on Day 56, ***unless required by local regulations. It is*** to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.	Footnote updated for clarification regarding ECG performance on Day 56. Footnote letter changed due to addition of the new footnote "a".
Section 3.11.1		
Results of mandatory testing of the CAG trinucleotide repeat length in the huntingtin gene and CYP2D6 genotype will be recorded for all patients who have given written informed consent.	~~Results of mandatory~~ t***T***esting of the CAG trinucleotide repeat length in the huntingtin gene and CYP2D6 genotype will be ~~recorded~~ ***done*** for all patients who have given written informed consent.	Clarification regarding CAG testing.
A patient who is screened and does not meet study entry criteria will not be considered for screening again.	~~A patient who is screened and does not meet study entry criteria will not be considered for screening again.~~ ***A patient who is screened but not randomized, eg, because enrollment did not occur within the specified time, or other logistical or operational issues occurred, may be considered for screening again.*** ***Re-screening will be permitted on a case by case basis. A new informed consent form should be signed in any case of re-screening, and screening procedures should be repeated. A new Subject Number will be assigned to the subject.***	The possibility of re-screening due to operational issues has been introduced.
The screening visit (Visit 0) will take place not more than 2 weeks before the baseline visit.	The screening visit (Visit 0) will take place not more than ~~2~~ ***12*** weeks before the baseline visit. ***However, the investigator should aim to perform the baseline visit as soon as possible after the screening visit.***	Longer period between screening and baseline visit.
(Not applicable)	***The procedures and assessments for the screening visit may be performed over several days, as long as they are completed within the defined time period.***	Clarification regarding performance of screening procedures.
Section 3.11.2 (Other sections affected by this change: 3.1; 7.7, Table 2)		
The following procedures will be performed at Baseline before the first dose on site: • review inclusion/exclusion criteria • vital signs measurements • inquire about AEs	The following procedures will be performed at Baseline before the first dose on site: • review inclusion/exclusion criteria • vital signs measurements • inquire about AEs	Since the screening period has been extended, a full physical and neurological examination has been added at baseline.

Previous approved wording	Amended or new wording	Reason/Justification for change
• inquire about concomitant medication • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis) • urine pregnancy test for women of child-bearing potential only ….	• inquire about concomitant medication • ***full physical and neurological examination (including weight)*** • ~~clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)~~ • urine pregnancy test for women of child-bearing potential only ….	The clinical laboratory tests will be performed post-dose.
The following procedures will be performed at the Baseline visit following administration of the first dose on site: • 12-lead ECG in triplicate (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest) • obtain a 4-mL blood sample for plasma drug assay (1 to 2 hours after dose administration); samples will be collected as close as possible to, but after the ECG recording.	The following procedures will be performed at the Baseline visit following administration of the first dose on site: • 12-lead ECG in triplicate (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest) • ***clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)*** • obtain a 4-mL blood sample for plasma drug assay (1 to 2 hours after dose administration); samples will be collected as close as possible to, but after the ECG recording.	As it is an unnecessary burden for the patient to have blood drawn twice per visit (both pre-dose for clinical labs, and post-dose for PK), this has been changed. Clinical labs should not change post-dose, and results from those labs are not required for dosing; hence, they can be drawn in conjunction with the PK samples.
Section 3.11.3.1.1		
Patients will be contacted by telephone on Days 6 and 20 to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage, and to allow the weekly dose increase during the titration period (see Section 3.4.1.1) that will take place on the following day (if applicable).	Patients will be contacted by telephone on Days 6 ***(± 3days)*** and 20 6 ***(± 3days)*** to evaluate tolerability to the study drug through assessment of AEs and concomitant medication usage, and to allow the weekly dose increase during the titration period (see Section 3.4.1.1) that will take place on the following day (if applicable).	Window of ±3days was added to the TC visits.
Section 3.11.3.1.2		
<u>Before Afternoon Dosing:</u> • AE inquiry • concomitant medication review • clinical laboratory tests (electrolytes only) • vital signs measurements • collect/dispense study drug	<u>Before Afternoon Dosing:</u> • AE inquiry • concomitant medication review • ***triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest)***	Clarification that a triplicate ECG will be performed before the afternoon dose at the visit, as described in section 7.6 and in Table 2. The clinical laboratory tests

Previous approved wording	Amended or new wording	Reason/Justification for change
• study compliance review	• ~~clinical laboratory tests (electrolytes only)~~ • vital signs measurements • collect/dispense study drug • study compliance review	will be performed post-dose.
<u>Following Afternoon Dosing:</u> • triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest) • obtain a 4-mL blood sample for plasma drug assay 1 to 2 hours after dose administration; PK samples will be collected as close as possible to, but after the ECG recording.	<u>Following Afternoon Dosing:</u> • triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest) • ***clinical laboratory tests (electrolytes only)*** • obtain a 4-mL blood sample for plasma drug assay 1 to 2 hours after dose administration; PK samples will be collected as close as possible to, but after the ECG recording.	As it is an unnecessary burden for the patient to have blood drawn twice per visit (both pre-dose for clinical labs, and post-dose for PK), this has been changed. Clinical labs should not change post-dose, and results from those labs are not required for dosing; hence, they can be drawn in conjunction with the PK samples.
Section 3.11.3.2.1 (Other sections affected by this change: Table 2)		
<u>Before Afternoon Dosing:</u> • AE inquiry • concomitant medication review • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis) • Days 28, 56, 84, 112, and 140 only: urine pregnancy test for women of child-bearing potential only • Days 28 and 84 only: full physical and neurological examination (including weight) • triplicate 12-lead ECG (performed after at least 5 minutes of supine rest) (Note: ECG is optional on Day 56, to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT	<u>Before Afternoon Dosing:</u> • AE inquiry • concomitant medication review • ~~clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)~~ • Days 28, 56, 84, 112, and 140 only: urine pregnancy test for women of child-bearing potential only • Days 28 and 84 only: full physical and neurological examination (including weight) • triplicate 12-lead ECG (performed after at least 5 minutes of supine rest) (Note: ECG is optional on Day 56, ***unless required by local regulations. It is*** to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation)	Updated for clarification regarding ECG performance on Day 56. The clinical laboratory tests will be performed post-dose.

Previous approved wording	Amended or new wording	Reason/Justification for change
prolongation) • vital signs measurements • C-SSRS (since last visit version) • Days 28, 42, and 112 only: obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording) • Days 28, 56, 84, 112, and 140 only: collect/dispense study drug • study compliance review	• vital signs measurements • C-SSRS (since last visit version) • Days 28, 42, and 112 only: obtain a 4-mL blood sample for plasma drug assay (as close as possible to, but after the ECG recording) • Days 28, 56, 84, 112, and 140 only: collect/dispense study drug • study compliance review	
Following Afternoon Dosing: • triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest) (Note: ECG is optional on Day 56, to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation) • Days 28, 42, 84, 112, and 140 only: obtain a 4-mL blood sample for plasma drug assay 1 to 2 hours after dose administration; PK samples will be collected as close as possible to, but after the ECG recording.	Following Afternoon Dosing: • triplicate 12-lead ECG (1 to 2 hours after dose administration) (performed after at least 5 minutes of supine rest) (Note: ECG is optional on Day 56, ***unless required by local regulations. It is*** to be performed at the investigator's discretion where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation) • ***clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)*** • Days 28, 42, 84, 112, and 140 only: obtain a 4-mL blood sample for plasma drug assay 1 to 2 hours after dose administration; PK samples will be collected as close as possible to, but after the ECG recording.	Updated for clarification regarding ECG performance on Day 56. The clinical laboratory tests will be performed post-dose.
(Not applicable)	***The procedures and assessments for Visits 4-8 may be performed over several days, as long as they are completed within the defined visit window (±5 days for Visits 4 and 5; ±7 days for Visits 6-8).***	Clarification regarding performance of procedures for Visits 4-8.
Section 3.11.3.2.3 (Other sections affected by this change: 3.11.4)		
(New text)	***The procedures and assessments for this visit may be performed over several days, as long as they are completed within the defined visit window (±7 days).***	Clarification regarding performance of procedures for Visits 9-10.
4 SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.1		
f. UHDRS-IS score below 90% at the screening visit.	f. UHDRS-IS score ~~below~~ ***equal to or less than*** 90% at the screening visit.	Updated to include also patients with an IS of 90%.

Previous approved wording	Amended or new wording	Reason/Justification for change
l. For patients taking allowed antipsychotic, antidepressant or other psychotropic medication, the dosing of medication must have been kept constant for at least 6 weeks before screening and must be kept constant during the study.	l. For patients taking allowed antipsychotic, antidepressant or other psychotropic medication, the dosing of medication must have been kept constant for at least 6 weeks before ~~screening~~ ***baseline*** and must be kept constant during the study.	Updated time frame of required stable dose.
Section 4.2		
a. A prolonged QTcF interval (defined as a QTcF interval of >450 msec) at the screening or baseline visit. If there is evidence of a prolonged QTcF interval at screening from the initial (single) measurement, then the electrocardiogram (ECG) will be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study.	a. A prolonged QTcF interval (defined as a QTcF interval of >450 msec) at the screening ~~or baseline~~ visit. If there is evidence of a prolonged QTcF interval at screening from the initial (single) measurement, then the electrocardiogram (ECG) will be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study.	Prolonged QTcF omitted from baseline visit as an eligibility criterion. Prolonged QT at baseline will be handled according to discontinuation rules.
f. Patients with serum potassium, magnesium and/or calcium levels outside of the central laboratory's reference range at the screening visit. Repeat testing is allowed (up to a maximum of 3 tests) if required to establish if values are within normal range.	f. 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 ~~if values are within normal range~~ ***whether values are within normal range or clinically significantly abnormal***.	Clarification regarding electrolyte exclusion criterion.
g. Patients receiving medications (within the last 6 weeks prior to screening) 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.	g. Patients receiving medications (within the last 6 weeks prior to ~~screening~~ ***baseline***) 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.	Updated time frame for QT-interval prolonging medications.
h. Patients receiving medications (within the last 6 weeks prior to screening) that are metabolized by CYP2D6 and have the potential of reducing seizure threshold.	h. Patients receiving medications (within the last 6 weeks prior to ~~screening~~ ***baseline***) that are metabolized by CYP2D6 and have the potential of reducing seizure threshold.	Updated time frame for CYP2D6 metabolized medications.
q. Treatment with tetrabenazine within 6 weeks of study screening.	q. Treatment with tetrabenazine within 6 weeks of study ~~screening~~ ***baseline***.	Updated time frame for treatment with tetrabenazine prior to study.
Section 4.3		
In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study drug at any time. Each investigator also has the right to withdraw a patient from the	In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each patient is free to withdraw from the study drug at any time. Each investigator also has the right to withdraw a patient from the study drug in the event	Reference to liver thresholds and DILI criteria (Section 7.1.1) clinical laboratory tests/ electrolytes (Section

Previous approved wording	Amended or new wording	Reason/Justification for change
study drug in the event of intercurrent illness, AEs, pregnancy (see Section 7.3), 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 drug as described in Sections 3.6, 3.11.5, 5.4, and 7.1.7.	of intercurrent illness, AEs, pregnancy (see Section 7.3), 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 drug as described in Sections 3.6, 3.11.5, 5.4, ***7.1.1*** ~~and~~ 7.1.7, ***7.4 and 7.6***.	7.4) and ECG (Section 7.6) added to section on withdrawal criteria.
5 TREATMENT OF PATIENTS		
Section 5.3.1 (Other sections affected by this change: inclusion criterion l; 5.3.2)		
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 screening and must be kept constant during the study. Allowed antipsychotic medications are olanzapine, quetiapine, thiothixene, acetophenazine, trifluprom azine, loxapine, tiapride, chlorprothixene, and bromperidol. Aripiprazole, risperidone, and perphenazine are permitted, subject to dose reductions (ie, keeping the dose as low as possible). 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), butriptyline, mianserin, moclobemide, tranylcypromine, buspiron, bupropion, reboxetine, and dibenzepin. Fluvoxamine, trimipramine, and mirtazapine are permitted, subject to dose reduction.	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 ~~screening~~ ***baseline*** and must be kept constant during the study. Allowed antipsychotic medications are olanzapine, quetiapine, thiothixene, acetophenazine, trifluprom azine, loxapine, tiapride, chlorprothixene, and bromperidol. Aripiprazole, risperidone, and perphenazine are permitted, ~~subject to dose reductions (ie, keeping the dose as low as possible)~~ ***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), butriptyline, mianserin, moclobemide, tranylcypromine, buspiron, bupropion, reboxetine, and dibenzepin. Fluvoxamine, trimipramine, and mirtazapine are permitted, ~~subject to dose reduction~~ ***at no more than usual recommended doses in the approved labeling***.	Updated time frame of required stable dose. Clarification regarding dosage of allowed antipsychotic and antidepressant medications.
Mexalatine and tocainide are allowed antiarrhythmic medications, subject to dose reduction.	~~Mexalatine~~ ***Mexiletine*** and tocainide are allowed antiarrhythmic medications, ~~subject to dose reduction~~ ***at no more than usual recommended doses in the approved labeling***.	Drug name corrected. Clarification regarding dosage of allowed antiarrhythmic medications.
Section 5.3.2 (Other sections affected by this change: inclusion criterion l; 5.3.1)		
5.3.2.1 Antipsychotic Medication Ziprasidone, clozapine, haloperidol, mesoridazine, thioridazine, pimozide, zuclopenthixol, chlorpromazine,	**5.3.2.1 Antipsychotic Medication** Ziprasidone, clozapine, haloperidol, mesoridazine, thioridazine, pimozide, zuclopenthixol, chlorpromazine, paliperidone,	Updated time frame of required stable dose.

Previous approved wording	Amended or new wording	Reason/Justification for change
paliperidone, iloperidone, fluphenazine, prochlorperazine, trifluoperazine/trifluroperazine, flupentixol, benperidol, amisulpride, and sulpiride are not allowed within 6 weeks of screening (Visit 0) 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 screening (Visit 0) 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 screening (Visit 0) 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 screening (Visit 0) and during the study **5.3.2.5 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 screening (Visit 0) 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.	iloperidone, fluphenazine, prochlorperazine, trifluoperazine/trifluroperazine, flupentixol, benperidol, amisulpride, and sulpiride are not allowed within 6 weeks of ~~screening (Visit 0)~~ ***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 ~~screening (Visit 0)~~ ***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 ~~screening (Visit 0)~~ ***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 ~~screening (Visit 0)~~ ***baseline (Visit 1)*** and during the study **5.3.2.5 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 ~~screening (Visit 0)~~ ***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.	
Section 5.5 (Other sections affected by this change: 8.2)		
The total volume of blood estimated to be collected from each	The total volume of blood estimated to be collected from each	The blood volume has been updated to require 12 mL of blood for PGx testing. Total

<table>
<tr><th>Previous approved wording</th><th>Amended or new wording</th><th>Reason/Justification for change</th></tr>
<tr><td>patient is detailed in Table 3.

Table 3: Total Blood Volume Collected from Each Patient
<table><tr><th>Type of Assessment</th><th>Number of Samples Collected</th><th>Volume per Sample</th><th>Total Volume for Assessment</th></tr><tr><td>Pharmacokinetic</td><td>13</td><td>4 mL</td><td>52 mL</td></tr><tr><td>Serum Chemistry</td><td>11</td><td>10.5 mL</td><td>115.5 mL</td></tr><tr><td>Hematology</td><td>9</td><td>3 mL</td><td>27 mL</td></tr><tr><td>Pharmacogenetic Analyses</td><td>1</td><td>10 mL</td><td>10 mL</td></tr><tr><td>Total</td><td></td><td></td><td>204.5 mL</td></tr></table></td><td>patient is detailed in Table 3.

Table 3: Total Blood Volume Collected from Each Patient
<table><tr><th>Type of Assessment</th><th>Number of Samples Collected</th><th>Volume per Sample</th><th>Total Volume for Assessment</th></tr><tr><td>Pharmacokinetic</td><td>13</td><td>4 mL</td><td>52 mL</td></tr><tr><td>Serum Chemistry</td><td>11</td><td>10.5 mL</td><td>115.5 mL</td></tr><tr><td>Hematology</td><td>9</td><td>3 mL</td><td>27 mL</td></tr><tr><td>Pharmacogenetic Analyses</td><td>1</td><td><s>10</s> 12 mL</td><td><s>10</s> 12 mL</td></tr><tr><td>Total</td><td></td><td></td><td><s>204.5</s> 206.5 mL</td></tr></table></td><td>blood volume has been updated as well.</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td colspan="3">6 ASSESSEMENT OF EFFICACY</td></tr>
<tr><td colspan="3">Section 6.3.1</td></tr>
<tr><td>At each subsequent visit in which the evaluation is performed (Visits 3, 5, 6, 7, 8, and 9), the CIBIC-Plus will be administered by the same independent rater, but without knowledge of other endpoint assessments or the AEs experienced by the patient during the study (so as not to confound the rating of CIBIC-Plus as an efficacy measure or to unblind the study).</td><td>At each subsequent visit in which the evaluation is performed (Visits 3, <s>5,</s> 6, <s>7, 8,</s> and 9), the CIBIC-Plus will be administered by the same independent rater, but without knowledge of other endpoint assessments or the AEs experienced by the patient during the study (so as not to confound the rating of CIBIC-Plus as an efficacy measure or to unblind the study).</td><td>Clarification that the CIBIC-Plus will only be completed at Visits 3, 6 and 9. It will not be completed at visits 5, 7, and 8.</td></tr>
<tr><td colspan="3">Section 6.3.2</td></tr>
<tr><td>The PDS will be used during the study as a measure of disability. Patients are scored on a scale from 10 ("Fixed posture requiring total care - gastrotomy, catheterization") to 100 ("Normal; no disease evident").[24]</td><td>The PDS will be used during the study as a measure of disability. Patients are scored on a scale from 10 ("Fixed posture requiring total care - gastrotomy, catheterization") to 100 ("Normal; no disease evident"). [24] Scores must end in 0 (e.g., 10%, 20% etc).</td><td>Clarification regarding PDS score.</td></tr>
<tr><td colspan="3">Section 6.3.4</td></tr>
<tr><td>CGI-S will be assessed at baseline (Day 0) and CGI-C will be used at all subsequent time points (Visits 3, 5, 6, 7, 8, and 9) to assess changes from baseline.</td><td>CGI-S will be assessed at baseline (Day 0) and CGI-C will be used at all subsequent time points (Visits 3, <s>5,</s> 6, <s>7, 8,</s> and 9) to assess changes from baseline.</td><td>Clarification that the CGI-C will only be completed at Visits 3, 6 and 9. It will not</td></tr>
</table>

Previous approved wording	Amended or new wording	Reason/Justification for change
		be completed at visits 5, 7, and 8.
7 ASSESSMENT OF SAFETY		
Section 7.1.1		
(Not applicable)	***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 him or herself, the patient should be referred for immediate psychiatric evaluation and an AE/SAE should be reported.***	New text regarding reporting of suicidality as an adverse event.
Section 7.1.5.3.1		
Each report of an 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. On the basis of this assessment, a decision will be made concerning the need for further medical intervention.	Each report of an 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. ~~On the basis of this assessment, a decision will be made concerning the need for further medical intervention.~~	Clarification regarding SAE assessment.
Section 7.1.6		
Reporting	**7.1.6 Protocol-Defined Adverse Events for Expedited Reporting** No protocol-defined adverse events for expedited reporting were identified for this study.	This section was previously accidentally omitted.
Section 7.1.9		
If a patient experiences an AE or medical emergency, departures from the protocol may be allowed on a case-by-case basis	**If a patient experiences an AE or medical emergency, ~~departures from the~~** protocol **~~may be allowed on a case-by-case basis~~** *departures from the protocol visit and dosing schedule will not necessarily be considered a reason for withdrawal, and will be considered on a case-by case basis.*	Clarification.
Section 7.5		
Vital signs will be measured at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), Day 182 (Visit 9) or Early Termination, and at the follow-up visit. Vital signs include the following: pulse, blood pressure, body temperature. Before pulse and blood pressure are measured, the patient must be in a supine position and resting for at least 5 minutes. Where applicable, measurements should be taken prior to	Vital signs will be measured at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), Day 182 (Visit 9) or Early Termination, and at the follow-up visit. Vital signs include the following: pulse, blood pressure (supine and standing), body temperature. Before pulse and blood pressure are measured, the patient must be in a supine position and resting for at least 5 minutes. Thereafter, blood pressure should be measured again after standing for 2	Clarification regarding blood pressure measurements during assessment of vital signs.

Previous approved wording	Amended or new wording	Reason/Justification for change
blood being drawn for clinical laboratory evaluations.	minutes. Where applicable, measurements should be taken prior to blood being drawn for clinical laboratory evaluations.	
Section 7.7 (Other sections affected by this change: 3.1; 3.11.2; Table 2)		
Physical and neurological examinations, including weight, will be performed at screening (Visit 0), Day 28 (Visit 3), Day 84 (Visit 6), Day 182 (Visit 9) or Early Termination, and at the follow-up visit.	Physical and neurological examinations, including weight, will be performed at screening (Visit 0), ***baseline (Visit 1)***, Day 28 (Visit 3), Day 84 (Visit 6), Day 182 (Visit 9) or Early Termination, and at the follow-up visit.	A full physical and neurological examination has been added at the baseline visit.
8 ASSESSMENT OF PHARMACOKINETICS AND PHARMACOGENOMICS		
Section 8.2 (Other sections affected by this change: 5.5)		
A blood sample (10 mL) will be collected in 2 dipotassium ethylenediaminetetraacetic acid (K2EDTA) plastic tubes at the screening visit for genetic analyses.	A blood sample (~~10~~ **12** mL) will be collected in 2 dipotassium ethylenediaminetetraacetic acid (K2EDTA) plastic tubes at the screening visit for genetic analyses.	The blood volume has been updated to require 12 mL of blood for PGx testing.
9 STATISTICS		
Section 9.6.3 (Other sections affected by this change: 3.2.3)		
• CGI-C at Week 26 as compared to baseline (rated by the qualified site personnel and the patient)	• CGI-C at Week 26 as compared to baseline (rated by the qualified site personnel ~~and the patient~~)	Clarification that the patient will not be rating the CGI-C at week 26.
17 REFERENCES		
[20] Wellbutrin label.	[20] Wellbutrin® (bupropion hydrochloride tablets, for oral use). Highlights of prescribing information. GlaxoSmithKline, Research Triangle Park, NC 27709 [Updated: July 2014, cited: September 2014]. Available from: https://www.gsksource.com/gskprm/htdocs/documents/WELLBUTRIN-TABLETS-PI-MG.PDF.	Full reference for Wellbutrin® prescribing information provided.

16.6. PROTOCOL AMENDMENT 02 DATED 03 FEBRUARY 2014

The revisions listed below have been made to the protocol and synopsis, as appropriate, and are considered substantial by the sponsor's Authorized Representative.

The primary reasons for this amendment were to lower the number of time points at which exploratory efficacy endpoints are assessed, to adjust the DSMB review process according to competent authority and ethic review board requirements for approval, and to clarify various aspects of study conduct. In addition, the possibility for patients to continue in the study after study drug discontinuation, due to safety or tolerability reasons, has been introduced.

Substantive changes from Amendment 01 to Amendment 02 are provided below.

Previous approved wording	Amended or new wording	Reason/Justification for change
TITLE PAGE		
Clinical Study Protocol with Amendment 01	Clinical Study Protocol with Amendment ~~01~~ ***02***	Change of number to reflect current amendment
Sponsor's Medical Expert Esther Lukasiewicz-Hagai, MD, PhD Director, Clinical Program Leader, CNS & Pain TA Teva Pharmaceutical Industries Ltd Tel: +972 9 86396 45	***Sponsor's Global Clinical Leader*** ~~**Medical Expert**~~ ~~Esther Lukasiewicz-Hagai, MD~~***Anna Wickenberg***, PhD ~~Director,~~ ***Global*** Clinical ~~Program~~ Leader, CNS & Pain TA Teva Pharmaceutical Industries Ltd Tel: +~~972 9 86396 45~~***46 72 721 9122***	Change to details of new Sponsor's global clinical leader
COORDINATING INVESTIGATOR AGREEMENT		
(Not applicable)	***Global Coordinating Investigator*** ~~***(Country)***~~***:*** ***Prof. Dr. G. Bernhard Landwehrmeyer, MD, FRCP*** ***Address of Investigational Center:*** ***Ulm University Hospital*** ***Department of Neurology*** Oberer Eselsberg 45/1 89081 Ulm Germany ***Tel: +49-731-500-631-01*** Fax: +49-731-500-630-82 ***Coordinating Investigator, North America:*** ***Karl D Kieburtz, MD, MPH*** ***Title: Robert J. Joynt Professor in Neurology; Director, Clinical & Translational Science Institute; Senior Associate Dean for Clinical Research; Director, Center for Human Experimental Therapeutics; Professor, Public Health Sciences and Environmental Medicine*** ***Address of Investigational Center:*** ***University of Rochester/CTSI*** 265 Crittenden Blvd CU 420708 Rochester, NY 14642 United States of America ***Tel: +1 (585)275-8911*** Fax: +1 (585)276-1122 ***Coordinating Investigator, Europe:*** ***Ralf Reilmann, MD, PhD***	New text – names and contact details of the coordinating investigators.

<table>
<tr><th>Previous approved wording</th><th>Amended or new wording</th><th>Reason/Justification for change</th></tr>
<tr><td></td><td>Title: Founding Director and CEO, George Huntington Institute; Chair - EHDN Huntington Center, University of Munster; Chair - Laboratory of Biomarkers and Neurodegeneration, University of Munster
Address of Investigational Center:
George-Huntington-Institute
Technology-Park - Deilmann Building IV
Johann-Krane-Weg 27
48149 Münster
Germany
Tel: secretary: +49-251-788-788-0
Tel: office: +49-251-788-788-11
Mobile: +49-151-106-499-44</td><td></td></tr>
<tr><td colspan="3">CLINICAL STUDY PERSONNEL CONTACT INFORMATION</td></tr>
<tr><td>Contact details for notifications of SAEs are as follows:<table><tr><td>Austria</td><td>signal@ratiopharm.at</td></tr><tr><td>Australia</td><td>Fax number: +65-6565-7939
e-mail: STUDY-MA-DL-075-070-Blinded@iconplc.com
24-hour hotline: +65-6896-0378</td></tr><tr><td>Canada</td><td>phv@tevacanada.com</td></tr><tr><td>Denmark</td><td>Safety.Denmark@tevapharm.dk</td></tr><tr><td>Germany</td><td>Safety.Germany@teva.de</td></tr><tr><td>Italy</td><td>safety_PhVItaly@tevaitalia.It</td></tr><tr><td>Netherlands</td><td>dso.nl@tevapharmachemie.com</td></tr><tr><td>Russia</td><td>Safety.Russia@teva.ru</td></tr><tr><td>UK</td><td>uk.safety@tevauk.com</td></tr><tr><td>USA</td><td>us.clinops.sae@tevapharm.com</td></tr></table></td><td>Contact details for notifications of SAEs are as follows:<table><tr><td>Austria</td><td>signal@ratiopharm.at</td></tr><tr><td>Australia</td><td>Fax number: +65-6565-7939
e-mail: STUDY-MA-DL-075-070-Blinded@iconplc.com
24-hour hotline: +65-6896-0378</td></tr><tr><td>Canada</td><td>phv@tevacanada.com</td></tr><tr><td>Denmark</td><td>Safety.Denmark@tevapharm.dk</td></tr><tr><td>France</td><td>safety.france@tevafrance.com</td></tr><tr><td>Germany</td><td>Safety.Germany@teva.de</td></tr><tr><td>Italy</td><td>safety_PhVItaly@tevaitalia.It</td></tr><tr><td>Netherlands</td><td>dso.nl@tevapharmachemie.com</td></tr><tr><td>Poland</td><td>safety.poland@teva.pl</td></tr><tr><td>Russia</td><td>Safety.Russia@teva.ru</td></tr><tr><td>UK</td><td>uk.safety@tevauk.com</td></tr></table></td><td>Addition of contact information for Poland and France for SAE notifications.</td></tr>
</table>

Previous approved wording	Amended or new wording		Reason/Justification for change
	USA	us.clinops.sae@tevapharm.com	
1 BACKGROUND INFORMATION			
Section 1.7 (Other sections affected by this change: 3.1, 4.1)			
The study population will consist of male or female patients aged ≥21 years and with body weight ≥50 kg, with HD diagnoses obtained with the identification of HD clinical features and confirmed by the presence of ≥36 CAG repeats in the huntingtin gene (from historical data).	The study population will consist of male or female patients aged ≥21 years and with body weight ≥50 kg, with HD diagnoses obtained with the identification of HD clinical features and confirmed by the presence of ≥36 CAG repeats in the huntingtin gene ~~(from historical data)~~.		Clarification.
2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES			
Section 2.2 (Many sections affected by this change)			
The secondary efficacy objective of the study is to assess the effect of 26 weeks of treatment with pridopidine 67.5 to 112.5 mg bid on the Physical Performance Test (PPT).	The secondary efficacy objective of the study is to assess the effect of 26 weeks of treatment with pridopidine 67.5 to 112.5 mg bid on the ***modified*** Physical Performance Test (***m***PPT).		Clarified to indicate that the modified PPT scale will be used.
Previous approved wording	**Amended or new wording**		**Reason/Justification for change**
3 STUDY DESIGN			
Section 3.1 (Other sections affected by this change: Section 7)			
Patients will be equally randomized (1:1:1:1:1) to receive pridopidine 45, 67.5, 90, or 112.5 mg or placebo bid for 26 weeks, including a 4-week progressive titration period. An independent DSMB meeting will be held to assess safety data, 6 weeks after 10 patients from each treatment arm (ie, a total of 50 patients) have been enrolled. In case of a significant emerging safety concern in 1 or more treatment arm(s), the DSMB will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatments arm(s) with safety concerns. A second DSMB meeting will be held to assess safety data, 6 weeks after approximately 20 patients from each treatment arm (ie, a total of 100 patients) have enrolled. At the second meeting, the DSMB will decide whether there is a need for additional meetings, and,	Patients will be equally randomized (1:1:1:1:1) to receive pridopidine 45, 67.5, 90, or 112.5 mg or placebo bid for 26 weeks, including a 4-week progressive titration period. ***During the study, an independent DSMB will review accumulating unblinded safety data. The DSMB will meet monthly until 20 patients from each treatment arm (i.e. a total of 100 patients) have completed two weeks of treatment on full dose (6 weeks in the study).*** ~~An independent DSMB meeting will be held to assess safety data, 6 weeks after 10 patients from each treatment arm (ie, a total of 50 patients) have been enrolled.~~ In case of a significant emerging safety concern in 1 or more treatment arm(s), the DSMB will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatments arm(s) with safety concerns. ~~A second DSMB meeting will be held to assess safety data, 6 weeks after approximately 20 patients from each~~		Increased frequency of DSMB meetings until 100 patients (20 from each treatment arm) have completed two weeks of treatment on full dose.

Previous approved wording	Amended or new wording	Reason/Justification for change
if needed, will determine when these will take place.	~~treatment arm (ie, a total of 100 patients) have enrolled.~~ ~~At the second meeting~~***Thereafter***, the DSMB will decide whether there is a need for additional meetings, and, if needed, will determine when these will take place.	
Section 3.1		
After having signed an informed consent, including consent to provide a blood sample for genetic analyses, patients will be screened for a period of up to 2 weeks in order to determine whether they are eligible to participate into the study.	After having signed an informed consent, including consent to provide a blood sample for genetic analyses, patients will be screened for a period of up to 2 weeks in order to determine whether they are eligible to participate into the study. ***Patients with a legal guardian should be consented according to local requirements.***	New text added for clarification.
Section 3.1		
The diagnostic of HD will be established based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene (from historical data).	The diagnostic of HD will be established based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene ~~(from historical data)~~.	Clarification.
Section 3.1		
In case the devices needed for the Q-Motor assessments are not available at all the sites, those evaluations will be done only in sites where devices are available.	In case the devices needed for the ***CAB and the*** Q-Motor assessments are not available at all the sites, those evaluations will be done only in sites where devices are available.	Clarification.
Section 3.1 (Other sections affected by this change: 3.2.3; 6.3.4; 9.6.3)		
At the baseline visit, before the first dose of study drug, the Clinician's Interview Based Impression of Severity (CIBIS) will be rated by an independent rater, while the study investigator will assess the PPT, the Clinical Global Impression of Severity (CGI-S), the Timed Up and Go (TUG) Test, the Physical Disability Scale (PDS), the UHDRS-TMS, the UHDRS-FA, the UHDRS-IS, the UHDRS Total Functional Capacity (TFC), the CAB (as defined in Section 6.3.10), and the Problem Behaviors Assessment-Short form (PBA-s). The patient will fill the Multiple Sclerosis Walking Scale (MSWS-12) and the HD-Quality of life scale (HD-QoL), and Q-Motor assessments will be performed. UHDRS-TMS and PPT should be evaluated prior to the other scales.	At the baseline visit, before the first dose of study drug, the Clinician's Interview Based Impression of Severity (CIBIS) will be rated by an independent rater, while ~~the study investigator~~ ***another qualified site personnel*** will assess the ***m***PPT, the Clinical Global Impression of Severity (CGI-S), the Timed Up and Go (TUG) Test, the Physical Disability Scale (PDS), the UHDRS-TMS, the UHDRS-FA, the UHDRS-IS, the UHDRS Total Functional Capacity (TFC), the CAB (as defined in Section 6.3.10), and the Problem Behaviors Assessment-Short form (PBA-s). The patient will fill the ~~Multiple Sclerosis Walking Scale (MSWS~~***Walk***-12) and the HD-Quality of life scale (HD-QoL), ***the EQ5D*** and Q-Motor assessments will be performed. UHDRS-TMS and ***m***PPT should be evaluated prior to the other scales.	Clarification regarding person who performs the assessments; change to Walk-12 and addition of EQ5D scale.
Section 3.1		
(Not applicable)	***At days 28, 56, 84, 112, 140, and 182, in addition to safety assessments, the UHDRS-TMS and the mPPT will be assessed by***	New text.

Previous approved wording	Amended or new wording	Reason/Justification for change
	qualified site personnel.	
Section 3.1 (Other sections affected by this change: 3.11; Table 2)		
At Days 28, 56, 84, 112, 140, and 182, in addition to safety assessments, the Clinician's Interview-based Impression of Change plus Caregiver Input (CIBIC-Plus) will be rated by an independent rater, while the study investigator will assess the UHDRS-TMS, the PPT, the PDS, the Clinical Global Impression of Change (CGI-C), the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, the CAB, and the PBA-s. The patient will fill the MSWS-12 and the HD-QoL scales and Q-Motor assessments will be performed. UHDRS-TMS and PPT should be evaluated prior to the other scales.	At Days 28, ~~56,~~ 84, ~~112, 140,~~ and 182, in addition to safety assessments ***and the UHDRS-TMS and mPPT***, the ~~Clinician's Interview-based Impression of Change plus Caregiver Input (~~CIBIC-Plus~~)~~ will be rated by an independent rater, while ~~the study investigator~~ ***another qualified site personnel*** will assess the ~~UHDRS-TMS, the ***m***PPT, the~~ PDS, the ~~Clinical Global Impression of Change (~~CGI-C~~)~~, the TUG Test, the UHDRS-FA, the UHDRS-TFC, the UHDRS-IS, ~~the CAB,~~ and the PBA-s. ***UHDRS-TMS and mPPT should be evaluated prior to the other scales.*** The patient will fill the ~~MSWS~~***Walk***-12 ~~and the HD-QoL scales~~ and Q-Motor assessments will be performed. ~~UHDRS-TMS and PPT should be evaluated prior to the other scales.~~***The UHDRS-FA, the UHDRS-TFC and the UHDRS-IS will also be performed on Day 140.The CAB will be performed on days 84 and 182 only. The HD-QoL and EQ5D scales will be completed on Day 182 only.***	Change to reflect new assessment time points; person performing assessments and change to Walk-12 scale name. The EQ5D has been added.
Section 3.1 (Other sections affected by this change: 9.3.4; 9.3.5)		
(Not applicable)	***Patients, who for safety or tolerability reasons have to stop study drug medication, will be asked to continue in the study and follow the visit schedule as outlined in the protocol, without taking study drug.***	The possibility for patients to continue in the study after study drug discontinuation, due to safety or tolerability reasons, has been introduced.
Section 3.2.3 (Other sections affected by this change: 9.6.3)		
• CGI-C at Week 26 as compared to baseline (rated by the study investigator and the patient)	• CGI-C at Week 26 as compared to baseline (rated by ~~the study investigator~~ ***qualified site personnel*** and the patient)	Clarification regarding person who performs the assessments.
Section 3.2.3 (Other sections affected by this change: 9.6.3)		
Patient Reported Outcomes: • Change from baseline in HD-QoL at Week 26 • Change from baseline in MSWS-12 at Week 26	**Patient Reported Outcomes:** • Change from baseline in HD-QoL at Week 26 • ***Change from baseline in EQ5D-5L at Week 26*** • Change from baseline in ~~MSWS~~***Walk***-12 at Week 26	Change of assessment name; addition of EQ5D-5L scale.
Section 3.4.1		
Each medication pack will contain 3 distinct labeled bottles in	Each medication pack will contain 3 distinct labeled bottles in	Clarification regarding the

Previous approved wording	Amended or new wording	Reason/Justification for change
accordance with the associated treatment arm. Each bottle will contain 30 capsules.	accordance with the associated treatment arm. Each bottle will contain 30 ***±1*** capsules.	number of capsules in the dispensed bottles.
Section 3.6.1 (Other sections affected by this change: 7.6)		
Patients should be discontinued if any of the following criteria relating to QTcF are met: • QTcF >500 msec (based on the mean value from the triplicate ECG measurements); • QTcF >480 msec with concurrent increase in QTcF >60 msec (ΔQTcF, based on the mean value from the triplicate ECG measurements) from baseline (Day 0); • If QTcF >480 msec or ΔQTcF >60 msec, a repeat ECG (in triplicate) will be recorded after 7 to 9 days; if the change is confirmed and electrolytes are normal, the patient will be withdrawn. Patients should also be discontinued if they experience a seizure or convulsions (regardless of the relationship to treatment), if their body weight decreases to <50 kg, and/or if creatinine clearance decreases to <60 mL/min (calculated using the Cockcroft-Gault equation).	Patients should be discontinued if any of the following criteria relating to QTcF are met: • QTcF >500 msec (based on the mean value from the triplicate ECG measurements); • QTcF >480 msec with concurrent increase in QTcF >60 msec (ΔQTcF, based on the mean value from the triplicate ECG measurements) from baseline (Day 0); • If QTcF >480 msec or ΔQTcF >60 msec, a repeat ECG (in triplicate) will be recorded after 7 to 9 days; if the change is confirmed and electrolytes are normal, the patient will be withdrawn. ***If the local ECG reading results at the site match any of the above discontinuation criteria, 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), if their body weight decreases to <50 kg, and/or if creatinine clearance decreases to <60 mL/min (calculated using the Cockcroft-Gault equation).	Clarification added per DSMB input.
Section 3.10		
Approximately 400 patients from approximately 40 investigational centers in multiple countries are planned to be enrolled in the study.	Approximately 400 patients from approximately ~~40~~ ***50*** investigational centers in multiple countries are planned to be enrolled in the study.	Updated number of investigational centers due to increased sample size.
Section 3.11 – Table 2		
The PBA-s, CIBIC-Plus, PDS, CGI-C, MSWS-12 and TUG test – to be performed on the following visits: baseline (V1); week 4 (V3), week 8 (V5), week 12 (V6), week 16 (V7), week 20 (V8) and week 26/early termination (V9)	The PBA-s, CIBIC-Plus, PDS, CGI-C, ~~MSWS~~***Walk***-12 and TUG test – to be performed on the following visits: baseline (V1); week 4 (V3), week 12 (V6) and week 26/early termination (V9).	Change to time points at which exploratory efficacy endpoints are assessed to remove burden from the patients; change of assessment name.

Previous approved wording	**Amended or new wording**	**Reason/Justification for change**
HD-QoL scale performed at baseline (V1); week 4 (V3), week 6 (v4), week 8 (V5), week 12 (V6), week 16 (V7), week 20 (V8) and week 26/early termination (V9)	HD-QoL scale performed at baseline (V1) and week 26/early termination (V9)	Change to time points at which this scale is assessed to remove burden from the patients.
(Not applicable)	***EQ5D-5L scale added to the table; will be performed at baseline (v1) and week 26/early termination (V9).***	Addition of EQ5D-5L scale.
Q-motor assessments performed at screening (V0), baseline (V1); week 4 (V3), week 8 (V5), week 12 (V6), week 16 (V7), week 20 (V8) and week 26/early termination (V9) and follow up.	Q-motor assessments performed at screening (V0), baseline (V1); week 4 (V3), week 12 (V6) and week 26/early termination (V9) and follow up.	Change to time points at which exploratory efficacy endpoints are assessed to remove burden from the patients.
Cognitive assessment battery – to be performed on the following visits: screening (V0); baseline (V1); week 4 (V3), week 8 (V5), week 12 (V6), week 16 (V7), week 20 (V8) and week 26/early termination (V9)	Cognitive assessment battery – to be performed on the following visits: screening (V0); baseline (V1); week 12 (V6), and week 26/early termination (V9).	Change to time points since the data from the CAB at these visits will not be used and therefore the Sponsor would like to remove this burden from the patients.
m. Includes symbol digit modalities test, Stroop word reading test, abbreviated Montreal cognitive assessment scale, and Trail Making Test B	m. Includes ~~symbol digit modalities test~~**SDMT**, ~~Stroop word reading test, abbreviated Montreal cognitive assessment scale~~; ***Emotion recognition***;~~and~~ Trail Making Test ***A***+B; ***HVLT-R; Paced Tapping Test and OTS.***	Footnote revised to reflect the procedures included in the cognitive assessment battery (CAB).
(Not applicable)	***s. Patients, who for safety or tolerability reasons have to stop study drug medication, will be asked to continue in the study and follow the visit schedule as outlined without taking study drug.***	New footnote regarding the possibility for patients to continue in the study after study drug discontinuation has been introduced.
MSWS-12	~~MSWS-12~~***Walk-12***	Revision of assessment name due to becoming a generic measure of walking and mobility.
V = Visit (on-site); TC = telephone call; BL = Baseline; W = Week; ET = early termination; FU = follow-up; ECG = electrocardiogram; C-SSRS = Columbia-Suicide Severity Rating Scale; UHDRS = Unified Huntington's Disease Rating Scale; CIBIS = Clinician's Interview-based Impression of Severity; CIBIC-Plus = Clinician's Interview-based Impression of Change plus Caregiver Input; CGI-S = Clinical Global Impression of	V = Visit (on-site); TC = telephone call; BL = Baseline; W = Week; ET = early termination; FU = follow-up; ECG = electrocardiogram; C-SSRS = Columbia-Suicide Severity Rating Scale; UHDRS = Unified Huntington's Disease Rating Scale; CIBIS = Clinician's Interview-based Impression of Severity; CIBIC-Plus = Clinician's Interview-based Impression of Change plus Caregiver Input; CGI-S = Clinical Global Impression of Severity; CGI-C = Clinical Global	New abbreviations added to table; PPT abbreviation revised; MSWS-12 abbreviation deleted.

Previous approved wording	Amended or new wording	Reason/Justification for change
Severity; CGI-C = Clinical Global Impression of Change; TUG = Timed Up and Go; PDS = Physical Disability Scale; PPT = Physical Performance Test; HD-QoL = Huntington's disease Quality of Life; MSWS-12 = Multiple Sclerosis Walking Scale; CAG = cytosine-adenine-guanine; TMS = Total Motor Score; IS = Independence Scale; PBA-s = Problem Behaviors Assessment-Short form; TFC = Total Functional Capacity; FA = Functional Assessment; Q-Motor = Quantitative motor; SAE = serious adverse event	Impression of Change; TUG = Timed Up and Go; PDS = Physical Disability Scale; ***m***PPT = ***modified*** Physical Performance Test; HD-QoL = Huntington's disease Quality of Life; ***HVLT-R = Hopkins Verbal Learning Test, revised;*** ~~MSWS-12 = Multiple Sclerosis Walking Scale;~~ CAG = cytosine-adenine-guanine; TMS = Total Motor Score; IS = Independence Scale; ***OTS = One Touch Stockings of Cambridge, abbreviated 10-trial version;*** PBA-s = Problem Behaviors Assessment-Short form; ***SDMT = Symbol Digit Modalities Test;*** TFC = Total Functional Capacity; FA = Functional Assessment; Q-Motor = Quantitative motor; SAE = serious adverse event	
Section 3.11.1		
A signed and dated informed consent form, including consent to genotyping (CAG analysis, CYP2D6 metabolizer status, genetic long QT syndrome for determination in patients who had QT prolongation following study drug administration, or any other genetic analyses related to pridopidine response or HD), will be obtained before screening procedures commence. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations.	A signed and dated informed consent form, including consent to genotyping (CAG analysis, CYP2D6 metabolizer status, genetic long QT syndrome for determination in patients who had QT prolongation following study drug administration, or any other genetic analyses related to pridopidine response or HD), will be obtained before screening procedures commence. ***Patients with a legal guardian should be consented according to local requirements.*** Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the protocol-specific evaluations.	New text added for clarification.
Section 3.11.2		
• review inclusion/exclusion criteria • vital signs measurements • inquire about AEs • inquire about concomitant medication • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis); results for electrolytes must be available before dosing • urine pregnancy test for women of child-bearing potential only • 12-lead ECG in triplicate (performed after at least 5 minutes of supine rest); the predose QTcF will be determined by the average of 3 ECGs (within 10 to 20 minutes of each other), each in triplicate (in total	• review inclusion/exclusion criteria • vital signs measurements • inquire about AEs • inquire about concomitant medication • clinical laboratory tests (hematology, biochemistry including electrolytes, urinalysis)~~results for electrolytes must be available before dosing~~ • urine pregnancy test for women of child-bearing potential only • 12-lead ECG in triplicate (performed after at least 5 minutes of supine rest); the predose QTcF will be determined by the average of 3 ECGs (within 10 to 20 minutes of each other), each in triplicate (in total 9 readings).	Clarification; electrolytes and potassium results from previous visit will be available. Addition of EQ5D scale to baseline visit; change of assessment names to Walk-12 and mPPT.

Previous approved wording	Amended or new wording	Reason/Justification for change
9 readings). • C-SSRS (since last visit version) • UHDRS-TMS • PPT • UHDRS-FA, UHDRS-TFC, UHDRS-IS • CGI-S • CIBIS, completed by an independent rater • PDS • TUG Test • HD-QoL • MSWS-12 • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) • PBA-s • obtain a 4-mL blood sample for plasma drug assay • dispense study drug (first dose taken at the site conditional to potassium level being within normal ranges) • review study compliance	• C-SSRS (since last visit version) • UHDRS-TMS • ***m***PPT • UHDRS-FA, UHDRS-TFC, UHDRS-IS • CGI-S • CIBIS, completed by an independent rater • PDS • TUG Test • HD-QoL • ***EQ5D-5L*** • ~~MSWS-12~~***Walk-12*** • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) • PBA-s • obtain a 4-mL blood sample for plasma drug assay • dispense study drug (first dose taken at the site ~~conditional to potassium level being within normal ranges~~) • review study compliance	
Section 3.11.3.1.2 (Other sections affected by this change: 3.11.2)		
<u>Before Afternoon Dosing:</u> • AE inquiry • concomitant medication review • clinical laboratory tests (electrolytes only); results for electrolytes must be available before dosing • vital signs measurements • collect/dispense study drug • study compliance review	<u>Before Afternoon Dosing:</u> • AE inquiry • concomitant medication review • clinical laboratory tests (electrolytes only)~~; results for electrolytes must be available before dosing~~ • vital signs measurements • collect/dispense study drug • study compliance review	Clarification; electrolytes result from previous visit will be available.
Section 3.11.3.2.1		
In addition, the following efficacy procedures/assessments will	~~In addition, the following efficacy procedures/assessments will be~~	Change to assessment time

Previous approved wording	Amended or new wording	Reason/Justification for change
be performed on Days 28, 56, 84, 112, and 140 only, either before or after the afternoon dose (with the time of the evaluation recorded), with UHDRS-TMS and PPT evaluated in priority: • UHDRS-TMS • PPT • CIBIC-Plus • PDS • UHDRS-FA, UHDRS-TFC, UHDRS-IS • CGI-C • TUG Test • HD-QoL • MSWS-12 • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) • PBA-s	~~performed on Days 28, 56, 84, 112, and 140 only, either before or after the afternoon dose (with the time of the evaluation recorded), with UHDRS-TMS and PPT evaluated in priority:~~ ***In addition, on Days 28, 56, 84, 112, and 140, the following efficacy procedures/assessments will be performed, in priority, either before or after the afternoon dose (with the time of the evaluation recorded):*** • ***UHDRS-TMS*** • ***mPPT*** In addition ***to the UHDRS-TMS and mPPT***, the following efficacy procedures/assessments will be performed on Days 28~~, 56,~~ ***and*** 84~~, 112, and 140~~ only, either before or after the afternoon dose (with the time of the evaluation recorded), with UHDRS-TMS and ***m***PPT evaluated in priority, ***as previously stated***: • ~~UHDRS-TMS~~ • ~~***m***PPT~~ • CIBIC-Plus • PDS • UHDRS-FA, UHDRS-TFC, UHDRS-IS - ***will also be performed on Day 140*** • CGI-C • TUG Test • ~~HD-QoL~~ • ~~MSWS~~***Walk***-12 • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) ***– on day 84 only*** • PBA-s	points.
Section 3.11.3.2.3 (Other sections affected by this change: 3.11.2)		
Before Dosing: • … • obtain a 4-mL blood sample for plasma drug assay (as	Before Dosing: • … • obtain a 4-mL blood sample for plasma drug assay (as close	Clarification; potassium result from previous visit will be available.

Previous approved wording	Amended or new wording	Reason/Justification for change
close as possible to, but after the ECG recording) • study compliance review • morning study drug dose administration (conditional to potassium level being within normal range) (Note: study drug will not be administered if Early Termination visit)	as possible to, but after the ECG recording) • study compliance review • morning study drug dose administration ~~(conditional to potassium level being within normal range)~~ (Note: study drug will not be administered if Early Termination visit)	
Section 3.11.3.2.3 (Other sections affected by this change: 3.11.2)		
The following efficacy procedures/assessments will be performed on Day 182 (Visit 9), before or after dosing (with the time of the evaluation recorded), with UHDRS-TMS and PPT evaluated in priority: • … • HD-QoL • MSWS-12 • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) • PBA-s	The following efficacy procedures/assessments will be performed on Day 182 (Visit 9), before or after dosing (with the time of the evaluation recorded), with UHDRS-TMS and ***m***PPT evaluated in priority: • … • HD-QoL • ***EQ5D-5L*** • ~~MSWS~~***Walk***-12 • Q-Motor assessments • CAB tests (SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS) • PBA-s	Change of assessment name; addition of the EQ5D-5L scale to the termination visit.
Section 3.11.5 (Other sections affected by this change: 9.3.4; 9.6.4.2)		
Patients who participate in the study in compliance with the protocol for at least 26 weeks of double-blind treatment will be considered to have completed the study. For patients who complete the study or withdraw prematurely, final evaluations will be performed at the Week 26/Early Termination visit (Visit 9). For patients who do not have a final visit within 7 days after their last dose of study drug, efficacy evaluations (see Section 6) should not be performed. Procedures for patients who withdraw prematurely from the study are described in Section 4.3. Data from any efficacy evaluations performed after the specified time or, where applicable, outside of the time windows indicated in Table 2.and Section 3.11, will not be collected on the CRF; in	Patients who participate in the study in compliance with the protocol for at least 26 weeks of double-blind treatment will be considered to have completed the study. For patients who complete the study or withdraw prematurely, final evaluations will be performed at the Week 26/Early Termination visit (Visit 9). For patients who do not have a final visit within 7 days after their last dose of study drug, efficacy evaluations (see Section 6) should not be performed. Procedures for patients who withdraw prematurely from the study are described in Section 4.3. ***Patients, who for safety or tolerability reasons have to stop study drug medication, will be asked to continue in the study and follow the visit schedule as outlined in the protocol, without taking study drug. Data from these visits will be collected, and included in the statistical analysis as described in Section 9.***	Clarification regarding patients who discontinue study drug medication but remain in study.

Previous approved wording	Amended or new wording	Reason/Justification for change
the event, however, that such data are collected, these data will not be analyzed. Patients with ongoing AEs or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.4, respectively.	~~Data from any efficacy evaluations performed after the specified time or, where applicable, outside of the time windows indicated in Table 2 and Section 3.11, will not be collected on the CRF; in the event, however, that such data are collected, these data will not be analyzed.~~ Patients with ongoing AEs or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2 and Section 7.4, respectively.	
4 SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4.1 (Other sections affected by this change: 1.7; 3.1)		
a. Diagnosis of HD based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene (from historical data).	a. Diagnosis of HD based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene ~~(from historical data)~~.	Clarification.
Section 4.1		
c. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study, including the follow-up period. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, or double barrier contraception, ie, condom and diaphragm). Abstinence is an acceptable method 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.	c. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study, including the follow-up period. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, or double barrier contraception, ie, 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.	New text added for clarification per competent authority input.
Section 4.1(Other sections affected by this change: Section 3.1; 3.11.1; 12.1)		
g. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit.	g. Able and willing to provide written informed consent prior to any study related procedure being performed at the screening visit. ***Patients with a legal guardian should be consented according to local requirements.***	New text added for clarification.
Section 4.2		
l. Patients with active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal	l. Patients with active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with	Clarification regarding the timeframe for suicidal

Previous approved wording	Amended or new wording	Reason/Justification for change
Ideation with Specific Plan and Intent) on the C-SSRS, 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) or patients who, in the opinion of the investigator, present a serious risk of suicide.	Specific Plan and Intent) on the C-SSRS, 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 within 1 year of screening***, or patients who, in the opinion of the investigator, present a serious risk of suicide.	behaviors
Section 4.3(Other sections affected by this change: 3.11.5)		
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 3.11.5).	~~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 3.11.5).~~ ***Safety evaluations will be performed for all recorded data.*** ***Efficacy evaluations will be performed as described in Section 9***.	Clarification.
Previous approved wording	**Amended or new wording**	**Reason/Justification for change**
6 ASSESSMENT OF EFFICACY		
Section 6		
Except where stated, efficacy assessments detailed in the following sections are performed on Day 0 (Visit 0, baseline), Day 28 (Visit 3), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), and Day 182 (Visit 9). Except for at Day 0, efficacy assessments can take place before or after the afternoon dose, with the time of the evaluation recorded. UHDRS-TMS and Q-Motor assessments will also be performed at the follow-up visit.	***Primary and secondary efficacy assessments (UHDRS-TMS and mPPT) will be performed on Day 0 (Visit 0, baseline), Day 28 (Visit 3), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), and Day 182 (Visit 9).*** ***Exploratory efficacy assessments will be performed only at Day 0 (Visit 0, baseline), Day 28 (Visit 3), Day 84 (Visit 6), and Day 182 (Visit 9); apart from the CAB, which will be performed only at Day 0 (Visit 0, baseline), Day 84 (Visit 6), and Day 182 (Visit 9); and UHDRS FA, UHDRS TFC, and UHDRS IS which will also be performed on Day 140.*** ~~Except where stated, efficacy assessments detailed in the following sections are performed on Day 0 (Visit 0, baseline), Day 28 (Visit 3), Day 56 (Visit 5), Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), and Day 182 (Visit 9).~~ Except for ~~at~~ Day 0, 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.***	Clarification of assessment time points; addition of statement regarding priority of UHDRS-TMS and mPPT

Previous approved wording	Amended or new wording	Reason/Justification for change
	UHDRS-TMS and Q-Motor assessments will also be performed at the follow-up visit.	
Section 6.2.1		
The PPT quantifies the patient's performance in physical tasks.[22] It is a standardized 9-item test that measures the patient's performance on functional tasks. Patients are given 2 chances to complete each of the 9 items, and 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.	The ***m***PPT quantifies the patient's performance in physical tasks.[22] It is a standardized 9-item test that measures the patient's performance on functional tasks. ~~Patients are given 2 chances to complete each of the 9 items, and a~~***A***ssistive 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.	To align with recent developments in administration of the mPPT scale.
Section 6.3.1		
(Not applicable)	***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.***	New text for clarification.
Section 6.3.4 (Other sections affected by this change: Section 3.1; 3.2.3; 9.6.3)		
The CGI-S scale was initially designed to assess treatment response in patients with mental disorders[25] but is now used widely in a range of illnesses. Illness severity is rated by the investigator on a 7-point scale (1 = normal, not at all ill to 7 = among the most extremely ill patients). The assessment is based on investigator judgment, supported by a comprehensive, semi-structured, patient/caregiver interview.	The CGI-S scale was initially designed to assess treatment response in patients with mental disorders[25] but is now used widely in a range of illnesses. Illness severity is rated by ~~the investigator~~ ***qualified site personnel*** on a 7-point scale (1 = normal, not at all ill to 7 = among the most extremely ill patients). The assessment is based on ~~investigator~~ ***qualified site personnel*** judgment, supported by a comprehensive, semi-structured, patient/caregiver interview.	Clarification regarding person who performs the assessments.
Section 6.3.7.1		
(Not applicable)	***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 caregiver/informant form should be omitted.***	New text for clarification.
Section 6.3.7.2 (Many other sections affected by this change: Section 3.11)		
6.3.7.2 Multiple Sclerosis Walking Scale MSWS-12 was originally developed to measure the impact of multiple sclerosis (MS) on walking. However, as other disabling neurological conditions affect a person's ability to walk, it was	**6.3.7.2 ~~Multiple Sclerosis Walking Scale~~ Walk-12** ***The Multiple Sclerosis Walking Scale (***MSWS-12***)*** was originally developed to measure the impact of multiple sclerosis (MS) on walking. However, as other disabling neurological conditions affect a	Renaming of scale to become a generic measure of walking and mobility.

Previous approved wording	Amended or new wording	Reason/Justification for change
adapted to become a generic measure of walking and mobility. It contains 12 items describing the impact of MS on walking which were generated from 30 MS patient interviews, expert opinion, and literature review.	person's ability to walk, it was adapted to become a generic measure of walking and mobility ***and renamed the Walk-12***. It contains 12 items describing the impact of MS on walking which were generated from 30 MS patient interviews, expert opinion, and literature review.	
Section 6.3.7.3		
(Not applicable)	***The EQ-5D 3 level version (EQ-5D-3L) was introduced in 1990[28]. It essentially consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In developing the 5L, the 5-dimensional structure of the original EQ-5D-3L was retained but the levels on each dimension were expanded to 5-levels based on qualitative and quantitative studies conducted by the EuroQol Group. The labels for each of the dimensions are: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The EQ-VAS is still an integral part of the EQ-5D-5L but has been adapted to make it more user-friendly. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score. The EQ5D could be completed by the patients with caregiver/informant assistance if needed.***	Newly created section with text describing added scale.
Section 6.3.10		
(Not applicable)	***The CAB 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.***	New text for clarification.
Section 6.3.10.4		
The HVLT-R offers a brief assessment of verbal learning and memory (recognition and recall). It is easy to administer and	The HVLT-R offers a brief assessment of verbal learning and memory (recognition and recall). It is easy to administer and score and is well	Clarification since the recognition trial will not be

Previous approved wording	Amended or new wording	Reason/Justification for change
score and is well tolerated even by significantly impaired individuals. Its use has been validated with brain-disordered populations (eg, Alzheimer's disease, HD, amnestic disorders) as a measure of verbal learning and memory. Each form consists of a list of 12 nouns (targets) with 4 words drawn from each of 3 semantic categories. The semantic categories differ across the 6 forms, but the forms are very similar in their psychometric properties. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index. The HVLT-R has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well established.	tolerated even by significantly impaired individuals. Its use has been validated with brain-disordered populations (eg, Alzheimer's disease, HD, amnestic disorders) as a measure of verbal learning and memory. Each form consists of a list of 12 nouns (targets) with 4 words drawn from each of 3 semantic categories. The semantic categories differ across the 6 forms, but the forms are very similar in their psychometric properties. ~~Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index.~~ ***Raw scores will be derived for Learning Trials 1-3 (i.e., Total Recall) and Trial 4 (e.g., Delayed Recall Trial).*** The HVLT-R has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well established.	administered and not all indexes listed will be derived.
Section 6.3.11		
(Not applicable)	***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.***	New text for clarification.
7 ASSESSMENT OF SAFETY		
Section 7 (Other sections affected by this change: Section 3.1)		
During the study, an independent DSMB will review accumulating safety data on 2 occasions: The first review will occur 6 weeks after 10 patients from each treatment arm (ie, a total of 50 patients) have been enrolled. In case of significant emerging safety concerns in 1 or more treatment arms, the DSMB will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatment arm(s) with safety concerns. The second review will occur 6 weeks after approximately 20 patients from each treatment arm (ie, a total of 100 patients) have been enrolled. At the second meeting, the DSMB will decide whether there is a need for additional meetings, and will determine the time point to do it.	During the study, an independent DSMB will review ***unblinded*** accumulating safety data ~~on 2 occasions:~~**.** ~~The first review will occur 6 weeks after 10 patients from each treatment arm (ie, a total of 50 patients) have been enrolled.~~ ***The DSMB will meet monthly until 20 patients from each treatment arm (i.e. a total of 100 patients) have completed two weeks of treatment on full dose (6 weeks in the study).*** In case of significant emerging safety concerns in 1 or more treatment arms, the DSMB will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatment arm(s) with safety concerns. ~~The second review will occur 6 weeks after approximately 20 patients from each treatment arm (ie, a total of 100 patients) have been~~	Increased frequency of DSMB meetings until 100 patients (20 from each treatment arm) have completed two weeks of treatment on full dose.

Previous approved wording	Amended or new wording	Reason/Justification for change
	~~enrolled. At the second meeting~~***Thereafter***, the DSMB will decide whether there is a need for additional meetings, and***, if needed***, will determine ~~the time point to do it~~ ***when these will take place***.	
(Not applicable)	***The DSMB can call a meeting at any time based on safety concerns, and that decisions about discontinuing patients, should that happen, will be explained in a report to all sites and patients.***	New text.
DSMB sessions can be open or closed. During open sessions, representatives of the sponsor and the Steering Committee may be present and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the DSMB and the designated unblinded statistician (if approved to be present). The data for this session are provided in a coded treatment label (eg, Group A, Group B, etc) without direct identification of the actual treatment arm. If there is a request to unblind any blinded treatment assignment, a written request from the DSMB (as a committee), signed by the DSMB chairperson, should be made to the unblinded statistician. The appropriate medical and operational staff will be notified but will not receive the unblinded treatment information. Any use of unblinded treatment assignments should be clearly documented and reported to the sponsor at study termination.	DSMB sessions can be open or closed. During open sessions, representatives of the sponsor and the Steering Committee may be present and information is provided and discussed in a blinded fashion. During closed sessions, the only participants are members of the DSMB and the designated unblinded statistician (if approved to be present). ~~The data for this session are provided in a coded treatment label (eg, Group A, Group B, etc) without direct identification of the actual treatment arm.~~ ~~If there is a request to unblind any blinded treatment assignment, a written request from the DSMB (as a committee), signed by the DSMB chairperson, should be made to the unblinded statistician. The appropriate medical and operational staff will be notified but will not receive the unblinded treatment information. Any use of unblinded treatment assignments should be clearly documented and reported to the sponsor at study termination.~~	The DSMB reviews unblinded data.
Section 7.1.1		
Worsening of the disease under study will be measured by UHDRS scales and the CAB and 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.	***New symptoms of HD or deterioration of previously existing symptoms***~~Worsening of the disease under study will be measured by UHDRS scales and the CAB and~~ 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.	Generalization of criteria regarding what should be recorded as an adverse event.
Section 7.1.5.3.1		
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), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator within 24 hours of when the investigator learns about it or, if the event occurs on a weekend	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), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator within 24 hours of when the investigator learns about it.~~or, if the event occurs on a weekend or national holiday, on the next~~	Revision made in accordance with competent authority input.

Previous approved wording	Amended or new wording	Reason/Justification for change
or national holiday, on the next working day.	~~working day.~~	
Section 7.6 (Other sections affected by this change: 3.6.1)		
A qualified physician at the central ECG vendor will be responsible for interpreting the ECG. However, every ECG should be reviewed immediately at site in order to detect any QTcF prolongation of potential clinical concern and allow dosing. Evaluation of the screening ECG(s) for inclusion in the study can be performed locally, ie, the interpretation from the central ECG vendor is not required for inclusion. Any ECG finding that is judged by the investigator or the physician from the central ECG vendor as a clinically significant change (worsening) compared with a baseline value will be considered an AE, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.	A qualified physician at the central ECG vendor will be responsible for interpreting the ECG. However, every ECG should be reviewed immediately at site in order to detect any QTcF prolongation of potential clinical concern and allow dosing. ***If the local ECG reading results at the site match any of the discontinuation criteria (see Section3.6.1), 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.*** Evaluation of the screening ECG(s) for inclusion in the study can be performed locally, ie, the interpretation from the central ECG vendor is not required for inclusion. Any ECG finding that is judged by the investigator or the physician from the central ECG vendor as a clinically significant change (worsening) compared with a baseline value will be considered an AE, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.	Clarification added per DSMB input.
Section 7.8.2		
(Not applicable)	***A referral for psychiatric evaluation is required for any increase in the scale from baseline.*** 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.	New text regarding the C-SSRS scale and suicidality assessment.
8 ASSESSMENT OF PHARMACOKINETICS AND PHARMACOGENOMICS		
Section 8.2		
A blood sample (10 mL) will be collected in 2 dipotassium ethylenediaminetetraacetic acid (K2EDTA) plastic tubes at the screening visit for genetic analyses. Analyses will include CAG repeats, CYP2D6 status, and genetic long QT syndrome	A blood sample (10 mL) will be collected in 2 dipotassium ethylenediaminetetraacetic acid (K2EDTA) plastic tubes at the screening visit for genetic analyses. Analyses will include CAG repeats, CYP2D6 status, and genetic long QT syndrome (assessed only	Clarification.

Previous approved wording	Amended or new wording	Reason/Justification for change
(assessed only in patients experiencing QT prolongation following study drug administration leading to study discontinuation). Additionally, any subpopulation of patients that responds differently to drug (in terms of exposure, efficacy, tolerability, or safety) should be investigated for genetic association, with the exact analysis selected according to the study results. The analyses of CAG repeats from the screening sample will not be used to assess eligibility for the study; that will be assessed using historical data.	in patients experiencing QT prolongation following study drug administration leading to study discontinuation). Additionally, any subpopulation of patients that responds differently to drug (in terms of exposure, efficacy, tolerability, or safety) should be investigated for genetic association, with the exact analysis selected according to the study results. ~~The analyses of CAG repeats from the screening sample will not be used to assess eligibility for the study; that will be assessed using historical data.~~	
9 STATISTICS		
Section 9.3.4		
The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment.	The full analysis set (FAS) will include all patients in the ITT population who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment. ***For patients that discontinue study drug, the FAS will include all efficacy observations that were measured under study drug and the closest next available single observation measured after study drug discontinuation. All other efficacy observations measured after study drug discontinuation will be excluded from the full analysis set, for these patients.***	Clarification regarding analysis of data after study drug discontinuation.
Section 9.3.5 (Other sections affected by this change: 9.3.4; 9.5; 9.6.4.2)		
(Not applicable)	***Section 9.3.5 Follow-Up Analysis Set (FUAS)*** ***The Follow-Up Analysis Set (FUAS) 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.***	New text.
Section 9.5 (Other sections affected by this change: 9.3.4; 9.3.5; 9.6.4.2)		
(Not applicable)	***The FUAS will be used for efficacy variables sensitivity analyses.***	New text.
Section 9.6.3 (Other sections affected by this change: Section 3.2.3)		
• CGI-C at Week 26 as compared to baseline (rated by the study investigator and the patient)	• CGI-C at Week 26 as compared to baseline (rated by the ~~study investigator~~ ***qualified site personnel*** and the patient)	Clarification regarding person who performs the assessments.
Section 9.6.3 (Other sections affected by this change: Section 3.2.3)		
Patient Reported Outcomes:	**Patient Reported Outcomes:**	Change of assessment name;

Previous approved wording	Amended or new wording	Reason/Justification for change
• Change from baseline in HD-QoL at Week 26 • Change from baseline in MSWS-12 at Week 26	• Change from baseline in HD-QoL at Week 26 • ***Change from baseline in EQ5D-5L at Week 26*** • Change from baseline in ~~MSWS~~***Walk***-12 at Week 26	addition of EQ5D-5L.
Section 9.6.4.2 (Other sections affected by this change: Section 9.3.4; 9.3.5; 9.5))		
(Not applicable)	***Additional sensitivity analysis will be performed for change from baseline in UHDRS-TMS on the FUAS population, including efficacy observations measured after study drug discontinuation.***	New text for clarification.
Section 9.6.4.4 (Other sections affected by this change: 3.2.3; 9.6.3)		
The odds of responders will be compared between the active groups and the placebo group using logistic regression analysis (SAS® LOGISTIC procedure) stratified by center using the STRATA sub-command with the following effects: treatment group, neuroleptic use or no use and baseline UHDRS-TMS score. The other efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS. For CIBIC-Plus, the CIBIS score at baseline will be included in the model instead of baseline UHDRS-TMS. For CGI-C, the CGI-S score at baseline will be included in the model instead of baseline UHDRS-TMS.	The odds of responders will be compared between the active groups and the placebo group using logistic regression analysis (SAS® LOGISTIC procedure) stratified by center using the STRATA sub-command with the following effects: treatment group, neuroleptic use or no use and baseline UHDRS-TMS score. ***The change from baseline in HD-QoL and in EQ5D-5L at week 26/Early Termination will be analyzed using an Analysis of Covariance (ANCOVA) Model. The model will include the following fixed effects: treatment, center, neuroleptic use or no use, and baseline HD-QoL or EQ5D-5L score. The last observation carried forward (LOCF) will be applied for these endpoints for early terminated subjects.*** The other efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS. For CIBIC-Plus, the CIBIS score at baseline will be included in the model instead of baseline UHDRS-TMS. For CGI-C, the CGI-S score at baseline will be included in the model instead of baseline UHDRS-TMS.	Addition of new text for the analysis of the HD-QoL and EQ5D.
12 ETHICS		
Section 12.1		
The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. 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 they are	The patient's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the patient. ***Patients with a legal guardian should be consented according to local requirements.*** The investigator will keep the original consent forms, and copies will be given to the	New text added for clarification.

Previous approved wording	Amended or new wording	Reason/Justification for change
free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.	patients. It will also be explained to the patients that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.	
17 REFERENCES		
[22] Reuben DB, Siu AL. An objective measure of physical function of elderly outpatients. The Physical Performance Test. J Am Geriatr Soc. 1990 Oct;38(10):1105-12.	[22] ~~Reuben DB, Siu AL. An objective measure of physical function of elderly outpatients. The Physical Performance Test. J Am Geriatr Soc. 1990 Oct;38(10):1105-12.~~ ***Brown M, Sinacore DR, Binder EF, Kohrt WM. Physical and performance measures for the identification of mild to moderate frailty. J Gerontol A Biol Sci Med Sci. 2000 Jun;55(6):M350-5.***	Updated reference for modified physical performance test (mPPT).
(Not applicable)	[28] The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.	Newly added reference for the EQ5D-5L scale.
[35] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643-62.	[35] ~~Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643-62.~~	Deleted due to change in cognitive assessments.
[36] Bezdicek O, Majerova V, Novak M, Nikolai T, Ruzicka E, Roth J. Validity of the Montreal Cognitive Assessment in the detection of cognitive dysfunction in Huntington's disease. Appl Neuropsychol Adult. 2013;20(1):33-40.	[36] ~~Bezdicek O, Majerova V, Novak M, Nikolai T, Ruzicka E, Roth J. Validity of the Montreal Cognitive Assessment in the detection of cognitive dysfunction in Huntington's disease. Appl Neuropsychol Adult. 2013;20(1):33-40.~~	Deleted due to change in cognitive assessments.

16.7. PROTOCOL AMENDMENT 01 DATED 24 SEPTEMBER 2013

The revisions listed below have been made to the protocol, and synopsis as appropriate, and are considered substantial by the sponsor's Authorized Representative.

The primary reasons for this amendment are to change the duration of treatment in the study from 12 weeks to 26 weeks, and to change the secondary objectives and endpoints.

Substantive changes from the original protocol to Amendment 01 are provided below.

<table>
<tr><th>Previous approved wording</th><th>Amended or new wording</th><th>Reason/Justification for change</th></tr>
<tr><td>TITLE PAGE</td><td></td><td></td></tr>
<tr><td>Teva Pharmaceutical Industries Ltd
12 Hatrufa St., P.O. Box 8077
Sapir Industrial Zone
Netanya, Israel</td><td>Teva Branded Pharmaceutical Products R&D, Inc
41 Moores Rd, Frazer
PA 19355
USA</td><td>Change to the specific details of the sponsor.</td></tr>
<tr><td>CLINICAL STUDY PERSONNEL CONTACT INFORMATION</td><td></td><td></td></tr>
<tr><td>Cell Phone: +65 92349266</td><td>Cell Phone: +65 6895-8256</td><td>Change to cell phone number for Australian sites</td></tr>
<tr><td>Katie Romberg
e-mail: kathleen.romberg@tevapharm.com</td><td>Katie Blatt<s>Romberg</s>
e-mail: kathleen.blatt<s>romberg</s>@tevapharm.com</td><td>Change to surname and e-mail address of operational lead</td></tr>
<tr><td>Send by facsimile to the sponsor's local safety officer (LSO)/ contract research organization (CRO). In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.</td><td>Contact details for notifications of SAEs are as follows:
<table>
<tr><td>Austria</td><td>signal@ratiopharm.at</td></tr>
<tr><td>Australia</td><td>Fax number: +65-6565-7939
e-mail: STUDY-MA-DL-075-070-Blinded@iconplc.com
24-hour hotline: +65-6896-0378</td></tr>
<tr><td>Canada</td><td>phv@tevacanada.com</td></tr>
<tr><td>Denmark</td><td>Safety.Denmark@tevapharm.dk</td></tr>
<tr><td>Germany</td><td>Safety.Germany@teva.de</td></tr>
<tr><td>Italy</td><td>safety_PhVItaly@tevaitalia.It</td></tr>
<tr><td>Netherlands</td><td>dso.nl@tevapharmachemie.com</td></tr>
<tr><td>Russia</td><td>Safety.Russia@teva.ru</td></tr>
<tr><td>UK</td><td>uk.safety@tevauk.com</td></tr>
<tr><td>USA</td><td>us.clinops.sae@tevapharm.com</td></tr>
</table></td><td>Specific contact details added for notifications of SAEs</td></tr>
</table>

Previous approved wording	Amended or new wording	Reason/Justification for change
1 BACKGROUND INFORMATION		
Section 1.3.2		
There were 3 cases with fatal outcome; none of them was considered related to the study medication.	**There were *6*~~3~~ cases with fatal outcome; none of them was considered related to the study medication.**	**Incorporates information from updated Investigator's Brochure.**
Section 1.3.2.1		
It has been shown that during multiple dose administration, pridopidine can inhibit its own CYP2D6-driven metabolism. Consequently, clearance in EM and PM at steady state do not differ significantly and therefore the CYP2D6 genotype has no impact on the exposure to pridopidine at steady state. Due to auto-inhibition of CYP2D6, the fraction metabolized decreases with multiple doses, and renal elimination becomes a more important elimination pathway than the polymorphic CYP2D6 metabolism. Renal clearance of pridopidine at steady state ranges from 90 to 116 mL/min which corresponds well to the glomerular filtration rate.	***In a dedicated PK study, the C_{max} and AUC in PMs compared with EMs is approximately 1.6- and 2.8-fold higher after a single bid dosing day, respectively. At steady-state, however, this difference is reduced to 1.3-fold for both C_{max} and AUC.*** ***A population PK model confirmed*** ~~**It has been shown**~~ **that*****, due to auto-inhibition of*** ~~**during multiple dose administration, pridopidine can inhibit its own**~~ **CYP2D6** ***in EMs***~~**-driven metabolism. Consequently**~~**, clearance in EMs and** ***PMs approach each other*** ~~**PM**~~ **at steady state*****, but they still*** ~~**do not**~~ **differ significantly** ***(9.22 L/h or 6.30 L/h in a typical EM or PM subject weighing 60 kg).*** ~~**and therefore the CYP2D6 genotype has no impact on the exposure to pridopidine at steady state.**~~ **Due to *this* auto-inhibition of CYP2D6, the fraction metabolized decreases with multiple doses, and renal elimination becomes a more important elimination pathway than the polymorphic CYP2D6 metabolism. Renal clearance of pridopidine at steady state ranges from 90 to 116 mL/min which corresponds well to the glomerular filtration rate.**	**Reflects updated population PK report.**
Section 1.4.2		
Psychiatric events were also observed frequently in the patients receiving pridopidine 90 mg bid.	**Psychiatric events *(including nightmare, aggression, depressive mood, anxiety, and abnormal dreams)* were also observed frequently in the patients receiving pridopidine 90 mg bid.**	**Clarification of psychiatric events.**
Section 1.4.5		
Safety margins calculated from the NOAEL compared to human predicted data by a population PK model were 3.4 for 90 mg bid and 2.6 for 112.5 mg bid.	**Safety margins *(based on AUC)* calculated from the NOAEL compared to human predicted data by a population PK model were 3.4 for 90 mg bid and 2.*7*~~6~~ for 112.5 mg bid.**	**Reflects updated population PK report.**

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 1.5		
However, the magnitude of pridopidine effect on motor function was not associated with any of the functional/global measures assessed. It is considered that without a more pronounced effect on UHDRS-TMS than that seen in Studies MermaiHD (ACR16C008) and HART, an effect on a global/functional scale is unlikely, and so increasing the dose of pridopidine is warranted. Consequently, higher doses of 67.5, 90, and 112.5 mg bid will be used in the present study.	**However, the magnitude of pridopidine effect on motor function *could*~~was~~ not *be shown to be of clinical significance to the patient, as measured by the* ~~associated with any of the~~ functional/global measures assessed. *Pridopidine has been shown to have a benign safety profile, similar to placebo,*~~It is considered that without a more pronounced effect on UHDRS-TMS than that seen~~ in *doses*~~Studies MermaiHD (ACR16C008) and HART, an effect on a global/functional scale is unlikely, and~~ so *far tested in patients with HD. Hence it is perceived as relevant to investigate higher doses, with the potential to increase the beneficial effects*~~increasing the dose~~ of pridopidine~~ is warranted~~. Consequently, ~~higher~~ doses of 67.5, 90, and 112.5 mg bid will be used in the present study**	**Clarification of rationale.**
Section 1.5.1 (Other sections affected by this change: Sections 3.11 and 4.2, Exclusion Criterion a)		
Based on those findings, patients with a prolonged QTc interval (defined as a QTc interval of >450 msec for males or >470 msec for females), or other clinically significant heart conditions are excluded from this study.	**Based on those findings, patients with a prolonged QTc interval (defined as a QTc interval of >450 msec~~ for males or >470 msec for females~~), or other clinically significant heart conditions are excluded from this study.**	**Gender difference no longer considered necessary.**
Section 1.5.2		
Based on PK modeling, it is anticipated that approximately 20% of the patients on the higher dose of 112.5 mg bid (and 30% of patients overall) will display C_{max} and AUC above the historical threshold set before substantial clinical safety data were collected.	**Based on PK modeling, it is anticipated that approximately *1.9*~~20~~% of the patients on the higher dose of 112.5 mg bid (and *2.1*~~30~~% of patients overall) will display C_{max} ~~and AUC~~ above the historical threshold set before substantial clinical safety data were collected.**	**Reflects updated population PK report.**
Section 1.5.2		
In the open-label extension of the HART study, 2 patients experienced convulsions. In one of these patients, the convulsions were considered related to concurrent encephalitis.	**In the open-label extension of the HART study, 2 patients experienced convulsions. In one of these patients, the convulsions were considered related to concurrent encephalitis. *In the other case, although there were certain confounding factors, relationship to the study medication could not be entirely excluded.***	**Clarification.**

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 1.5.3 (Other sections affected by this change: Sections 3.1 and 3.3)		
Additionally, the Safety Committee may decide to discontinue 1 or more treatment arms if more than 30% of the patients in the treatment arm have discontinued dosing due to intolerable AEs	**Additionally, the *Drug* Safety *Monitoring Board (DSMB)*~~Committee~~ may decide to discontinue 1 or more treatment arms if more than 30% of the patients in the treatment arm have discontinued dosing due to intolerable AEs**	**Change to nomenclature of committee.**
2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES		
Section 2.1 (Most other sections affected by this change)		
The present clinical study is planned to primarily assess the effects and dose-response of 4 dose levels of pridopidine (45, 67.5, 90, and 112.5 mg bid), compared with placebo, on improvement in motor function in patients with HD after 12 weeks of treatment	**The present clinical study is planned to primarily assess the effects and dose-response of ~~4 dose levels of~~ pridopidine ~~(45, 67.5, 90, and 112.5 mg bid)~~, compared with placebo, on improvement in motor function in patients with HD after *26*~~12~~ weeks of treatment**	**Increase in duration of treatment.**
Section 2.2		
The primary objective of this study is to assess the efficacy and dose-response of pridopidine 45 to 112.5 mg bid on motor impairment in patients with HD after 12 weeks of treatment using the UHDRS-TMS. **The secondary efficacy objectives of the study are to assess the effect and dose-response of 12 weeks treatment with pridopidine on various functional scales:** **The Clinician's Interview-based Impression of Change plus Caregiver Input (CIBIC-Plus)** **The Physical Disability Scale (PDS)** **UHDRS Functional assessment (FA)** **The other secondary objectives are as follows:** **To evaluate the safety and tolerability of a range of pridopidine doses in patients with HD during 12 weeks of treatment** **To explore the PK of pridopidine in the study population** **To investigate the relationship between exposure to pridopidine and outcome measures (eg, clinical efficacy and toxicity parameters)**	**The primary objective of this study is to assess the efficacy ~~and dose-response~~ of pridopidine *67.5* ~~45~~ to 112.5 mg bid on motor impairment in patients with HD after *26*~~12~~ weeks of treatment using the UHDRS-TMS.** **The secondary efficacy objective~~s~~ of the study *is*~~are~~ to assess the effect ~~and dose-response~~ of *26*~~12~~ weeks *of* treatment with pridopidine *67.5 to 112.5 mg bid* on *the PPT*.~~various functional scales:~~ **The Clinician's Interview-based Impression of Change plus Caregiver Input (CIBIC-Plus)** **The Physical Disability Scale (PDS)** **UHDRS Functional assessment (FA)** **The other secondary objectives are as follows:** **To evaluate the safety and tolerability of a range of pridopidine doses in patients with HD during *26*~~12~~ weeks of treatment** **To explore the PK of pridopidine in the study population** **To investigate the relationship between exposure to pridopidine and outcome measures (eg, clinical efficacy and toxicity**	**Change to objectives, including removal of the 45 mg dose from the efficacy analyses.**

Previous approved wording	Amended or new wording	Reason/Justification for change
Exploratory efficacy endpoints will also be analyzed; these are detailed in Section 3.2.4.	**parameters)** ***Other*~~Exploratory~~ efficacy endpoints will also be analyzed; these are detailed in Section 3.2.3.**	
3 STUDY DESIGN		
Section 3.1		
This is a multicenter, multinational, randomized, parallel-group, double-blind, placebo-controlled study to compare the efficacy and safety of pridopidine 45, 67.5, 90, and 112.5 mg bid versus placebo in the treatment of motor impairment in HD.	**This is a multicenter, multinational, randomized, parallel-group, double-blind, placebo-controlled study to compare the efficacy and safety of pridopidine 45, 67.5, 90, and 112.5 mg bid versus placebo in the treatment of motor impairment in HD. *The 45 mg dose level will not be formally included in the efficacy analyses.***	**Removal of the 45 mg dose from the efficacy analyses.**
Section 3.1 (Other sections affected by this change: Section 7)		
An independent Safety Committee meeting will be held to assess safety data once 10 patients from each treatment arm (ie, a total of 50 patients) have been exposed to their respective full dose for at least 2 weeks (ie, after 6 weeks of treatment). In case of a significant emerging safety concern in 1 or more treatment arm(s), the Safety Committee will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatments arm(s) with safety concerns. A second Safety Committee meeting will be held to assess safety data once approximately 20 patients from each treatment arm (ie, a total of 100 patients) have been exposed to their respective full dose for at least 2 weeks. At the second meeting, the Safety Committee will decide whether there is a need for additional meetings, and, if needed, will determine when these will take place.	**An independent *DSMB*~~Safety Committee~~ meeting will be held to assess safety data, *6 weeks after* ~~once~~ 10 patients from each treatment arm (ie, a total of 50 patients) have been *enrolled*~~exposed to their respective full dose for at least 2 weeks (ie, after 6 weeks of treatment)~~. In case of a significant emerging safety concern in 1 or more treatment arm(s), the *DSMB*~~Safety Committee~~ will have the authority to discontinue enrolled patients from study drug administration in the treatment arm(s) with safety concerns, and stop randomization of new patients into the treatments arm(s) with safety concerns. A second *DSMB*~~Safety Committee~~ meeting will be held to assess safety data, *6 weeks after* ~~once~~ approximately 20 patients from each treatment arm (ie, a total of 100 patients) have *enrolled*~~been exposed to their respective full dose for at least 2 weeks~~. At the second meeting, the *DSMB*~~Safety Committee~~ will decide whether there is a need for additional meetings, and, if needed, will determine when these will take place.**	**Change to timing of DSMB meetings.**
Section 3.1 (Other sections affected by this change: Sections 1.7 and 4.1 Inclusion Criterion a)		
The diagnostic of HD will be established based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene.	**The diagnostic of HD will be established based on clinical features and the presence of ≥36 CAG repeats in the huntingtin gene *(from historical data)*.**	**Clarification.**

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 3.1 (Other sections affected by this change: Section 3.11)		
CIBIS, UHDRS-TMS, UHDRS-TFC, and PDS should be evaluated prior to the other scales.	**~~CIBIS,~~ UHDRS-TMS~~, UHDRS-TFC,~~ and *PPT*~~PDS~~ should be evaluated prior to the other scales.**	**Change to priority to reflect reordering of endpoints.**
Section 3.1 (Other sections affected by this change: Section 3.11)		
During the on-site visit at Day 14, before the administration of the study drug, a 12-lead ECG will be performed in triplicate and blood samples will be taken for PK sampling and electrolyte monitoring; if hypokalemia is observed, dosing will be interrupted until normal electrolyte values are confirmed and maintained for 7 days. Vital signs will be assessed in addition to the inquiry about AEs and concomitant medications. Additional 12-lead ECGs will be performed in triplicate 1 to 2 hours after dose administration, followed by collection of the PK sample.	**During the on-site visit at Day 14, before the *afternoon dose* ~~administration~~ of the study drug, a ~~12-lead ECG will be performed in triplicate and~~ blood sample~~s~~ will be taken for ~~PK sampling and~~ electrolyte monitoring; if hypokalemia is observed, dosing will be interrupted 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.* Vital signs will be assessed in addition to the inquiry about AEs and concomitant medications. *Twelve*~~Additional 12~~ lead ECGs will be performed in triplicate 1 to 2 hours after *the afternoon* dose *of study drug on Day 14*~~administration~~, followed by collection of *a* ~~the~~ PK sample.**	**Assessments are now performed relative to the afternoon dose. Time period applied for normalization of electrolytes.**
Section 3.1 (Most other sections affected by this change)		
During the full treatment dose period (Days 28 to 84), there will be a total of 4 on-site visits at Days 28, 42, 56, and 84 (or at early termination) and a phone call on Day 35. During the phone call at Day 35, inquiries about AEs and concomitant medication will be conducted. At each of the on-site visits, safety variables will be assessed, including triplicate ECG evaluation at predose and 1 to 2 hours after dose administration at the site (ECG is optional on Day 56), and clinical laboratory evaluations. In addition, PK sampling for determination of the levels of pridopidine and TV-45065 will be done on Days 28, 42 and 84 before first dose, 1 to 2 hours after dose administration at the site, and on Days 42 and 84 also before leaving the site. When concomitant to ECG, PK samples will be collected after the ECG recording.	**During the full treatment dose period (Days 28 to *182*~~84~~), there will be a total of *7*4 on-site visits at Days 28, 42, 56, *84, 112, 140,* and *182* ~~84~~ (or at early termination) and a phone call on Day 35. *Visits and procedures during the full dose period will be scheduled around the afternoon dose, with the exception of Day 182 where only the morning dose is administered.* During the phone call at Day 35, inquiries about AEs and concomitant medication will be conducted. At each of the on-site visits, safety variables will be assessed, including triplicate ECG evaluation *before* ~~at predose~~ and 1 to 2 hours after dose administration at the site (ECG is optional on Day 56), and clinical laboratory evaluations. ~~In addition,~~ PK sampling for determination of the levels of pridopidine and TV-45065 will be done on Days 28, 42*, and 112 (before* and ~~84 before first dose,~~ 1 to 2 hours after *the afternoon dose),* ~~dose administration at the site, and~~ on Days *84 and 140***	**Additional visits added due to extended duration of study.**

Previous approved wording	Amended or new wording	Reason/Justification for change
	***(1 to 2 hours after the afternoon dose),*~~42~~ and *on Day 182 (before the morning dose)*~~84 also before leaving the site~~. When concomitant to ECG, PK samples will be collected after the ECG recording.	
Section 3.1 (Other sections affected by this change: Sections 3.11 and 7.6)		
Additional 12-lead ECG evaluations should be performed on site, at the investigators discretion, 1 to 2 hours after the afternoon dose for patients who, after their morning dose, show an increase from baseline in their QTcF value >50 msec (see Section 7.6). This optional afternoon ECG measurement is included for safety reasons, as the concentration of study drug may be higher in the afternoon than in the morning.	**(Text deleted)**	**No longer necessary as assessments will now be performed relative to afternoon dosing.**
Section 3.1		
(Not applicable)	***Patients who complete this study may have the opportunity to enter an open-label extension study.***	**New information.**
Section 3.2.1 (Other sections affected by this change: Section 9.6.1)		
The primary efficacy variable and endpoint for this study is: **Change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week 12**	**The primary efficacy variable and endpoint for this study is:** **Change from baseline in the UHDRS-TMS (defined as the sum of all UHDRS motor domains ratings) at Week *26*~~12~~**	**Change to time point for end point due to extended duration of study.**
Section 3.2.2 (Other sections affected by this change: Section 9.6.2)		
The secondary functional efficacy variables and endpoints for this study are as follows: **CIBIC-Plus global score at Week 12 as compared to baseline (rated by an independent investigator)** **Change from baseline in the PDS score at Week 12** **Change from baseline in UHDRS-FA at Week 12**	**The secondary functional efficacy variables~~ and endpoints~~ for this study ~~are as follows~~ *is*** ***Change from baseline in the PPT at Week 26*** **CIBIC-Plus global score at Week 12 as compared to baseline (rated by an independent investigator)** **Change from baseline in the PDS score at Week 12** **Change from baseline in UHDRS-FA at Week 12**	**Change to secondary endpoint.**
Section 3.2.3 (Other sections affected by this change: Section 9.6.3)		
Other functional efficacy variables and endpoints for this study are as follows:	***Global Functional Scales:*** ***CIBIC-Plus global score at Week 26 as compared to baseline***	**Endpoints moved into this section from original**

Previous approved wording	Amended or new wording	Reason/Justification for change
CGI-C at Week 12 as compared to baseline (rated by the study investigator and the patient) **Change from baseline in UHDRS-TFC at Week 12** **Change from baseline in UHDRS-IS at Week 12**	***(rated by an independent investigator)*** ***Change from baseline in the PDS score at Week 26*** ***Change from baseline in UHDRS-FA at Week 26*** **CGI-C at Week *26~~12~~* as compared to baseline (rated by the study investigator and the patient)** **Change from baseline in UHDRS-TFC at Week *26~~12~~*** **Change from baseline in UHDRS-IS at Week *26~~12~~*** ***Patient Reported Outcomes:*** ***Change from baseline in HD-QoL at Week 26*** ***Change from baseline in MSWS-12 at Week 26*** ***UHDRS-TMS Subscores:*** ***Change from baseline in hand movement score (defined as the sum of UHDRS domains finger taps, pronate-supinate hands and luria [fist-hand-palm test]) at Week 26*** ***Change from baseline in Gait and balance score (defined as the sum of UHDRS domains gait, tandem walking and retropulsion pull test) at Week 26*** ***Change from baseline in UHDRS-mMS (defined as the sum of UHDRS domains dysarthria, tongue protrusion, finger taps, pronate-supinate hands, luria, rigidity, bradykinesia, gait, tandem walking, retropulsion pull test) at Week 26*** ***Change from baseline in UHDRS-Chorea at Week 26*** ***Change from baseline in UHDRS-Dystonia at Week 26*** ***Responders, defined as patients with UHDRS-TMS change from baseline ≤0 at Week 26*** ***Other Motor Assessments:*** ***Change from baseline in Q-Motor measurements at Week 26 including digitomotography (speeded index finger tapping), dysdiadochomotography (pronation/supination hand tapping), manumotography and choreomotography (grip force and chorea analysis) and pedomotography (speeded foot tapping)*** ***Change from baseline in the TUG test at Week 26***	**Section 3.2.2 and also the deleted original Section 3.2.4 (Exploratory/ Other Efficacy Variables and Endpoints). Additionally, new endpoints of UHDRS-Chorea and UHDRS-Dystonia.**

Previous approved wording	Amended or new wording	Reason/Justification for change
	Cognitive/Psychiatric Assessments: ***Change from baseline in CAB at Week 26: SDMT, Emotion Recognition, Trail Making Test, HVLT-R, Paced Tapping at 3 Hz, OTS*** ***Change from baseline in PBA-s at Week 26***	
Section 3.4.1.1 (Other sections affected by this change: Sections 3.4, 3.4.1.2, 3.4.2.1, 3.4.2.2,)		
Weeks 1 to 4: Titration Period	**Weeks 1 to 4 *(up to Day 27)*: Titration Period**	**Structure of study weeks redefined such that Day 28 falls at end of Week 4 (not start of Week 5).**
Section 3.5		
For each patient, the duration of participation is planned to be up to 16 weeks, consisting of a screening period of up to 2 weeks, a 12-week randomized double-blind treatment period (comprised of a 4-week titration and 8-week full dose period), and a 2-week follow-up period following the last dose of study medication. **The total duration of the study is estimated to be approximately 40 weeks.**	**For each patient, the duration of participation is planned to be up to *30~~16~~* weeks, consisting of a screening period of up to 2 weeks, a *26~~12~~*-week randomized double-blind treatment period (comprised of a 4-week titration and *22~~8~~*-week full dose period), and a 2-week follow-up period following the last dose of study medication.** **The total duration of the study is estimated to be approximately ~~40 weeks~~ *15 months*.**	**Extension of study duration.**
Section 3.6.1		
If hypokalemia is observed (serum potassium <4 mmol/L), dosing will be interrupted and should not be started again until normal electrolyte values are confirmed and maintained for 7 days. **Patients should be discontinued if either of the following criteria relating to QTcF is met:** **QTcF >500 msec (based on the mean value from the triplicate ECG measurements)** **QTcF >480 msec with concurrent increase in QTcF >60 msec (based on the mean value from the triplicate ECG measurements) from baseline (Day 0)**	**If hypokalemia is observed ~~(serum potassium <4 mmol/L)~~, 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.*** **Patients should be discontinued if *any*~~either~~ of the following criteria relating to QTcF *are* ~~is~~ met:** **QTcF >500 msec (based on the mean value from the triplicate ECG measurements)*;*** **QTcF >480 msec with concurrent increase in QTcF >60 msec**	**Modifications to rules for discontinuation of individual patients.**

Previous approved wording	Amended or new wording	Reason/Justification for change
	(Δ*QTcF*, based on the mean value from the triplicate ECG measurements) from baseline (Day 0)*;* ***If QTcF >480 msec or ΔQTcF >60 msec, a repeat ECG (in triplicate) will be recorded after 7 to 9 days; if the change is confirmed and electrolytes are normal, the patient will be withdrawn.***	
Section 3.6.2		
The Safety Committee should consider stopping a treatment arm if: **the largest placebo-corrected mean change from baseline QTcF (ΔΔQTcF) exceeds 40 msec** **if more than 30% of the patients have discontinued dosing based on QTc stopping criteria;** **if there are findings of concern following review of the relationship between any convulsions and PK data;** **if more than 30% of the patients in the treatment arm have discontinued dosing due to intolerable AEs.**	***If any of the following conditions related to a treatment arm are met, the DSMB*~~The Safety Committee~~ should *review the data and* consider stopping *that*~~a~~ treatment arm ~~if~~:** ***If ≥20% of the patients in a treatment arm have discontinued dosing based on QTc stopping criteria (as defined in Section 3.6.1), provided there are at least 3 events;*** **If the largest placebo-corrected mean change from baseline QTcF (ΔΔQTcF) *for a treatment arm* exceeds 40 msec*;*** **if more than 30% of the patients have discontinued dosing based on QTc stopping criteria;** **If there are findings of concern following review of the relationship between any convulsions and PK data *for a treatment arm*;** **If >~~if more than~~ 30% of the patients in the treatment arm have discontinued dosing due to intolerable AEs.** ***These conditions are not discontinuation criteria, but are triggers for a review by the DSMB, who may decide to discontinue the treatment arm following their review.***	**Modifications to rules for discontinuation of treatment arm.**
Section 3.8		
Blinded PK data may be assessed during the study. The individuals responsible for sample bioanalysis and PK analysis and other responsible staff members will know who received study drug and who received placebo during the study but will not have access to any clinical data. The unblinded person responsible for PK analysis will provide concentration data to other staff members in a manner that will not identify individual	***Unblinded*~~Blinded~~ PK *and ECG* data may be assessed during the study. The individuals responsible for sample bioanalysis and PK analysis and other responsible staff members *supporting the unblinded data review by the DSMB* will know who received study drug and who received placebo during the study but will not have access to any clinical data. The unblinded person responsible for PK analysis will provide concentration data to**	**Clarification of blinding procedures.**

Previous approved wording	Amended or new wording	Reason/Justification for change
patients (ie, a dummy patient identifier will be linked to an individual patient's concentration data). **For information about personnel who may be aware of treatment assignments, see Section 3.3. These individuals will not be involved in conduct of any study procedures or assessment of any AEs.** **The Safety Committee can request unblinding if deemed necessary for appropriate safety evaluation.**	**other staff members in a manner that will not identify individual patients (ie, *mean values only or* a dummy patient identifier will be linked to an individual patient's concentration data).** ***The DSMB can request unblinding if deemed necessary for appropriate safety evaluation.*** **For information about personnel who may be aware of treatment assignments, see Section 3.3. These individuals will not be involved in conduct of any study procedures or assessment of any AEs. *The sponsor personnel involved in the safety and efficacy analysis of the study will remain blinded to the treatment allocation.*** **The Safety Committee can request unblinding if deemed necessary for appropriate safety evaluation.**	
Section 3.10		
The study is expected to start in September 2013 (first patient enrolled) and be completed in June 2014 (last patient last visit), with a duration of approximately 9 months. **Approximately 250 patients from approximately 25 to 30 investigational centers in multiple countries are planned to be enrolled in the study.**	**The study is expected to start in *Q1 2014*~~September 2013~~ first patient enrolled) and be completed in *Q2 2015* ~~June 2014~~ (last patient last visit), ~~with a duration of approximately 9 months.~~** **Approximately *400*~~250~~ patients from approximately *40*~~25 to 30~~ investigational centers in multiple countries are planned to be enrolled in the study.**	**Change to start and end dates of study, change to number of investigational centers due to increased sample size.**
Section 3.11.3.1.2 (Other sections affected by this change: Section 3.4)		
The following procedures/assessments will be performed at Week 3 on the Day 14 (±3 days) visit (Visit 2):	**The following procedures/assessments will be performed at Week *2*~~3~~ on the Day 14 (±3 days) visit (Visit 2)*; tolerability to the study drug will be evaluated through assessment of AEs and concomitant medication usage, to allow the weekly dose increase during the titration period*:**	**Structure of study weeks redefined such that Day 14 falls at end of Week 2 (not start of Week 3). Also, clarification regarding dose titration.**
Section 3.11.3.2.1		
The following procedures/assessments will be performed on Days 28 (±4 days), 42 (±5 days), and 56 (±5 days) at Weeks 5, 7, and 9 (Visits 3, 4, and 5):	**The following procedures/assessments will be performed *in conjunction with afternoon dosing* on Days 28 (±4 days), 42 (±5 days), ~~and~~ 56 (±5 days), *84 (±7 days), 112 (±7 days), and 140 (±7 days),* at Weeks *4, 6, 8, 12, 16*~~5, 7~~, and *20*~~9~~ (Visits 3 *to 8*~~, 4,~~**	**Full dose period redefined as study duration has been extended.**

Previous approved wording	Amended or new wording	Reason/Justification for change
	~~and 5~~):	
4 SELECTION AND WITHDRAWAL OF PATIENTS		
Section 4		
(Not applicable)	***Inclusion/exclusion criteria should be documented throughout the screening process and the investigator should document review of inclusion/exclusion criteria prior to randomization. The patients should continue to meet inclusion/exclusion criteria at the Baseline visit. If a patient no longer meets inclusion/exclusion criteria at Baseline then the patient will not be eligible for the study. Baseline laboratory values will not be known until after randomization; if there is a finding in the Baseline laboratory values which would cause the patient to be ineligible for the study, the site should review this with the Medical Monitor.***	**New text.**
Section 4.1		
c. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study, including the follow-up period. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, or double barrier contraception, ie, condom and diaphragm, diaphragm and spermicidal gel or foam). Abstinence is an acceptable method of contraception. Males have to be compliant in using adequate birth control with their partners (as defined above) throughout the duration of the study.	**c. Females of child bearing potential have to be compliant in using adequate birth control throughout the duration of the study, including the follow-up period. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, or double barrier contraception, ie, condom and diaphragm~~, diaphragm and spermicidal gel or foam~~). Abstinence is an acceptable method of contraception. *Male study participants*~~Males~~ have to be compliant in using adequate birth control with their partners (as defined above) throughout the duration of the study.**	**Clarification**
Section 4.1 (Other sections affected by this change: Section 6.3.1)		
k. Availability and willingness of a caregiver, informant or family member to accompany the patient to the clinic at study visits assessing CIBIC-Plus and HD-QoL	**k. Availability and willingness of a caregiver, informant or family member to accompany the patient to the clinic at study visits assessing CIBIC-Plus, ~~and~~ HD-QoL, *and CGI-S/CGI-C. For the purposes of this study, a caregiver is recommended to be someone who attends to the patient at least 2 to 3 times per week for at least 3 hours per occasion, and the suitability of the caregiver should be judged by the investigator.***	**Clarification**

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 4.2		
b. Patients with clinically significant heart disease at the screening visit	**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.***	**Clarification**
Section 4.2		
c. Patients with a history of Long QT Syndrome or a first degree relative with this condition.	**c. Patients with a *known* history of Long QT Syndrome or a first degree relative with this condition.**	**Clarification**
Section 4.2 (Other sections affected by this change: Section 7.4.1)		
f. Patients with serum potassium, magnesium and/or calcium levels outside of the central laboratory's reference range at the screening visit	**f. Patients with serum potassium, magnesium and/or calcium levels outside of the central laboratory's reference range at the screening visit*. Repeat testing is allowed (up to a maximum of 3 tests) if required to establish if values are within normal range.***	**Clarification**
Section 4.2		
i. Creatinine clearance <60 mL/min at screening, calculated using the Cockcroft-Gault equation	**i. 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)***	**Clarification**
Section 4.2		
k. Ongoing alcohol and/or drug abuse (within the 6 months prior to screening) as defined by Diagnostic and Statistical Manual – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse.	**k. *Alcohol*~~Ongoing alcohol~~ and/or drug abuse ~~(~~within the 6 months prior to screening~~)~~ as defined by Diagnostic and Statistical Manual – Fourth Edition Text Revision (DSM-IV TR) criteria for substance abuse.**	**Clarification**

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 4.2		
l. Patients with active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the C-SSRS	**l. Patients with active suicidal ideation as measured by a most severe suicide ideation score of 4 (Active Suicidal Ideation with Some Intent to Act, without Specific Plan) or 5 (Active Suicidal Ideation with Specific Plan and Intent) on the C-SSRS, *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), or patients who, in the opinion of the investigator, present a serious risk of suicide.***	**Clarification**
Section 4.2		
m. Patients with known intracranial risk or history of stroke or hemorrhage	**m. Patients with known intracranial *neoplasms, vascular malformations,* ~~risk or~~ history of *cerebrovascular accident,*~~stroke~~ or *intracranial* hemorrhage.**	**Clarification**

Previous approved wording	Amended or new wording	Reason/Justification for change
5 TREATMENT OF PATIENTS		
Section 5.3.1		
Aripiprazole, risperidone, and perphenazine are permitted, subject to dose reductions.	**Aripiprazole, risperidone, and perphenazine are permitted, subject to dose reductions *(ie, keeping the dose as low as possible)*.**	**Clarification**
Section 5.3.1		
(Not applicable)	***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. 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.***	**New text**
Section 5.3.1		
Allowed medications lowering seizure thresholds are baclofen, bupropion, ciprofloxacin, cyclosporine, isoniazid, lindane, methylphenidate, metronidazole, penicillins, theophylline, amantadine, morphine, buprenorphine, diphenoxylate, alfentanil, fentanyl, remifentanil, meptazinol, and pethidine.	**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.**	**Clarification**
Section 5.5		
(See Section 5.5 of original protocol for previous version of Table 3; total blood volume was 167 mL)	**(See Section 5.5 of this amended protocol for revised version of Table 3; new blood volume is 204.5 mL)**	**Changes to blood volumes.**
6 ASSESSMENT OF EFFICACY		
Section 6 (Other sections affected by this change: Section 3.11)		
Except where stated, efficacy assessments detailed in the following sections are performed on Day 0 (Visit 0, baseline),	**Except where stated, efficacy assessments detailed in the following sections are performed on Day 0 (Visit 0, baseline),**	**Change of time points due to extended duration**

Previous approved wording	Amended or new wording	Reason/Justification for change
Day 28 (Visit 3), Day 56 (Visit 5), and Day 84 (Visit 6). UHDRS-TMS and Q-Motor assessments will also be performed at the follow-up visit.	**Day 28 (Visit 3), Day 56 (Visit 5), ~~and~~ Day 84 (Visit 6), *Day 112 (Visit 7), Day 140 (Visit 8), and Day 182 (Visit 9). Except for at Day 0, efficacy assessments can take place before or after the afternoon dose, with the time of the evaluation recorded.* UHDRS-TMS and Q-Motor assessments will also be performed at the follow-up visit.**	**of study and also clarification that procedures will be relative to afternoon dosing.**
Section 6.3.7.1		
(Not applicable)	***HD-QoL will be assessed by both caregiver and patient.***	**New text**
Section 6.3.8.4 (Other sections affected by this change: Section 3.11)		
(Not applicable)	***6.3.8.4 UHDRS-Chorea*** ***In the UHDRS, maximal chorea is scored from 0 (absent) to 4 (marked/prolonged) on each of the following items: face, mouth, trunk, right upper extremity, left upper extremity, right lower extremity, and left lower extremity. Maximal chorea is the sum of all scores.***	**New section**
Section 6.3.8.5 (Other sections affected by this change: Section 3.11)		
(Not applicable)	***6.3.8.5. UHDRS-Dystonia*** ***In the UHDRS, maximal dystonia is scored from 0 (absent) to 4 (marked/prolonged) on each of the following items: trunk, right upper extremity, left upper extremity, right lower extremity, and left lower extremity. Maximal dystonia is the sum of all scores.***	**New section**
Section 6.3.10 (Other sections affected by this change: Sections 3.1, 3.11, 9.6.3)		
6.4.4.1. Symbol Digit Modalities Test **The SDMT is a paper/pencil test that requires patients to look at a key that pairs specific symbols to the digits 1 to 9, and then to look at a series of symbols and fill in the corresponding missing numbers.** **6.4.4.2. Stroop Word Reading Test** **The Stroop interference test measures the ability of the patient to concentrate and ward off distractions.[35] The test consists of 3 items; naming color rectangles (red, green, or blue), reading**	***6.3.10.1. Symbol Digit Modalities Test*** ***The SDMT is a paper-and-pencil test of psychomotor speed and working memory. Participants view a 'key' at the top of the page containing symbols paired with numbers. The remainder of the page displays rows of symbols, and the participant has 90 seconds to write the corresponding number that matches each symbol.*** ***6.3.10.2. Emotion Recognition*** ***Emotion recognition of facial expressions of emotions is examined using computerized presentations of photographs depicting 6 basic***	**Change to cognitive assessments.**

Previous approved wording	Amended or new wording	Reason/Justification for change
color words written in black, and naming the color of the ink of incongruent color words. Each test comprises 100 stimuli presented on a card. The test is scored as the number of correct responses made in 45 seconds. **6.4.4.3. Montreal Cognitive Assessment Scale (Partial)** **The MoCA is a freely available paper and pencil test, designed as a screening for mild cognitive impairment.[36] It includes assessments of visuospatial and executive function, memory, attention, language, abstraction, delayed recall (optional), and orientation. For this study, an abbreviated version of the MoCA will be used, ie, the MoCA partial (including 3 sub-items - memory, language, and fluency – that will be assessed)** **6.4.4.4. Trail Making Tests A and B** **In the Trail Making Test, part A, the patient sees a scattered display of circled numbers and has to "connect the dots" by tracing a line going through each number in increasing, sequential order. The Trail Making Test, part B is similar except the patient has to alternate between letters and numbers (A-1-B-2-C-3, etc).[30] Trail A is used only as part of the training.**	***emotions or a neutral expression. Participants are asked to indicate the emotion expressed in each photograph by selecting from the words fear, disgust, happy, sad, surprise, angry, and neutral (10 stimuli per emotion).*** ***6.3.10.3. Trail Making Tests A and B*** ***Visual attention and task switching are assessed using the Trail Making test, which consists of 25 circles on a standard sheet of paper. For Trails A, participants are required to connect, as quickly as possible, circles containing numbers in ascending numerical order. For Trails B, participants are to connect, as quickly as possible, circles containing numbers and letters, alternating between numbers and letters in ascending order (eg, 1, A, 2, B, 3, C, etc. Trail A is used only as part of the training.*** ***6.3.10.4. Hopkins Verbal Learning Test, revised*** ***The HVLT-R offers a brief assessment of verbal learning and memory (recognition and recall). It is easy to administer and score and is well tolerated even by significantly impaired individuals. Its use has been validated with brain-disordered populations (eg, Alzheimer's disease, HD, amnestic disorders) as a measure of verbal learning and memory. Each form consists of a list of 12 nouns (targets) with 4 words drawn from each of 3 semantic categories. The semantic categories differ across the 6 forms, but the forms are very similar in their psychometric properties. Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index. The HVLT-R has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well established.*** ***6.3.10.5. Paced Tapping test*** ***Psychomotor function is assessed in a Paced Tapping test. Participants tap on left and right mouse buttons, alternating between thumbs, at 3.0 Hz. They first listen to a tone presented at the desired tapping rate, and then begin tapping to the tone. After 11 taps with the tone, the repetition of the tone is discontinued, and participants attempt to continue tapping at the same rate until the end of the trial (31 taps later).***	

Previous approved wording	Amended or new wording	Reason/Justification for change
	6.3.10.6. One Touch Stockings of Cambridge ***OTS is a spatial planning task which gives a measure of frontal lobe function. OTS is a variant of the Stockings of Cambridge task, and places greater demands on working memory as the participant has to visualize the solution. As with Stockings of Cambridge, the participant is shown 2 displays containing 3 colored balls. The displays are presented in such a way that they can easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam. This arrangement makes the 3-dimensional concepts involved apparent to the participant, and fits with the verbal instructions.*** ***There is a row of numbered boxes along the bottom of the screen. The test administrator first demonstrates to the participant how to use the balls in the lower display to copy the pattern in the upper display, and completes 1 demonstration problem, where the solution requires 1 move. The participant must then complete 3 further problems, 1 each of 2 moves, 3 moves, and 4 moves.*** ***Next, the participant is shown further problems, and must work out in their head how many moves the solutions to these problems require, then touch the appropriate box at the bottom of the screen to indicate their response.***	
7 ASSESSMENT OF SAFETY		
Section 7.4 (Other sections affected by this change: Section 3.11)		
Clinical laboratory tests (serum chemistry including electrolytes, hematology and urinalysis) will be performed at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2; electrolytes only), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 or Early Termination (Visit 6), and at the follow-up visit	**Clinical laboratory tests (serum chemistry including electrolytes, hematology and urinalysis) will be performed at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2; electrolytes only), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 *(Visit 6), Day 112 (Visit 7), Day 140 (Visit 8), Day 182 (Visit 9)* or Early Termination ~~(Visit 6)~~, and at the follow-up visit**	**Change to time points due to extended duration of study.**
Section 7.4.3.1 (Other sections affected by this change: Sections 3.11 and 7.4.3.1)		
Human chorionic gonadotropin (HCG) serum test will be performed for all women of childbearing age at screening.(Visit 0). HCG urine tests will be performed for all women of childbearing age at Day 28 (Visit 3), Day 56 (Visit 5), Day 84 or	**Human chorionic gonadotropin (HCG) serum test will be performed for all women of childbearing age at screening (Visit 0). *An indeterminate reading for the serum pregnancy test should be checked twice (urine test) and the patient referred to a***	**Change to time points due to extended duration of study and also clarification regarding**

Previous approved wording	Amended or new wording	Reason/Justification for change
Early Termination (Visit 6), at the follow-up visit, and if clinically indicated at any other time.	***gynecologist if required; no study drug will be administered until this is resolved.*** **HCG urine tests will be performed for all women of childbearing age at *baseline (Visit 1)*, Day 28 (Visit 3), Day 56 (Visit 5), Day 84 *(Visit 6)*, *Day 112 (Visit 7)*, *Day 140 (Visit 8)*, *Day 182 (Visit 9)* or Early Termination ~~(Visit 6)~~, at the follow-up visit, and if clinically indicated at any other time.**	**indeterminate readings. Additionally, a urine test has been added at baseline.**
Section 7.5 (Other sections affected by this change: Section 3.11)		
Vital signs will be measured at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 or Early Termination (Visit 6), and at the follow-up visit.	**Vital signs will be measured at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 *(Visit 6)*, *Day 112 (Visit 7)*, *Day 140 (Visit 8)*, *Day 182 (Visit 9)* or Early Termination ~~(Visit 6)~~, and at the follow-up visit.**	**Change to time points due to extended duration of study.**
Section 7.6 (Other sections affected by this change: Section 3.11)		
A single resting 12-lead ECG will be conducted at screening (Visit 0). If there is evidence of a prolonged QTcF interval at screening (defined as a QTcF interval of >450 msec for males or >470 msec for females) then the ECG will be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study. **ECGs will be performed in triplicate prior to dosing on site and 1 to 2 hours after dosing on site at baseline (Visit 1), Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), and Day 84 or Early Termination (Visit 6). At the discretion of the investigator, 12-lead ECG measurements can also be performed on Day 56 (Visit 5) where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.** **Additional 12-lead ECG evaluations should be performed on site, at the investigators discretion, 1 to 2 hours after the afternoon dose for patients who, after their morning dose, show an increase from baseline in their QTcF value >50 msec. The site will compare the machine produced QTcF value from the morning ECG to the central ECG vendor reported Baseline QTcF; if the change is >50 msec then the afternoon ECG**	**A single resting 12-lead ECG will be conducted *after at least 5 minutes of supine rest* at screening (Visit 0). If there is evidence of a prolonged QTcF interval at screening (defined as a QTcF interval of >450 msec ~~for males or >470 msec for females~~) then the ECG will be repeated twice, and the mean of the 3 screening measurements will be used to determine whether or not the patient is suitable for inclusion in the study.** ***At the Baseline visit, the predose QTcF will be determined by the average of 3 ECGs (within 10 to 20 minutes of one another), each in triplicate (in total 9 recordings). A postdose ECG will be performed in triplicate 1 to 2 hours after first dosing.*** **ECGs will be performed in triplicate prior to dosing on site and 1 to 2 hours after dosing on site at ~~baseline (Visit 1),~~ Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), ~~and~~ Day 84 *(Visit 6)*, *Day 112 (Visit 7)*, *Day 140 (Visit 8)*. *On Day 182 (Visit 9)* or Early Termination*, a triplicate ECG will be performed before the morning dose.* ~~(Visit 6).~~ At the discretion of the investigator, 12-lead ECG measurements can also be performed on Day 56 (Visit 5) where there are clinical circumstances that justify an additional ECG, eg, patients with a previous episode of hypokalemia without QT prolongation.**	**Change to time points due to extended duration of study and also various points of clarification.**

Previous approved wording	Amended or new wording	Reason/Justification for change
evaluations should be performed. This optional afternoon ECG measurement is included for safety reasons, as the concentration of study drug may be higher in the afternoon than in the morning. **ECG will also be performed in triplicate at the follow-up visit only for patients with a previously observed cardiac concern and/or QTc change from baseline.** **Where applicable, ECG measurements should be taken prior to vital sign measurements and blood being drawn for clinical laboratory or PK evaluations.** **A qualified physician at the central ECG vendor will be responsible for interpreting the ECG. However, every ECG should be reviewed immediately at site in order to detect any QTcF prolongation of potential clinical concern and allow dosing.**	**Additional 12-lead ECG evaluations should be performed on site, at the investigators discretion, 1 to 2 hours after the afternoon dose for patients who, after their morning dose, show an increase from baseline in their QTcF value >50 msec. The site will compare the machine produced QTcF value from the morning ECG to the central ECG vendor reported Baseline QTcF; if the change is >50 msec then the afternoon ECG evaluations should be performed. This optional afternoon ECG measurement is included for safety reasons, as the concentration of study drug may be higher in the afternoon than in the morning.** **ECG will also be performed in triplicate at the follow-up visit only for patients with a previously observed cardiac concern and/or QTc change from baseline.** ***The patient must be in a supine position and resting for at least 5 minutes prior to each ECG measurement.*** **Where applicable, ECG measurements should be taken prior to vital sign measurements and blood being drawn for clinical laboratory or PK evaluations.** **A qualified physician at the central ECG vendor will be responsible for interpreting the ECG. However, every ECG should be reviewed immediately at site in order to detect any QTcF prolongation of potential clinical concern and allow dosing.** ***Evaluation of the screening ECG(s) for inclusion in the study can be performed locally, ie, the interpretation from the central ECG vendor is not required for inclusion.***	
Section 7.7 (Other sections affected by this change: Section 3.11)		
Physical and neurological examinations, including weight will be performed at screening (Visit 0), baseline (Visit 1), Day 14 (Visit 2), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), Day 84 or Early Termination (Visit 6), and at the follow-up visit.	**Physical and neurological examinations, including weight will be performed at screening (Visit 0),** ~~**baseline (Visit 1), Day 14 (Visit 2),**~~ **Day 28 (Visit 3), Day** ~~**42 (Visit 4), Day 56 (Visit 5), Day**~~ **84** ***(Visit 6), Day 182 (Visit 9)*** **or Early Termination** ~~**(Visit 6)**~~**, and at the follow-up visit.**	**Change to time points due to extended duration of study and also a reduction in the frequency of examinations.**
Section 7.8.2 (Other sections affected by this change: Section 3.11)		

Previous approved wording	Amended or new wording	Reason/Justification for change
The C-SSRS will be completed at screening (Visit 0), baseline (Visit 1), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), and Day 84 or Early Termination (Visit 6).	**The C-SSRS *Baseline version* will be completed at screening (Visit 0), *while the C-SSRS Since Last Visit version will be completed at* baseline (Visit 1), Day 28 (Visit 3), Day 42 (Visit 4), Day 56 (Visit 5), *Day 84 (Visit 6), Day 112 (Visit 7), Day 140 (Visit 8),* and Day *182 (Visit 9)* ~~84~~ or Early Termination ~~(Visit 6)~~.**	**Change to time points due to extended duration of study and also clarification of process.**
8 ASSESSMENT OF PHARMACOKINETICS AND PHARMACOGENOMICS		
Section 8.1.1 (Other sections affected by this change: Section 3.11)		
<u>Titration Period</u> Day 0 (baseline) – predose and 1 to 2 hours postdose Day 14 – predose and 1 to 2 hours postdose <u>Full Treatment Dose Period</u> Day 28 – predose and 1 to 2 hours postdose Day 42 – predose, 1 to 2 hours postdose, and before leaving the site Day 84 – predose, 1 to 2 hours postdose, and before leaving the site Follow-up visit	**<u>Titration Period</u> Day 0 (baseline) – *prior*~~predose~~ and 1 to 2 hours post *first* dose Day 14 – ~~predose and~~ 1 to 2 hours post *afternoon* dose <u>Full Treatment Dose Period</u> Day 28 – pre *afternoon* dose and 1 to 2 hours post *afternoon* dose *Day 42 – pre afternoon dose and 1 to 2 hours post afternoon dose* Day 42 – predose, 1 to 2 hours postdose, and before leaving the site Day 84 – ~~predose,~~ 1 to 2 hours *post afternoon dose* *Day 112 – pre afternoon dose*~~postdose,~~ and *1 to 2 hours post afternoon dose*~~before leaving the site~~ *Day 140 – 1 to 2 hours post afternoon dose* *Day 182 – prior to morning dose* Follow-up visit**	**Change to time points due to extended duration of study and also assessments now being performed relative to afternoon dose.**
Section 8.2		
A blood sample (6 mL) will be collected at the screening visit for potential genetic analyses. Analyses will include CAG repeats, CYP2D6 status, and genetic long QT syndrome (assessed only in patients experiencing QT prolongation following study drug administration leading to study discontinuation), or any other genetic analyses related to pridopidine response or HD.	**A blood sample (*10*~~6~~ mL) will be collected *in 2 dipotassium ethylenediaminetetraacetic acid (K2EDTA) plastic tubes* at the screening visit for ~~potential~~ genetic analyses. Analyses will include CAG repeats, CYP2D6 status, and genetic long QT syndrome (assessed only in patients experiencing QT prolongation following study drug administration leading to study discontinuation). *Additionally, any subpopulation of patients that responds differently to drug (in terms of exposure,***	**Clarification**

Previous approved wording	Amended or new wording	Reason/Justification for change
	efficacy, tolerability,* or *safety) should be investigated for~~any other~~ genetic association, with the exact analysis selected according to the study results. The* analyses *of CAG repeats from the screening sample will not be used to assess eligibility for the study; that will be assessed using historical data~~related to pridopidine response or HD~~.	
9 STATISTICS		
Section 9.2 (Other sections affected by this change: Section 3.1)		
It is estimated that approximately 50 patients per arm will enable a power of 80% to detect a beneficial effect of 4.5 points or more in the change from baseline in TMS of an active pridopidine arm compared to placebo, assuming SD of 7.8 (as estimated from the MermaiHD [ACR16C008] study) and type I error of 5%.	It is estimated that approximately ***80~~50~~*** patients per arm will enable a power of ***84~~80~~***% to detect a beneficial effect of 4.***0~~5~~*** points or more in the change from baseline in ***UHDRS***-TMS of an active pridopidine arm compared to placebo, assuming SD of ~~7.8~~***8.5*** (as estimated from the MermaiHD [ACR16C008] study) and type I error of 5%. ***Eighty patients per arm will enable a power of 71% to detect a beneficial effect of 2.0 points or more in the change from baseline in PPT of an active pridopidine arm compared to placebo, assuming SD of 5.0.***	Change to sample size calculation.
Section 9.6.4.1		
(Not applicable)	***The pridopidine dose group of 45 mg bid comparison to placebo will serve as a bridging comparison to the legacy pridopidine studies (ACR16C008 [MermaiHD] and ACR16C009 [HART]), where the pridopidine dose of 45 mg bid was the maximal dose. This comparison to historical data will be performed descriptively.*** ***In addition, any treatment group that will be discontinued due to safety issues will not be formally tested for efficacy and hence not controlled for type I error.***	New text
Section 9.6.4.1		
The estimated means at the Week 12 visit of the change from baseline in TMS will be compared between the active treatment arms and the placebo arm.	The estimated means at the ***Week 26***~~Week 12~~ visit of the change from baseline in ***UHDRS***-TMS will be compared between the active treatment arms ***(the arms from: 67.5, 90, or 112.5 mg bid that are not discontinued due to safety issues)*** and the placebo arm.	Clarification

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 9.6.4.2		
No sensitivity analyses are planned for this study.	***A sensitivity analysis to evaluate if the observed effect in UHDRS-TMS is driven by the Chorea UHDRS-TMS sub-score, the Dystonia UHDRS-TMS sub-score, or the Involuntary Movements (Chorea + Dystonia) UHDRS-TMS sub-score will be performed according to the following:*** ***Three variables will be calculated:*** ***The change from baseline to Week 26 in the sum of the UHDRS-TMS items except the Chorea items*** ***The change from baseline to Week 26 in the sum of the UHDRS-TMS items except the Dystonia items*** ***The change from baseline to Week 26 in the sum of the UHDRS-TMS items except the Chorea and Dystonia items*** ***These variables will be analyzed in the same way as the primary efficacy endpoint except that the variable evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.***	Addition of sensitivity analysis.
Section 9.6.4.3		
The secondary efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline TMS. For CIBIC-Plus, the CIBIS score at baseline will be included in the model instead of baseline TMS.	***Any statistically significant dose that will be observed in the primary analysis will continue to be tested for the secondary endpoint at an alpha level of 5%.*** ***The change from baseline in PPT will be analyzed using a Repeated Measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical week in study by treatment interaction, center, neuroleptic use or no use, and baseline PPT score. The unstructured covariance matrix for repeated observations within patients will be used. In case that the model will not converge, the ML estimation method will be used instead of the default REML. If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: ARH(1), CSH, AR(1), and CS. The estimated means at the Week 26 visit of the change from baseline in PPT will be compared between the active treatment arms and the placebo arm.***	Major change to section as secondary efficacy endpoint has changed.

Previous approved wording	Amended or new wording	Reason/Justification for change
Section 9.6.4.4		
9.6.5.4 Other Functional Efficacy Variables Analyses The other functional efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline TMS. For CGI-C, the CGI-S score at baseline will be included in the model instead of baseline TMS 9.6.5.5 Exploratory/Other Efficacy Analyses The exploratory/other efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline TMS.	***The odds of responders will be compared between the active groups and the placebo group using logistic regression analysis (SAS® LOGISTIC procedure) stratified by center using the STRATA sub-command with the following effects: treatment group, neuroleptic use or no use and baseline UHDRS-TMS score.*** ***The other efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint except that the efficacy endpoint evaluation at baseline will be included in the model instead of baseline UHDRS-TMS.*** ***For CIBIC-Plus, the CIBIS score at baseline will be included in the model instead of baseline UHDRS-TMS.*** ***For CGI-C, the CGI-S score at baseline will be included in the model instead of baseline UHDRS-TMS.***	Major change to section (combination of 2 sections from original protocol)
Section 9.6.4.6		
A PK/PD model will be developed to describe the relationship between exposure and UHDRS-TMS. The model will consist of the following elements: (i) structural function relating UHDRS-TMS, pridopidine exposure (dose, AUC), and time; (ii) variance components characterizing inter-patient variability in model parameters; (iii) variance components characterizing residual variability. Model evaluation and selection will be based on standard model diagnostics, goodness of fit criteria and simulation-based assessments (eg, posterior predictive checks). Similar PK/PD models will be attempted for the secondary efficacy endpoints.	***A correlation between Cmax/AUC and efficacy and safety measures will be done.***	Major change to section as precise analysis will instead be documented in statistical analysis plan.
Section 9.7		
The Hochberg's Step-Up method for multiple comparisons between treatment arms and multiple secondary endpoints will be used to maintain the experiment-wise type I error of 5% level. First, the Hochberg method will be applied for the 4 comparisons of the 4 active doses to placebo. Then, any statistically significant dose will continue to be tested for the 3 secondary endpoints using the	***The Hochberg's Step-Up method for multiple comparisons between treatment arms in combination with the hierarchical method between the primary efficacy endpoint and the secondary efficacy endpoint, will be used to maintain the experiment-wise type I error of 5% level.*** ***The pridopidine dose group of 45 mg bid comparison to placebo***	Major change to section as only 3 of the 4 doses will be analyzed in this way.

Previous approved wording	Amended or new wording	Reason/Justification for change
Hochberg method.	***will serve as a bridging comparison to the legacy pridopidine studies (ACR16C008 [MermaiHD] and ACR16C009 [HART]), where the pridopidine dose of 45 mg bid was the maximal dose. Hence, only a maximum of 3 multiple dose comparisons to placebo will be performed and controlled for type I error in this study: 67.5, 90, and 112.5 mg bid. First, the Hochberg method will be applied for the comparisons of the 3 (or less) active doses (67.5, 90, and 112.5 mg bid) to placebo. Then, using the hierarchical method, any statistically significant dose will continue to be tested for the secondary endpoint at an alpha level of 5%.*** ***In addition, any treatment group that will be discontinued due to safety issues will not be formally tested for efficacy and hence not controlled for type I error.***	

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